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Preface

Volume 85 of Advances in Heterocyclic Chemistry comprises three chapters and indexes.

The first chapter covers organometallic complexes of boron, silicon, and phosphorus analogs of azoles. This chapter continues the series by A. P. Sadimenko (Fort Hare, South Africa) in which he is treating comprehensively organometallic complexes of heterocyclic compounds. So far, he has covered, in the volumes of AHC indicated, complexes of the following heterocycles:

Thiophenes and furans in volume 77.
Pyrroles, indoles, carbazoles, phospholes, siloles and boroles in volume 79.
Pyrazoles in volume 80.
Pyrazolyl borates in volume 81.
Poly heteroatom azoles other than pyrazole in volume 83.

Taken together, these chapters and those which will follow provide an unparalleled picture of the highly important organometallic complexes of heterocycles which span an enormous diversity of structure.

The second chapter (A. Schmidt, Clausthal, Germany) provides a concise review of heterocyclic mesomeric betaines and their analogs as found in natural products. Finally, I. Hermecz (Budapest, Hungary) provides part two of his survey of pyrido-oxazines, pyrido-thiazines, pyrido-diazines and their benzologs. This encompasses a large variety of heterocycles, many of which are of increasing importance because of their physiological activity. Much of this material has not been reviewed for decades and the subject has advanced enormously in this period.

As an index volume, volume 85 of Advances in Heterocyclic Chemistry also includes cumulative indexes of authors and titles of chapters in volumes 1 though 85, together with a cumulative subject index for volumes 81 to 85. Previous cumulative subject indexes have appeared in volumes 60, 70, 75 and 80.

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Organometallic Complexes of Boron, Silicon, and Phosphorus Analogues of Azoles

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Abbreviations

Ad	adamantyl
Alk	alkyl
AN	acetonitrile
Bu	butyl
CDT	cyclodecatriene
cod	cyclooctadiene-1,5
COE	cyclooctene
Cp	cyclopentadienyl

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Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
DME	dimethoxyethane
DMF	dimethylformamide
Et	ethyl
Me	methyl
Mes	mesityl
nbd	2,5-norbornadiene
Np	neopentyl
pip	piperidino
OTf^-	triflate
Ph	phenyl
Pr	propyl
py	pyridine
TCNE	tetracyanoethylene
TCNQ	7,7,8,8-tetracyano-*p*-quinodimethane
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine

I. Introduction

Following the forgoing reviews of the classical five-membered heteroaromatic ligands (five-membered monoheterocycles (01AHC(78)1, 01AHC(79)115) and azoles (01AHC(80)157, 01AHC(81)167, 02AHC(83)117, 02AHC(84)191), an analysis is now presented of the trends in the coordination chemistry of azole analogues where nitrogen is replaced by another element. The reason for this is the frequent strikingly different behavior of these compounds as ligands in organometallic complexes. This difference is especially well manifested on comparison of azoles with P,N-ligands as well as with di-, tri-, and pentaphospholes. However, we start our discussion with five-membered heterocycles containing two or three boron heteroatoms (di- and triborolyls), and continue with B,S- and B,N-combinations (thiaborolyls and azaborolyls, respectively), which most often act as the η^5-donors and form extended multidecker complexes of interest for materials chemistry. For the di- and triborolyl systems we have had to exclude capped and proton-bridged carboranes because of space problems. This exclusion can be justified by the fact that these compounds have been well reviewed as shown in the references below.

Azaphospholes and especially di-, tri- and pentaphospholyl systems offer a wide variety of coordination modes that frequently cannot be found in

azole chemistry. Similarity is found in carbene complexes of the azol-2-ylidene type but in the other respects there is a sharp contrast in the ligand behavior, the reasons for which still deserve detailed theoretical analysis.

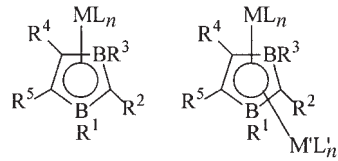
II. Complexes of Di- and Triborolyl Ligands

A. Iron Group

The di- and triborolyl ligands not only have a clear tendency to form η^5-coordination but are also able to bind metals from both sides of the heteroring to yield stable multidecker complexes (72SCI462, 75MI1, 76JA3219, 79CCR(28)47, 81IC863, 82MI1, 83AICR55, 85AGE943, 87PAC847, 87PAC947, 90IC516, 91MI1, 91PAC369, 92CRV251, 92MI3, 92OM2397, 93ADOC187, 93CB1587, 93CRV1081, 93JA6143, 93JCLS297, 94MI1, 94MI2, 95CCR(143)71, 95MI1, 95MI2, 95OM4668, 96AOC209, 99JOM(581)1, 99JOM(581)13, 00CCR(200)773). Thus, the $Et_2C_2B_3H_3^{4-}$ ligand is electronically similar to the cyclopentadienyl anion (88MI1). One of their remarkable features is the stabilization of oxidation states such as iron(III) and ruthenium(III) in the metal arene derivatives (82MI2, 89OM1580, 91OM3545, 92JA5214, 94JA9359).

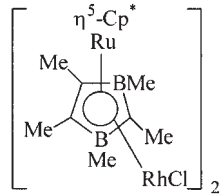
The triple-decker complex **2** [ML_n=$M'L'_n$ = Fe(η^5-Cp), $R^1 = R^3 = R^4 = R^5$ = Et, R^2 = Me] is assumed to be formed via an intermediate sandwich **1** [ML_n = Fe(η^5-Cp), $R^1 = R^3 = R^4 = R^5$ = Et, R^2 = Me] (83OM1666). These two species follow simultaneously from the corresponding 2,3-dihydro-1,3-diborole and [(η^5-Cp)Fe(η^4-cod)] (94AGE203, 96CEJ487). 2,3-Dihydro-1,3-diboroles containing the bulkier *iso*-propyl groups when treated with sodium hydride and then [(η^5-Cp)FeCl] gave only the analogue of sandwich **2** containing *i*-Pr-groups instead of Et in the 4 and 5 positions of the heteroring. The corresponding diborolene ligand reacts simultaneously with [(η^5-Cp)Fe(CO)$_2$]$_2$ and [(η^5-Cp)Co(CO)$_2$] and the diamagnetic triple-decker 30-valence electron species **2** [ML_n = Fe(η^5-Cp), $R^1 = R^2 = R^3 = R^4 = R^5$ = Me, $M'L'_n$ = Co(η^5-Cp)] acts analogously (77AGE857). Similar ruthenium complexes **1** [ML_n = Ru(η^5-Cp*), $R^1 = R^3$ = Et, R^2 = Me, $R^4 = R^5$ = *i*-Pr, R^2 = Et) result from various 2,3-dihydro-1,3-diboroles, sodium hydride, and [(η^5-Cp*)RuCl]. When 2,3-dihydro-4,5-diethyl-1,3-borole reacts with *tert*-butyl lithium followed by [(η^5-Cp*)RuCl], sandwich **1** [ML_n = Ru(η^5-Cp*, $R^1 = R^4 = R^5$ = Et, R^2 = Me, R^5 = *t*-Bu] is the product having an unusually folded diborolyl ring (78ZN(B)1410, 94ZN(B)315). 2,3-Dihydro-pentamethyl- and -1,2,3-trimethyl-4,5-diethyl-1,3-diboroles react with sodium hydride and [(η^5-Cp*)RuCl] to give the triple-decker compounds **2** [ML_n = Ru(η^5-Cp*), $M'L'_n$ = RuH(η^5-Cp*), $R^1 = R^2 = R^3 = R^4 = R^5$ = Me;

$R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$]. Sandwiches **1** [$ML_n = Ru(\eta^5\text{-Cp*})$, $R^1 = Et$, $R^2 = R^3 = R^4 = R^5 = Me$; $R^1 = R^3 = R^4 = R^5 = Et$, $R^3 = t\text{-Bu}$] react with carbon monoxide to give **1** [$ML_n = Ru(\eta^5\text{-Cp*})(CO)$, $R^1 = Et$, $R^2 = R^3 = R^4 = R^5 = Me$; $R^1 = R^3 = R^4 = R^5 = Et$, $R^3 = t\text{-Bu}$].



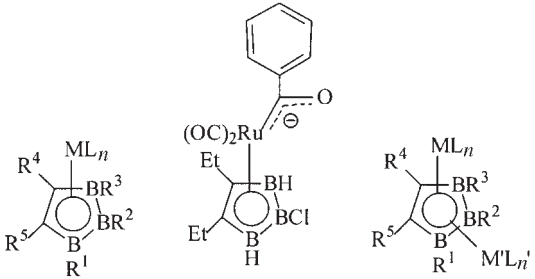
1 **2**

The range of the ruthenium sandwiches, their derivatives and stacking products was subsequently extended (99EJIC1685). Thus, some 2,3-dihydro-1,3-diboroles react first with methyllithium and then with $[(\eta^5\text{-Cp*})RuCl]_4$ or $[(\eta^5\text{-}C_5Me_4Et)RuCl]_4$ to yield a set of sandwiches **1** [$ML_n = Ru(\eta^5\text{-Cp*})$, $Ru(\eta^5\text{-}C_5Me_4Et)$, $R^1 = R^2 = R^3 = R^4 = R^5 = Me$; $ML_n = Ru(\eta^5\text{-Cp*})$, $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = Et$; $ML_n = Ru(\eta^5\text{-Cp*})$, $R^1 = R^3 = CH_2SiMe_3$, $R^2 = R^4$ $R^5 = Me$; $ML_n = Ru(\eta^5\text{-Cp*})$, $Ru(\eta^5\text{-}C_5Me_4Et)$, $R^1 = R^3 = R^4 = R^5 = Me$, $R^2 = Et$]. Similar to the aforementioned reaction with carbon monoxide, sandwiches **1** [$ML_n = Ru(\eta^5\text{-Cp*})$, $R^1 = R^4 = R^5 = Et$, $R^2 = R^3 = Me$; $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = Et$] add *tert*-butyl isocyanide to give **1** [$ML_n = Ru(\eta^5\text{-Cp*})(CNBu^t)$, $R^1 = R^4 = R^5 = Et$, $R^2 = R^3 = Me$; $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = Et$]. Addition of molecular hydrogen can proceed in several directions-towards dihydrogen, $Ru(H_2)$, and two types of the dihydride products, $Ru(H)_2$ and RuH, BH. Existing data favor the $Ru(H)_2$ series **1** [$ML_n = Ru(\eta^5\text{-Cp*})(H)_2$, $R^1 = R^4 = R^5 = Et$, $R^2 = R^3 = Me$; $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = Et$]. Products **1** [$ML_n = Ru(\eta^5\text{-Cp*})(H)_2$, $R^1 = R^4 = R^5 = Et$, $R^2 = R^3 = Me$; $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = Et$] oxidatively add $BH_3 \cdot THF$. In this process, reductive elimination of H_2 and rearrangement to *closo*-RuC_3B_3 ruthenacarboranes take place. Sandwich **1** [$ML_n = Ru(\eta^5\text{-Cp*})$, $R^1 = R^2 = R^3 = R^4 = R^5 = Me$] also reacts with $[(\eta^2\text{-}C_2H_4)_2RhCl]$ to give the tetranuclear product **3** formulated as a pentadecker species with two central bridging chlorine atoms.



3

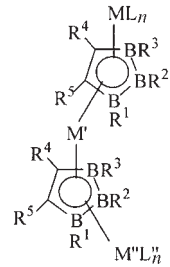
Displacement of cyclooctatetraene from $[(\eta^6\text{-}C_8H_{10})Fe(Et_2C_2B_3H_4)]^-$ in the presence of $[(\eta^5\text{-Cp})Co(CO)_2]$ gives the iron-cobalt triple-decker species of composition $[(\eta^5\text{-Cp})Fe(Et_2C_2B_3H_3)Co(\eta^5\text{-Cp})]$ (74IC1138, 89JA4776). Complex **4** [$ML_n = Ru(CO)_3$, $R^1 = R^3 = H$; $R^2 = Cl$, $R^4 = R^5 = Et$] can be prepared as the result of interaction of the dianions $[(\eta^5\text{-Cp*})Co(\eta^5\text{-}Et_2C_2B_3H_2Cl)]^{2-}$ and $[(OC)_3RuCl_2]_2$. With phenyl lithium and subsequent alkylation with Me_3OBF_4, species **4** [$ML_n = Ru(CO)_3$, $R^1 = R^3 = H$; $R^2 = Cl$, $R^4 = R^5 = Et$] is derivatized and gives the Fischer type methoxycarbene compound **5** (92JA8733). *Nido*-$[(\eta^6\text{-cymene})Ru(Et_2C_2B_3H_5)]$ is deprotonated with *tert*-butyl lithium in two steps—to the mono- and then the dianion, and the latter reacts with $[(\eta^6\text{-cymene})RuCl_2]$ to yield the triple-decker **6** [$ML_n = M'L'_n = Ru(\eta^6\text{-cymene}$; $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$] (89JA4776). The other triple-decker, **6** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$], follows from the reaction of the aforementioned monoanion with sodium cyclopentadienyl and cobalt(II) chloride. Treatment of **6** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] with ruthenium(III) chloride gives the product of substitution at the triborolyl heterocycle, **6** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = R^5 = Et$]. The ruthenium-containing starting dianion also reacts with $[(\eta^6\text{-cymene})OsCl_2]$ to give the corresponding triple-decker **6** [$ML_n = Os(\eta^6\text{-cymene})$, $M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$], which on further interaction with osmium(II) chloride gives the substitution product **6** [$ML_n = Os(\eta^6\text{-cymene})$, $M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = R^5 = Et$]. *Nido*-$[(\eta^5\text{-Cp})Co(Et_2C_2B_3H_5)]$ can also be deprotonated in two steps with *tert*-butyl lithium, and further give the cobalt-osmium triple-decker **6** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Os(\eta^6\text{-cymene})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] together with some **6** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Os(\eta^6\text{-cymene})$, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = R^5 = Et$].



4 **5** **6**

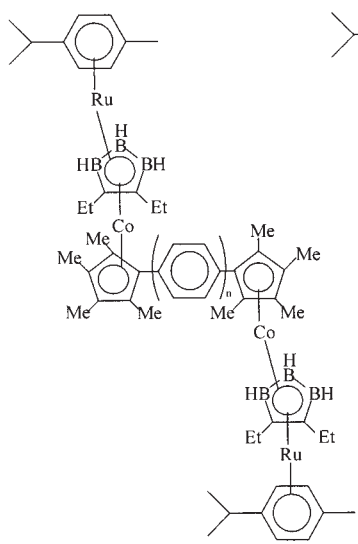
The ruthenium starting materials of composition *nido*-$[(\eta^6\text{-}MeC_6H_4Pr\text{-}i)Ru(2,3\text{-}Et_2C_2B_3H_4\text{-}5\text{-R})]$ (R = Me, Cl) with *tert*-butyl lithium and then

cobalt(II) chloride give the tetradecker species **7** [$ML_n = M''L''_n = Ru(\eta^6$-cymene); $M' = CoH$; $R^1 = R^3 = H$; $R^2 = R^{2'} = Me$, Cl; $R^4 = R^5 = Et$] but the methyl derivative could not be isolated (95OM3683). In moist air they are readily converted to a series **7** [$ML_n = M''L''_n = Ru(\eta^6$-cymene); $M' = Co$; $R^1 = R^3 = H$; $R^2 = R^{2'} = Me$, Cl; $R^2 = Me$, $R^{2'} = Et$; $R^2 = Cl$, $R^{2'} = H$; $R^4 = R^5 = Et$]. The methyl-containing starting material after a similar sequence of transformations but with nickel chloride gives the nickel analogue of **7** [$ML_n = M''L''_n = Ru(\eta^6$-cymene); $M' = Ni$, $R^1 = R^3 = H$; $R^2 = R^{2'} = Me$; $R^4 = R^5 = Et$].

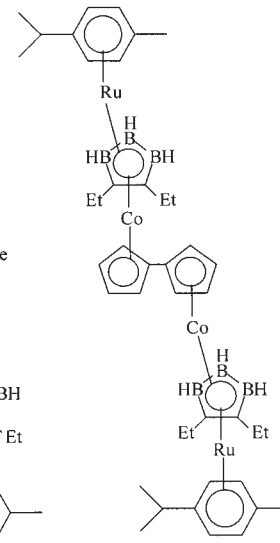


7

The reaction of $C_5Me_4(C_6H_4)_n(C_5Me_4)$ ($n = 1, 2$) with [(η^6-cymene)$Ru(Et_2C_2B_3H_4)]^-$ in the presence of cobalt(II) chloride gives **8** ($n = 2, 3$) (89JA4784). The reaction of $[C_5H_4–C_5H_4]^{2-}$ with [(η^6-cymene)Ru$(Et_2C_2B_3H_4)]$ and $CoCl_2$ forms **9**.

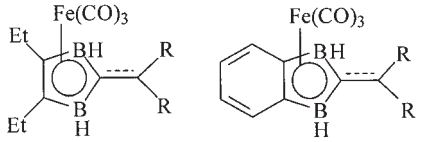


8



9

In the complexes of 1,3-boroles containing the unsaturated substituents (89CB633, 90CB2273, 94CB2393), the coordination mode is η^5 in the case of iron tricarbonyl complexes **10** and **11** (R = H, Me).



10 **11**

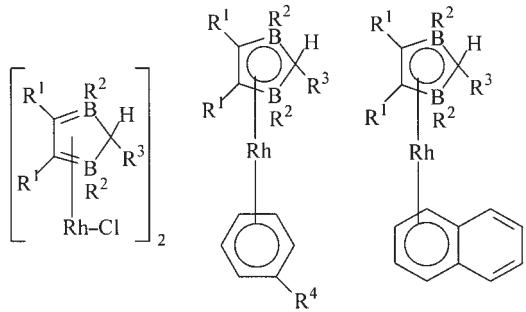
B. Cobalt Group

1. *Sandwiches and Triple-deckers*

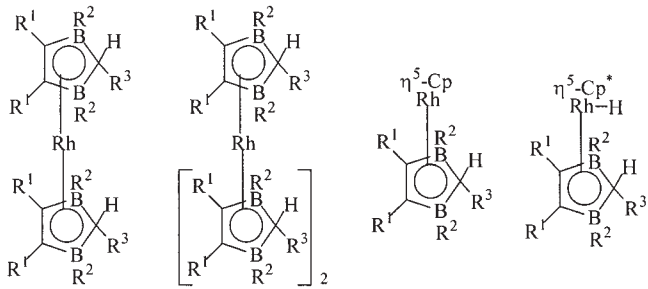
Generally, precursors of the triple- and multiple-deckers are the metallocarboranes of composition $[LM(C_2B_3H_5)]$ where LM = (η^5-Cp)Co, (η^5-Cp*)Co, (η^6-arene)Fe, and (η^6-arene)Ru (89OM2492, 90OM1171, 90OM1177, 92OM2404). They are subject to the so-called re-capitation reactions (96IC6703, 97IC3602). Another opportunity is the product of interaction of 1,3,4,5-tetraethyldiborole with $[Co_2(CO)_8]$, $[HCo(CO)_4]$, or $[(\eta^3\text{-}C_3H_5)Co(CO)_3]$, which leads to the sandwich **1** [$ML_n = Co(CO)_3$, $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = Et$] (85AGE248, 85CB401, 87JOM(324)57). Reaction of thallium cyclopentadienyl with [(η^5-1,3,4,5-tetramethyl-2,3-dihydro-1H-1,3-diborolene)cobalt(η^5-cylopentadienyl)] gives neutral complexes **2** [$ML_n = Tl(\eta^5\text{-Cp})$, $M'L'_n = Co(\eta^5\text{-Cp})$, $R^1 = R^2 = R^3 = R^4 = R^5 = Me$] (85AGE71, 87JOM(324)57).

2,3-Dihydro-1,3-diborole derivatives react with $[(C_2H_4)_2RhCl]_2$ to yield the dimers **12** ($R^1 = R^2 = Me, R^3 = MesCH_2$; $R^1 = Et, R^2 = R^3 = Me$; $R^1 = Me$, $R^2 = t$-Bu, $R^3 = Me$) (98JOM(571)107, 01JOM(619)7). The product undergoes dehydrohalogenation in benzene or toluene in the presence of methyl lithium to yield species **13** ($R^1 = R^2 = Me$, $R^3 = MesCH_2$, $R^4 = H$; $R^1 = Et$, $R^2 = R^3 = Me$, $R^4 = Me$, H; $R^1 = Me$, $R^2 = t$-Bu, $R^3 = R^4 = Me$). 1,3,4,5-Tetramethyl-2,3-dihydro-1,3-diborole interacts with *tert*-butyl lithium, methyl lithium, or potassium hydride, and $[(C_2H_4)_2RhCl]_2$ in toluene to yield **13** ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = R^4 = H$). Dimer **12** ($R^1 = Et$, $R^2 = R^3 = Me$) in the presence of naphthalene in THF and *tert*-butyl lithium gives **14** ($R^1 = Et$, $R^2 = R^3 = Me$). Pure 1,3-diborolyl sandwich **15** ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = Me$) can be prepared from **13** ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = R^4 = Me$), methyl lithium and the 1,3-diborole ligand (01JOM(619)7). The by-product of this reaction is the triple-decker species

16 ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = Me$). Dimeric compound **12** ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = Me$) experiences cleavage of the chlorine bridges under the action of sodium cyclopentadienyl or lithium pentamethylcyclopentadienyl and gives sandwiches **17** ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = Me$) with rhodium(I) center and **18** ($R^1 = Me$, $R^2 = t$-Bu, $R^3 = Me$) with rhodium(III) center, respectively.



12 **13** **14**



15 **16** **17** **18**

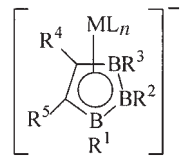
The reactions of the Group VIII di- and triborolyl or carboranes sandwiches are directed basically to their extension to multidecker derivatives.

Anionic carborane complex $[(\eta^5\text{-Cp}^*)Co(Et_2C_2B_3H_4)]^-$ with $[Mo(CO)_4Cl(\mu\text{-Cl})]_2$ gives triple-decker and tetradecker species **6** [$ML_n = Mo(CO)_4$, $M'L'_n = Co(\eta^5\text{-Cp}^*)$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] and **7** [$ML_n = M''L''_n = Co(\eta^5\text{-Cp}^*)$, $M' = Mo(CO)_2$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$], respectively (98IC102). The tetradecker derivative of the same kind as **7** is known for the diboroles and can be formulated as $[(\eta^5\text{-Cp})Co(Et_2HC_3B_2Me_2)]_2Sn$ (83OM1899). Compound **7** [$ML_n = M''L''_n = Co(\eta^5\text{-Cp}^*)$, $M' = Mo(CO)_2$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] is the only product of interaction of $[(\eta^5\text{-Cp}^*)Co(Et_2C_2B_3H_4)]^-$ and $[Mo(CO)_4Br(\mu\text{-Br})]_2$ but

the triple-decker species is not formed (98IC102). The reaction of the same cobalt precursor with $[W(CO)_4Br(\mu\text{-}Br)]_2$ gives the tungsten analogue of **6** [$ML_n = W(CO)_4$, $M'L'_n = Co(\eta^5\text{-}Cp^*)$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$]. Complex **6** [$ML_n = Mo(CO)_4$, $M'L'_n = Co(\eta^5\text{-}Cp^*)$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] with phenyl lithium in the presence of trimethyloxonium tetrafluoroborate in toluene gives **6** [$ML_n = Mo(CO)_4$, $M'L'_n = Co(\eta^5\text{-}Cp^*)$, $R^1 = PhCH_2$, $R^2 = R^3 = R^4 = R^5 = Et$].

Nido-$[(\eta^5\text{-}Cp^*)Co(Et_2C_2B_3H_4)]^-$ and $CpTaCl_4$, Cp^*TaCl_4, and $CpNbCl_4$ yield the triple-deckers **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, Me, X = X′ = Cl; M = Nb, R = H, X = X′ = Cl; $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$] as the main products (95OM3014). With an alkylating or arylating agent, complex **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = X′ = Cl); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$] undergoes the following transformations: with Me_2Zn or $AlMe_3$—to **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = Me, X′ = Cl); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$], MeLi or MeMgBr—to **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = X′ = Me); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$], with $Zn(CH_2Ph)_2$—to **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = $PhCH_2$, X′ = Cl); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$], with $PhCH_2MgBr$—to **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = X′ = $PhCH_2$); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$], with $Np_2Mg \cdot$ dioxane—to **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = *t*-$BuCH_2$, X′ = Cl); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$], and with NpLi = to **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = MXX'(\eta^5\text{-}C_5R_5)$ (M = Ta, R = H, X = X′ = *t*-$BuCH_2$, X′ = Cl); $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$]. Treatment of **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$, $M'L'_n = TaCl_2(\eta^5\text{-}Cp)$, $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Et$] with N-bromo- or N-iodosuccinimide gives **6** [$ML_n = Co(\eta^5\text{-}Cp^*)$; $M'L'_n = TaCl_2(\eta^5\text{-}Cp)$; $R^1 = R^2 = R^3 = Cl$, Br; $R^4 = R^5 = Et$] (00OM2200).

Reaction of the anionic sandwich **19** [$ML_n = Co(\eta^5\text{-}Cp^*)$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] as its lithium salt with $[(\eta^5\text{-}Cp^*RuCl]_4$ gives the triple-decker **6** [$ML_n = Ru(\eta^5\text{-}Cp^*)$, $M'L'_n = Co(\eta^5\text{-}Cp^*)$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] (97JOM(536)115).



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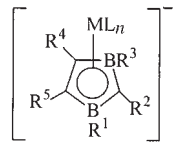
Similar triple-decker complexes are known, e.g., $[(\eta^6\text{-}p\text{-}MeC_6H_4CHMe_2)Ru(\eta^5\text{-}Et_2C_2B_3H_3)Ru(\eta^6\text{-}p\text{-}MeC_6H_4CHMe_2)]$ and $[(\eta^5\text{-}Cp)Co(\eta^5\text{-}Et_2C_2B_3H_3)$

$Ru(\eta^6\text{-}p\text{-}MeC_6H_4CHMe_2)]^+$, and their redox properties were studied by electrochemical techniques (79JA3399, 90JEAC139, 92JA9846, 99IC93). Species **6** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] and **6** [$ML_n = M'L'_n = Ru(\eta^6\text{-cymene})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] are fully delocalized (92JA9846). However, this is not the case for the triple-decker species **6** [$ML_n = Fe(\eta^5\text{-Cp})$, $M'L'_n = Co(\eta^5\text{-Cp})$, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Et$] (92JA5214, 94IC4211, 95IC2058).

Nido-[$(\eta^5\text{-Cp*})Co(Et_2C_2B_3H_4\text{-}5\text{-}R)$] (R = H, Cl, Br) undergo bridge-deprotonation with *n*-butyl lithium, and then react with $[(\eta^5\text{-Cp*})FeCl]_2$ in THF in the presence of air to give triple-deckers **6** [$ML_n = Fe(\eta^5\text{-Cp*})$; $M'L'_n = Co(\eta^5\text{-Cp*})$; $R^1 = R^3 = H$; R^2 = H, Cl, Br, $R^4 = R^5 = Et$] (95IC2058). They contain iron in the formal oxidation state of +3. The same assignment of the iron oxidation number is valid for $[(\eta^5\text{-Cp})Co(Et_2MeC_3B_2Et_2)Fe(Et_2C_2B_4H_4)]$ (89OM1300).

The cobalt anionic sandwich complex **20** [$ML_n = Co(\eta^5\text{-Cp})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] (82AGE148, 83OM1666) reacts with *nido*-6-Me-5,6,9-$C_3B_7H_9^-$ anions in the presence of $FeCl_2 \cdot THF$, $CoCl_2$, or $NiBr_2 \cdot DME$ to give the triple-deckers **2** [$ML_n = Co(\eta^5\text{-Cp})$; $M'L'_n = Fe(\eta^6\text{-5-Me-2,3,5-}C_3B_7H_9)$, $Co(\eta^6\text{-2-Me-2,3,5-}C_3B_7H_9)$, $Ni(\eta^4\text{-8-Me-7,8,10-}C_3B_7H_9)$; $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] (95OM1911). In the latter case the $\eta^6 \rightarrow \eta^4$ cage distortion takes place. Other known triple-deckers include **2** [$ML_n = Co(\eta^5\text{-Cp})$; $M'L'_n = Fe(\eta^5\text{-Cp})$, $Co(\eta^5\text{-Cp})$, $Ni(\eta^5\text{-Cp})$; $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] (83JA2582).



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A series of cobalt neutral and charged triple-deckers was prepared as early as in 1973 when $[(\eta^5\text{-Cp})Co(\eta^5\text{-}C_2B_3H_5)Co(\eta^5\text{-Cp})]$ was first synthesized (73JA3046). The end rings in the triple-deckers may include cyclopentadienyl, pentamethylcyclopentadienyl, arene and hetarene (e.g. pyrrolyl and phospholyl groups) (91OM2631). Bromination of the sandwich $[(\eta^5\text{-Cp})Co(\eta^5\text{-}C_2Et_2B_3H_3)Co(\eta^5\text{-Cp})]$ by N-bromosuccinimide occurs at three boron atoms and gives $[(\eta^5\text{-Cp})Co(\eta^5\text{-}C_2Et_2B_3Br_3)Co(\eta^5\text{-Cp})]$ (95OM4661).

The cobalt analogues **6** [$ML_n = M'L'_n = Co(\eta^5\text{-Cp*})$; $R^1 = R^3 = R^4 = Me$, $R^2 = Cl$, Me] are prepared from the corresponding capped precursors $[(\eta^5\text{-Cp*})Co(Me_2C_2B_3H_2\text{-}4,5,6\text{-}Me_3)]$ and $[(\eta^5\text{-Cp*})Co(Me_2C_2B_3H_3\text{-}4,6\text{-}Me_2\text{-}5\text{-}Cl)]$, respectively, as a result of the sequence of lithiation (*n*-BuLi) and reaction with $[(\eta^5\text{-Cp*})CoCl]_2$ (81JA1399, 92IC3904). A similar approach

provides the triple-decker complexes **6** [$ML_n = M'L'_n = Co(\eta^5\text{-Cp*})$; $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = H$, $SiMe_3$].

Sandwich *nido*-[$(\eta^5\text{-Cp*})Ir(2,3\text{-}Et_2C_2B_3H_5)$] on bridge-deprotonation with *n*-butyl lithium, and further treatment with $[(\eta^5\text{-Cp*})IrCl_2]_2$ leads to the triple-decker species **6** [$ML_n = M'L'_n = Ir(\eta^5\text{-Cp*})$, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = R^5 = Et$] (96IC7027). The heterobimetallic cobalt–iridium analogue **6** [$ML_n = Ir(\eta^5\text{-Cp*})$, $M'L'_n = Co(\eta^5\text{-Cp*})$, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = R^5 = Et$] follows from the anionic nido-$[(\eta^5\text{-Cp*})Co(Et_2C_2B_3H_4)]^-$ and $[(\eta^5\text{-Cp*})IrCl_2]_2$.

A group of studies is devoted to cases where a carborane ligand serves as the terminal chain of triple-deckers. Complexes **2** [$ML_n = Co(\eta^5\text{-Cp})$; $M'L'_n = M(MeC_3B_7H_9)$ (M = Fe, Co, Ni); $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] (95OM1911), **2** [$ML_n = Co(\eta^5\text{-Cp})$; $M'L'_n = M(Et_2C_2B_4H_4)$ (M = Co, Ni); $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] (90IC5157), **2** [$ML_n = Co(\eta^5\text{-Cp})$; $M'L'_n = M(nido\text{-}C_2B_9H_{11})$ (M = Co, Ni); $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] (M = Co, Ni) (93JCS(D)1783) serve as examples. Deprotonation of the complex $[(\eta^5\text{-Cp})Co\{\eta^5\text{-}(EtC)_2(EtB)_2CHMe\}]$ (83OM1666) gives the anionic sandwich **20** [$ML_n = Co(\eta^5\text{-Cp})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$], which further reacts with cobalt(II) chloride and *nido*-4,5-$C_2B_6H_5^-$ to yield the triple-decker **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(2,3\text{-}C_2B_5H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] (96CB213). In a similar reaction where *arachno*-4,5-$C_2B_2H_{12}^-$ participates, the triple-decker **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(6,9\text{-}C_2B_7H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] is formed. On heating, **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(6,9\text{-}C_2B_7H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] isomerizes to **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(1,6\text{-}C_2B_7H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] and at higher temperatures to **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(1,10\text{-}C_2B_7H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$]. If $RhCl_2$ is used in this reaction, the product is **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Rh(1,6\text{-}C_2B_7H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$].

Interaction of the lithium salt of $[(\eta^5\text{-Cp})Co(\eta^5\text{-}(EtC)_2(EtB)_2(CMe))]^-$ (83OM1666) with the boranyl $B_9H_{14}^-$ and cobalt(II) chloride gives the triple-decker species **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(B_9H_{13})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] (97CB329). If in a similar reaction *arachno*-$C_S^+SB_9H_{12}^-$ is used, the diamagnetic triple-decker complex **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(SB_9H_9)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] results. The product is **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(6,8\text{-}S_2B_6H_8)$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] when *arachno*-6,8-$S_2B_7H_8^-$ is one of the reactants.

2. *Multidecker Compounds*

When species *nido*-$[(\eta^5\text{-Cp*})Co(Et_2C_2B_3H_4\text{-}5\text{-}X)]$ (X = Me, Cl) are deprotonated with *n*-butyl lithium and then reacted with iron(II) chloride,

they give after work-up on alumina, tetradecker complexes **7** [$ML_n = Co(\eta^5$-Cp); M = FeH; $M''L''_n = Co(\eta^5$-Cp*); $R^1 = R^3 = H$; $R^2 = H$, Cl, Me; $R^4 = R^5 = Et$]. Here the iron site is in the oxidation state +3 (95IC6509).

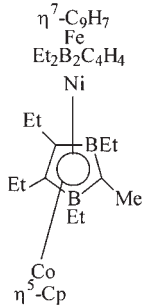
Sandwich *nido*-[(η^5-Cp*)Ir(2,3-$Et_2C_2B_3H_4$-5-Cl)] appeared to be a starting material for various rhodium-containing tetradecker compounds. Thus, first reacting with *n*-butyl lithium and then with [$Rh(AN)_3Cl_3$], the iridium sandwich yields complex **7** [$ML_n = M''L''_n = Ir(\eta^5$-Cp*), M′ = RhH, $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = R^5 = Et$] separated from a mixture of various products. Joint application of two anionic sandwiches *nido*-[(η^5-Cp*)Ir(2,3-$Et_2C_2B_3H_4$-5-Cl)]$^-$ and nido-[(η^5-Cp*)Co($Et_2C_2B_3H_3Cl$)]$^-$ in their reaction with *n*-butyl lithium and then [$Rh(AN)_3Cl_3$] allows the preparation of a mixture of tetradecker compounds **7** [$ML_n = M''L''_n = Ir(\eta^5$-Cp*), M′ = RhH, $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = R^5 = Et$], **7** [$ML_n = Co(\eta^5$-Cp*), M′ = RhH, $M''L''_n = Ir(\eta^5$-Cp*), $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = R^5 = Et$], **7** [$ML_n = M''L''_n = Co(\eta^5$-Cp*), M′ = RhH, $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = R^5 = Et$] (96IC7027).

Reaction of monoanion [($Et_2C_2B_3H_4$)Co(η^5-$C_2Et_2CMeB_2Et_2$)Co(η^5-Cp)]$^-$ with [(η^5-Cp*)$CoCl]_2$ gives the tetradecker species **7** [$ML_n = M''L''_n = Co(\eta^5$-Cp*); M′ = Co; $R^1 = R^2 = H$; $R^3 = H$, Cl; $R^4 = R^5 = Et$, $R^{2'} = R^{3'} = R^{4'} = R^{5'} = Et$; $R^{2'} = Me$] (90IC5164). This and two subsequent species contain two different triborolyl ligands, and substituents bearing the Co(η^5-Cp*) moiety labeled as $R^{n'}$ ($n = 1$–5). Preliminary deprotonation of the same anion with $LiHBEt_3$ and treatment of the resultant dianion with [(η^5-Cp*)$RhCl_2]_2$ or [(η^6-cymene)$RuCl_2$] gives the heteronuclear tetradecker species **7** [$ML_n = Rh(\eta^5$-Cp); M′ = Co; $M''L''_n = Co(\eta^5$-Cp*); $R^1 = R^2 = H$; $R^3 = H$, Cl; $R^4 = R^5 = Et$, $R^{1\prime} = R^{3\prime} = R^{4\prime} = R^{5\prime} = Et$; $R^{2\prime} = Me$] and **7** [$ML_n = Ru(\eta^6$-cymene); M′ = Co; $M''L''_n = Co(\eta^5$-Cp*); $R^1 = R^2 = H$; $R^3 = H$, Cl; $R^4 = R^5 = Et$, $R^{1\prime} = R^{3\prime} = R^{4\prime} = R^{5\prime} = Et$; $R^{2\prime} = Me$], respectively.

With a capped cobalt precursor, the sequence of lithiation and transition-metal stacking with nickel(II) bromide gives the cobalt nickel tetradecker **7** [$ML_n = M''L''_n = Co(\eta^5$-Cp*), M′ = Ni, $R^1 = R^3 = H$, $R^2 = R^4 = R^5 = Me$] (92IC3904). This complex as well as tetradecker species **7** [$ML_n = M''L''_n = Co(\eta^5$-Cp*); M′ = Co; $R^1 = H$; $R^2 = Me$, COMe, Cl, Br, I, $CH_2C{\equiv}CBu^t$; $R^3 = H$, Cl; $R^4 = R^5 = Et$] and **7** [$ML_n = M''L''_n = Co(\eta^5$-Cp*); M′ = Ni; $R^1 = H$; $R^2 = Me$, COMe, Cl, Br, I, $CH_2C{\equiv}CBu^t$; $R^3 = H$, Cl; $R^4 = R^5 = Et$] are characterized by an extended electron delocalization (93OM4452, 93OM4459).

The carborane anionic sandwiches *nido*-[(η^5-Cp*)Co($RR'C_2B_3H_3X$)] (X = H, Cl, Br, I, Me, COMe, $CH_2C{\equiv}CMe$; R, R′ = Alk, H) upon reaction with *n*-butyl lithium and then metal salts experience stacking and formation of the tetradecker heterometallic species **7** [$ML_n = M''L''_n = Co(\eta^5$-Cp*); M′ = Co, Ni, Ru; $R^1 = R^3 = H$; $R^2 = Me$, COMe, H, Cl, Br, I, $CH_2C{\equiv}CMe$; $R^4 = R^5 = H$, Me, Et] (92IC5202, 93JA6143, 93OM4452, 93OM4459).

The anionic sandwich $[(\eta^5\text{-Cp})Co(\eta^5\text{-}Et_2MeC_3B_2Et_2]^-$ when reacted with $[(\eta^5\text{-}C_9H_7)Fe(Et_2C_4B_4H_4)]^-$ in the presence of nickel(II) bromide gives the tetradecker **21** (83JOM(257)275, 90IC5157, 91JA3061). In a similar reaction with $[(\eta^5\text{-Cp*})Fe(Et_2C_2B_4H_4)]$, potassium, and nickel(II) bromide, **22** [$ML_n = M''L''_n = Co(\eta^5\text{-Cp})$; $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$; $R^{1'} = R^{2'} = R^{3'} = H$; $R^{4'} = R^{5'} = Et$] is formed. Again for the mixed-ligand species, the labeling of one of the heterocycles is $R^{n'}$ ($n = 1$–5).



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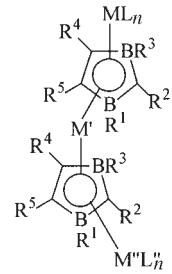

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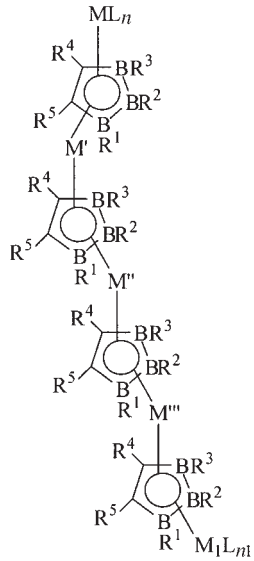
1,3,4,5-Tetraethyl-1*H*-2,3-dihydro-2-methyl-1,3-diborole and $[(\eta^5\text{-Cp})Co(\eta^2\text{-}C_2H_4)_2]$ give the neutral sandwich $[(\eta^5\text{-Cp})Co(C_3B_2HMeEt_4)]$ (85ZN(B)326), which can be deprotonated with *n*-butyl lithium in THF to give the anionic sandwich **20** [$ML_n = Co(\eta^5\text{-Cp})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] (93JCS(D)1783). The latter reacts with the carborane dianion $[7,8\text{-}C_2B_9H_{11}]^{2-}$ and bis(pentane-2,4-dionato)nickel(II) to yield a mixture of species **22** [$ML_n = M''L''_n = Co(\eta^5\text{-Cp})$, $M' = Ni$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$], **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Ni(7,8\text{-}C_2B_9H_{11})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$], **2** [$ML_n = Co(\eta^5\text{-Cp})$, $M'L'_n = Co(7,8\text{-}C_2B_9H_{11})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] Complex **22** [$ML_n = M''L''_n = Co(\eta^5\text{-Cp})$, $M' = Ni$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] can alternatively be prepared from the cobalt anionic sandwich **20** [$ML_n = Co(\eta^5\text{-Cp})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] and $[(\eta^5\text{-Cp})Ni(CO)_2]$ (82AGE149). A series of tetradecker species can be made using this route, including $[(\eta^5\text{-Cp})Co(C_2B_3R_5)]_2M$ (M = Cr, Mn, Fe, Co, Ni, Cu, Zn). The electronic characteristics of these complexes predicted quantum-mechanically (90JA722) correlate well with experimental data.

The B(5)-acetyl complex $[(\eta^5\text{-Cp*})Co(Et_2C_2B_3H_4\text{-}5\text{-COMe})]$ (91JA680) can be deprotonated with *n*-butyl lithium and then react with nickel(II) bromide to yield the tetradecker **7** ($ML_n = M'L'_n = Co(\eta^5\text{-Cp*})$, $M' = Ni$, $R^1 = R^3 = H$, $R^2 = COMe$, $R^4 = R^5 = Et$] (91JA681). In this complex, cobalt has the oxidation state of +3 and nickel of +4. The pentadecker $[(\eta^5\text{-Cp})_2Co_2Ni_2(\eta^5\text{-}Et_2MeC_3B_2Et)_3]$ (82AGE453) was prepared and the existence of the corresponding Co_2Ni_3 hexadecker was postulated (85ZN(B)167).

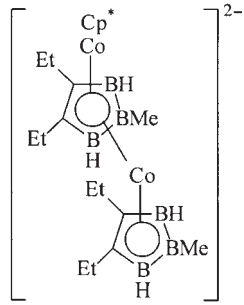
Interaction of the carborane sandwiches of composition [(η^5-$RR'C_2B_3H_3X$)Co(η^5-Cp*)] (R = Me, Et, $SiMe_3$; X = H, Cl, Br, I, Me, COMe, $CH_2C{\equiv}CMe$) with *n*-butyl lithium followed by Co^{2+}, CoH^+, Ni^{2+}, Ru^{2+} gives the tetradecker species **7** ($ML_n = M''L''_n = Co(\eta^5\text{-Cp*})$; $M' = Co^{IV}$, $Co^{III}H$, Ni^{IV}, Ru^{IV}; $R^1 = R^3 = H$; R^2 = H, Cl, Br, I, Me, COMe, $CH_2C{\equiv}CMe$; $R^4 = R^5$ = Et, $SiMe_3$] (92IC5202, 93JA6143, 93OM4452, 93OM4459). The iron-centered tetradecker species are more difficult to isolate (93IC2156). In a series of reactions of triple-decker compounds, [(η^5-Cp*)Co($Et_2C_2B_2H_2BMe$)CoH(η^5-$C_2Et_2B_3H_4$)] with sodium hydride, then air, followed by *n*-butyl lithium, and finally cobalt(II) chloride or platinum(II) bromide, three hexadecker complexes **23** ($ML_n = M_1L_{n1} = Co(\eta^5\text{-Cp*})$; $M' = Co$, $M'' = Co$, CoH, Pt; $M''' = CoH$; $R^1 = R^3 = H$; R^2 Me; $R^4 = R^5$ = Et] were synthesized (94JA2687). In a similar manner, pentadecker species **24** ($ML_n = M_1L_{n1} = Co(\eta^5\text{-Cp*})$; $M' = Co$, CoH, Pt; $M'' = CoH$; $R^1 = R^3 = H$; $R^2 = Me$; $R^4 = R^5$ = Et] follow from [(η^5-$Et_2C_2B_3H_3Me$)Co(η^5-Cp*)] and [(η^5-$Et_2C_2B_3H_3Me$)Co(η^5-$Et_2C_2B_3H_3Me$)Co(η^5-Cp*)] in the presence of M^{2+} and air. Such a synthetic approach may lead to polymers similar to the nickel-diborolyl sandwich polymer having semiconducting properties (86AGE105, 87SM757, 88PAC1345, 93ZN(B)1512).



23 **24**

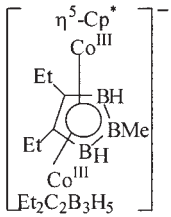
The dianionic triple-decker species **25** in the presence of cobalt(II) and nickel(II) salts, molecular oxygen, and [(η^5-Cp*)Co(C_2Et_2BHX)]$^-$ (X = H,

Me) give the pentadecker species **24** ($ML_n = M_1L_{n1} = Co(\eta^5\text{-Cp*})$; $M' = Co^{IV}$, Ni^{IV}; $M'' = CoH$; $R^1 = R^3 = H$; $R^2 = Me$; $R^4 = R^5 = Et$], while cobalt(II) and platinum(II) salts in the presence of molecular oxygen yield the hexadecker complexes **23** ($ML_n = M_1L_{n1} = Co(\eta^5\text{-Cp*})$; $M' = Co$, CoH; $M'' = Co^{IV}$, Ni^{IV}; $M''' = CoH$; $R^1 = R^3 = H$; $R^2 = Me$; $R^4 = R^5 = Et$] (95JA12218, 95JA12227).



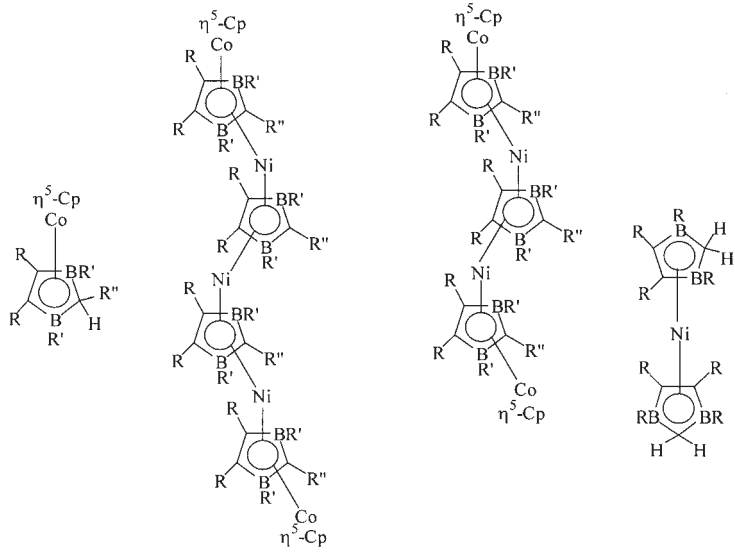
25

Nido-[(η^5-Cp*)Co($Et_2C_2B_3H_4$-5-Me)] can be deprotonated with *n*-butyl lithium and then allowed to react with cobalt(II) chloride to yield a mixture of triple-deckers **6** ($ML_n = Co^{III}(\eta^5\text{-Cp*})$, $M'L'_n = M(Et_2C_4B_4H_4)$ ($M = Co^{III}H$, Co^{IV}); $R^1 = R^3 = H$; $R^2 = Me$, $R^4 = R^5 = Et$] (94JA2687). In moist TMEDA, they are converted to diamagnetic species **6** ($ML_n = Co^{III}(\eta^5\text{-Cp*})$, $M'L'_n = Co^{III}H(Et_2C_2B_3H_5)$, $R^1 = R^3 = H$; $R^2 = Me$, $R^4 = R^5 = Et$], which can be deprotonated at the $Co^{III}H$ site to give the anionic diamagnetic compound **26**. The latter in air gives the paramagnetic Co^{III}/Co^{IV} derivative **6** ($ML_n = Co^{III}(\eta^5\text{-Cp*})$, $M'L'_n = Co^{IV}(Et_2C_2B_3H_5)$, $R^1 = R^3 = H$; $R^2 = Me$, $R^4 = R^5 = Et$]. When **6** ($ML_n = Co^{III}(\eta^5\text{-Cp*})$, $M'L'_n = Co^{IV}(Et_2C_2B_3H_5)$, $R^1 = R^3 = H$; $R^2 = Me$, $R^4 = R^5 = Et$] is deprotonated with *n*-butyl lithium and then treated with cobalt(II) chloride, paramagnetic hexadeckers **23** ($ML_n = M_1L_{n1} = Co(\eta^5\text{-Cp*})$; $M' = CoH$, Co; $M'' = Co$; $M''' = CoH$; $R^1 = R^3 = H$; $R^2 = Me$; $R^4 = R^5 = Et$] are formed.



26

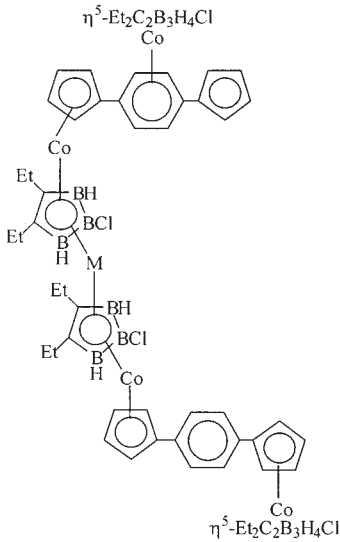
Thermolysis of **22** [$Ml_n = M''L''_n = Ni(\eta^3\text{-allyl})$, $M' = Ni$, $R^1 = R^3 = Me$, $R^3 = H$, $R^4 = R^5 = Et$] and **27** ($R = Et$, $R' = Me$, $R'' = H$) gives **28** ($R = Et$, $R' = Me$, $R'' = H$), **2** [$ML_n = M'L'_n = Co(\eta^5\text{-Cp})$, $R^1 = R^3 = Me$, $R^2 = H$, R^4 $R^5 = Et$], and **22** [$ML_n = M''L''_n = Co(\eta^5\text{-Cp})$, $M' = Ni$, $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = R^5 = Et$]. The same reaction of **22** [$MI_n = M''L''_n = Ni(\eta^3\text{-allyl})$, $M' = Ni$, $R^1 = R^3 = Me$, $R^3 = H$, $R^4 = R^5 = Et$] and **27** ($R = R' = Et$, $R'' = Me$) yields an analogue of **28** ($R = R' = Et$, $R'' = Me$) and species **29** ($R = R' = Et$, $R'' = Me$) (87JOM(324)57). An alternative way to complex **28** ($R = R' = Et$, $R'' = Me$) containing diborolyl rings with two different substituent sets uses the reaction of **2** [$ML_n = Ni(\eta^3\text{-allyl})$, $M'L'_n = Co(\eta^5\text{-Cp})$, $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = R^5 = Et$] and **30** ($R = Me$). Two rings surrounding the nickel atoms have methyl groups and two others carrying ethyl groups.



27 **28** **29** **30**

Linked sandwich systems are of considerable practical interest (97MI1). Thus (93JA6143) the interaction of [$(\eta^5\text{-}Et_2C_2B_3H_4Cl)Co(\eta^5\text{-}C_5H_4C_6H_4C_5H_4)Co(\eta^5\text{-}Et_{2q}C_2B_3H_4Cl)$] with *n*-butyl lithium and then cobalt(II) or nickel(II) chloride gives a kind of tetradecker-linked complex **31** (M = Co, Ni), which on further interaction with *n*-butyl lithium and MCl_2 (M = Co, Ni) gives **32** (M = Co, Ni) with a potential to form oligomers. The derivatives based on $(C_5H_4)_2$ or fulvalene units **33** (M = Co, Ni) can also be made by a similar synthetic approach and lead to higher oligomers. Here the xylyl-bridged bis(triple-decker) species **34** may be mentioned. It is made from *p*-[$(\eta^5\text{-Cp*})Co((SiMe_3)(C_2B_3H_5)CH_2]_2C_6H_4$ through the steps of

lithiation by *n*-butyl lithium and further reaction with $[(\eta^5\text{-Cp}^*)\text{CoCl}]_2$ (91IC2836, 92IC3897).



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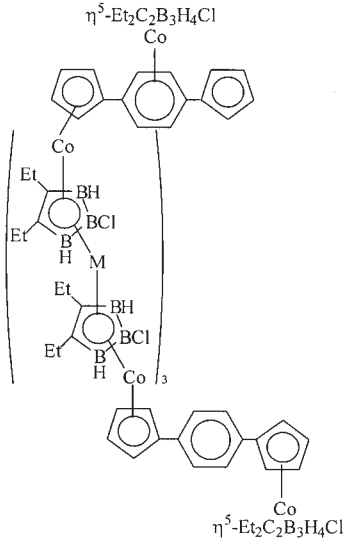

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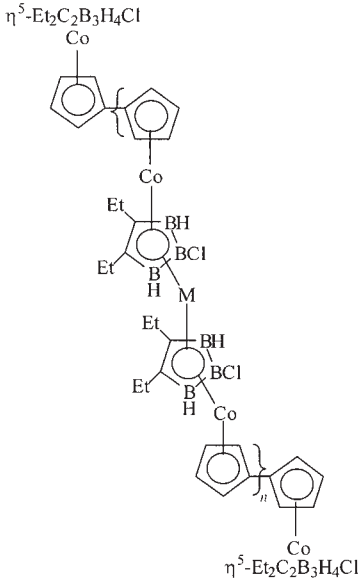

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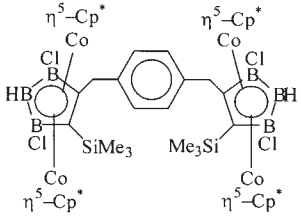


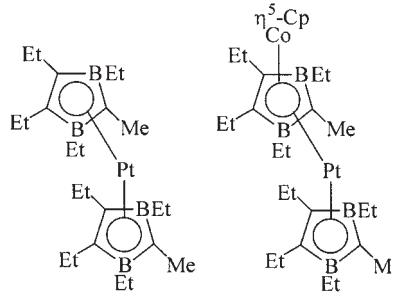
34

C. Nickel Group

Sandwich **1** [$ML_n = Ni(\eta^5\text{-Cp})$, $R^1 = R^2 = R^3 = R^4 = R^5 = Me$] with [$(\eta^5\text{-Cp})_2M$] (M = Co, Ni) forms the triple-decker species **2** [$ML_n = Ni(\eta^5\text{-Cp})$; $M'L'_n = Co(\eta^5\text{-Cp})$, $Ni(\eta^5\text{-Cp})$; $R^1 = R^2 = R^3 = R^4 = R^5 = Me$] (81JOM(215)255). Similar nickel sandwiches and triple-deckers are known (77AGE468, 78ZN(B)1410, 81JOM(207)343). The latter can be reduced to the anionic species using metallic potassium (81JOM(208)137).

Alkyl-2,3-dihydrodiboroles on treatment with bis(η^3-allyl)- or bis(η^3-methylallyl)nickel give the tetradecker complexes **2** [$ML_n = M'L'_n = Ni(\eta^3\text{-allyl})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] (86JOM(305)199). The following mixed carborane-diborole nickel complexes are known: sandwich **1** [$ML_n = Ni(nido\text{-}2,3,5\text{-}R_6C_3B_3)$ (R = Me, Et); $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] and triple-deckers **2** [$ML_n = M'L'_n = Ni(nido\text{-}2,3,5\text{-}R_6C_3B_3)$ (R = Me, Et); $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] and **2** [$ML_n = Ni(nido\text{-}2,3,5\text{-}R_6C_3B_3)$ (R = Me, Et); $M'L'_n = Ni(\eta^5\text{-Cp})$; $R^1 = R^3 = R^4 = R^5 = Et$; $R^2 = Me$] (84AGE965, 86AGE1099, 88OM2316). Species $\mu\text{-}\eta^5{:}\eta^5$-(2-benzyl-1,3,4,5-tetramethyl-2,3-dihydro-1,3-diborolyl)(η^3-allyl)(η^4-1,5-hexadiene)dinickel and $\mu\text{-}\eta^5{:}\eta^5$-[2-(2,4,6-trimethylbenzyl)-1,3,4,5-tetramethyl-2,3-dihydro-1,3-diborolyl](η^3-allyl)(η^4-1,5-hexadiene)dinickel serve as representative triple-decker complexes (01ZN(B)73).

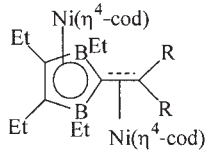
Reaction of bis(η^5-2,3-dihydro-1,3-diborolyl)platinum with [$(\eta^5\text{-Cp})Fe(C_8H_{12})$] gives the tetradecker complex **22** [$ML_n = Ni(\eta^5\text{-Cp})$, $M' = Pt$, $M''L''_n = Fe(\eta^5\text{-Cp})$, $R^1 = R^3 = R^4 = R^5 = Et$, $R^2 = Me$] (87JOM(318)157). Sandwich **35** (84ZN(B)50) and [$(\eta^5\text{-Cp})Co(C_2H_4)_2$] give the triple-decker **36** (87JOM(324)57). The list of tetradecker species also includes [$(\eta^5\text{-Cp})M(C_3B_2R_5)$]$_2$Pt (M = Fe, Ni) (85CB729).



35 **36**

Simultaneous coordination of the type $\eta^5{:}\eta^2$, via the heteroring and saturated substituent, makes the Ni(η^4-cod) complexes **37** and **38** different

from the similar tricarbonyliron derivatives **10** and **11** (89CB633, 90CB2273, 94CB2393).



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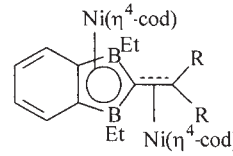
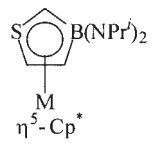


38

III. Complexes of Thiaborolyl Ligands

Benzo-1,3-thiaborolide (98OM2379) and N,N-di-*iso*-propyl-3-amino-1,3-thiaborolide (99OM1821) are interesting ligands. The latter reacts with $[(\eta^5\text{-Cp*})RuCl]_4$ or $[(\eta^5\text{-Cp*})ZrCl_3]$ to yield sandwiches **39** (M = Ru, $ZrCl_2$) (99OM1821). 1,2-Benzothiaborole enters similar complex forming processes to yield **40** (M = Ru, $ZrCl_2$) (00OM4681).



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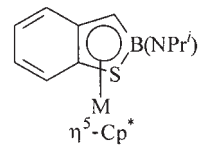
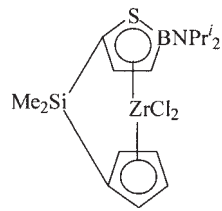


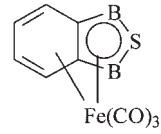
40

The lithium salt of 2-(di-*iso*-propylamino)-1,2-thiaborolide with $[(\eta^5\text{-Cp*})RuCl]_4$ or $[(\eta^5\text{-Cp*})ZrCl_3]$ yields sandwiches similar to **39** (M = Ru, $ZrCl_2$) (00OM4935). The same anionic ligand enters a sequence of reactions with dimethylchlorosilane, lithium cyclopentadienyl, lithium di-*iso*-propylamide, and zirconium(IV) chloride to give sandwich **41**.



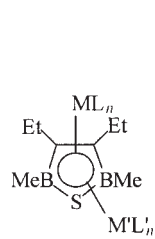
41

1,2,5-Benzothiadiborolene with $[Fe_2(CO)_9]$ and $[Fe_3(CO)_{12}]$ forms species **42**, where the annulated benzene ring is not delocalized and behaves like the cyclohexatriene system (75AGE262).



42

The B–S five-membered heterocycles attract occasional attention of chemists since the mid 1970s (77JOM(131)1, 86CB971). 1,2,5-Thiadiborolene with $[Mn_2(CO)_{10}]$ forms the diamagnetic complex **43** $[ML_n = M'L'_n = M_n(CO)_3]$ (76AGE434). 3,4-Diethyl-2,5-dimethyl-1,2,5-thiadiborolene also reacts with $[(\eta^5\text{-Cp})Fe(CO)_2]_2$ and gives the triple-decker species **43** $[ML_n = M'L'_n = Fe(\eta^5\text{-Cp})]$ (76AGE779). With $[Co_2(CO)_8]$, the triple-decker complex with three thiadiborolyl chains, **44**, results (77AGE333). Also $[(\eta^5\text{-}C_2Et_2B_2Me_2S)_2Ni]$ is known (76ZN(B)803).



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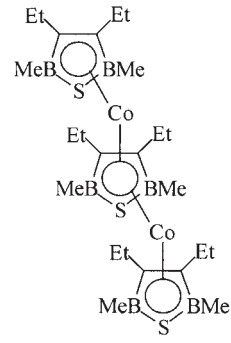
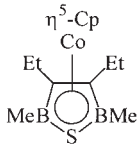


44

Complex **45** is formed on thermolysis of $[(\eta^5\text{-Cp})Co(CO)_2]$ and thiadiborole (87JOM(324)57). The bis(thiadiborole)iron carbonyl complex is known (85JOM(282)297). Triple-deckers of composition $[(\eta^5\text{-Cp})Fe(C_2B_2SR_4)]_2M$ (M = Fe, Co) (80AGE746) and $[(C_2B_2SR_4)Co(C_2B_2SR_4)]_2Fe$ (79AGE949) are also representatives of 1,2,5-thiadiborolyl organometallic chemistry. 1,2,5-Thiadiborolene reacts with $[(\eta^5\text{-Cp})Fe(C_8H_{12})]_2Zn$ to yield the trinuclear complex **46** (80AGE746). Further interaction of the latter gives sandwich **47** (88JOM(343)78), which is the starting material for the tetradecker species **48** (M = Fe, Co) made by stacking with iron(II) or cobalt(II) chloride. In the case of iron(II) chloride the process is complicated and gives **44** $[ML_n = M'L'_n = Fe(\eta^5\text{-Cp})]$ together with **48** (M = Fe) and $[(\eta^5\text{-Cp})Fe(H)(\eta^5\text{-}Et_2C_2B_2(Me_2)S)]$. The latter contains the Fe–H $\cdots$ B three-center two-electron bond.



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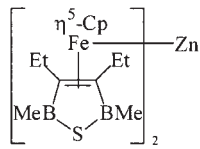

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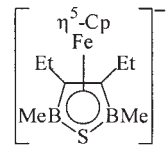

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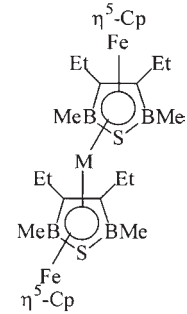

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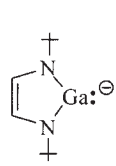
IV. Complexes of Azaborolyl Ligands

2,3-Dihydro-1*H*-1,3,2-diazaboroles (90IC4421) form stable adducts with 1,3-dialkyl-4,5-dimethylimidazol-2-ylidenes (alkyl = Me, *i*-Pr) of a carbene type (97CB705, 98EJIC1145, 99EJIC491, 00OM2891, 01OM5248). This property is also typical for 3,4-dihydro-2*H*-1,2,4,3-triazaboroles (99EJIC1193).

Another aspect of this problem is the existence of heterocyclic carbenes containing a low-valent gallium center, **49** (95JA5421, 98EJIC305, 99JA9758, 01JCS(D)3459). 1,4-Bis(2,6-di-*iso*-propylphenyl)-1,4-diazabuta-1,3-diene and 1,4-bis(2,6-diethylphenyl)-1,4-diazabuta-1,3-diene with [(η^5-Cp*)Ga] yield **50** (R = 2,6-di-*iso*-propylphenyl-, 2,6-diethylphenyl-) (01OM1965, 01OM5492). 1,4-Di-*tert*-butyl-1,4-diazabuta-1,3-diene in these conditions produces compound **51** perhaps through intermediate **50** (R = *t*-Bu). Some developments with aluminum (01OM3367) and indium (02OM1167) ligands open a perspective to the study of organometallic adducts.



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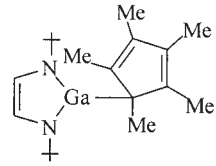

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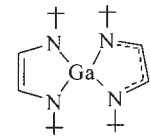

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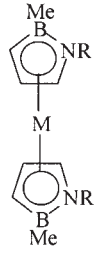
Complex [Sn(η^5-N(Bu^t)B(Me)C(Me)(CH)$_2$)$_2$] is known (85AGE602). Bis(1,2-azaborolyl)complexes of various metals represent the η^5-coordinated sandwiches (80AGE54, 80CB2348, 80JOM(193)83, 82CB3830, 83CB951, 83ZN(B)485, 83ZN(B)1094, 84CB1052, 84ZN(B)1082, 85CIC17, 87OM435, 88AGE952, 89JOM(375)21, 00OL2089). 1,2-Azaborolyls are prospective ligands in the sense that they are isoelectronic with cyclopentadienyl.

The lithium salt of 2-methyl-1-trimethylsilyl-1,2-azaborolinyl with iron(II) and cobalt(II) bromides gives sandwiches **52** (M = Fe, Co, R = $SiMe_3$) (82CB732). Lithium 1-*tert*-butyl-2-methyl-1,2-azaborolinyl reacts with iron(II) and cobalt(II) bromide to yield sandwiches **52** (M = Fe, Co, R = *t*-Bu) and with titanium(IV) bromide to give **52** (M = $TiBr_2$, R = *t*-Bu) (82CB3830). Neutral 2-methyl-1-trimethylsilyl-Δ^3-1,2-azaboroline with vanadium in a vapor-phase synthesis gives sandwich **52** (M = V, R = $SiMe_3$). Sandwich **52** (M = Fe, R = $SiMe_3$) (80JOM(193)83, 81CB1297, 82AGE68, 82CB3830) can be lithiated at the nitrogen heteroatom using Li(TMP) to yield **52** (M = Fe, R = Li) (83CB951). The latter with *tert*-butanol gives **52** (M = Fe, R = H) and **52** (M = Fe, R = Me, Et) with methyl iodide or ethyl bromide. Species **53** [R = Cl, $ML_n = Fe(CO)_2I$] follows from the corresponding B-chloroboracycle with iron pentacarbonyl and then molecular iodine (02AGE174). Further interaction of the product with thallium (η^5-cyclopentadienyl) gives **53** [R = Cl, $ML_n = Fe(\eta^5\text{-Cp})$]. Complex **53** [R = Me, $ML_n = Co(CO)_2$] undergoes photolysis with ethylene to give **53** [R = Me, $ML_n = Co(C_2H_4)_2$] (90ZN(B)1235). With 2-butyne, diphenylethyne, 3-hexyne, and 4-octyne, the species **53** [R = Me, $ML_n = Co(C_2H_4)_2$] forms two types of compounds: the products of cyclotrimerization-the 1,3-cyclohexadiene sandwiches **54** with R = Me, Ph, Et, and *n*-Pr, respectively (92OM1789, 95JOM(492)185), and the products of cyclodimerization-the cyclobutadiene sandwiches **55** (R = Ph, Et, *n*-Pr) for diphenylethyne, 3-hexyne, and 4-octyne (95JOM(492)185). Note that 2-butyne forms only the cyclotrimerized complex **54** (R = Me). Complex **56** is the product of interaction of 1-*tert*-butyl-3-methyl-2-phenyl-Δ^3-azaboroline and [$Fe(CO)_5$] (80AGE54).



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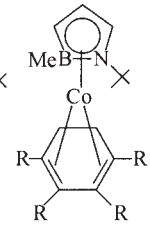

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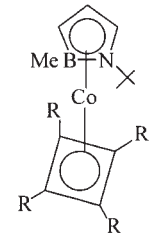

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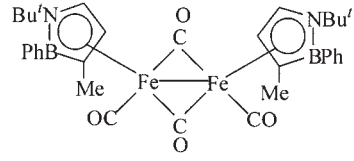
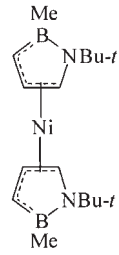


56

Oxidation of the borazole complexes $[(\eta^5\text{-}C_3H_3B(Me)NR)_2Co]$ (R = Me, *t*-Bu, $SiMe_3$) by iodine leads to $[(\eta^5\text{-}C_3H_3B(Me)NR)_2Co]_n$ ($n = 3$–5). The hexafluorophosphate salts are obtained by oxidation using ferricinium hexafluorophosphate (83JOM(256)225, 86JOM(305)1).

1-*tert*-Butyl-2-methyl-1,2-azaborolinyl ligand in the nickel complex **57** reveals the properties of a three- rather than a five-electron donor (86JOM(305)199).



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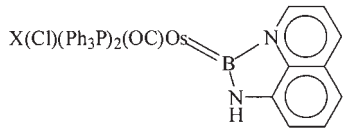
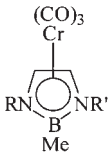
1,2-Dihydro[1,3,2]diazaborolo[1,5-*a*]pyridines are useful as well (01JCS(D)378). They are interesting η^5- (π-) ligands (85CB2418, 91AGE1015, 96MI4), and form $Cr(CO)_3$ complexes (77AGE249, 81CB495).

An interesting case of the benzannulated B, N complex is species **58** (X = Cl) (00AGE948), prepared from $[(OC)Os(PPh_3)_2Cl(BCl_2)]$ and 8-aminoquinoline. It reacts with tetra-*n*-butyl ammonium iodide and forms **58** (X = I).



58

A series of 1,3,2-diazaboroles in a thermal substitution reaction with $[Cr(CO)_3(AN)_3]$ forms the η^5-coordinated complexes **59** (R = R′ = Me, Et, *i*-Pr; R = Me, R′ = Et) (90IC4421). The corresponding dimeric ligand in this reaction yields complex **60** where only one heteroring is η^5-coordinated.



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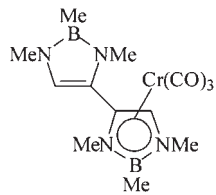

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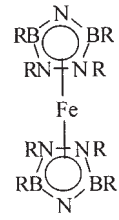
Interaction of iron(II) chloride with the lithium salt of $R_4B_2N_3^-$ (R = Me, Et) gives sandwiches **61** (R = Me, Et) (67ZAAC1, 96MI4), resembling in electronic properties those of ferrocene (99ICA(288)17). The π- (η^5-) complex stems from the further complex-formation of **61** (R = Me, Et) with mercury(II) salts via the unsubstituted nitrogen atom.



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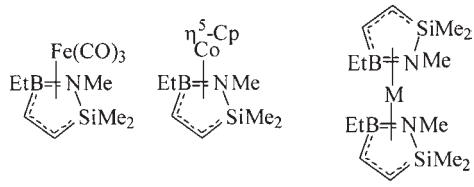
4,5-Dimethyl-1,2,2,3-tetramethyl-Δ^3-1,2,5-azasilaboroline with $[Fe_2(CO)_9]$ gives sandwich **62** and sandwich **63** (82AGE207, 82CB738) with $[(\eta^5\text{-Cp})Co(C_2H_4)_2]$. With [Ni(CDT)] or in a vapor phase with metallic nickel, sandwich **64** (M = Ni) is formed. The vapor-phase synthesis with iron gives **64** (M = Fe). In all these sandwiches, **62**–**64**, the η^4-coordination of the heterocyclic ligand is realized.

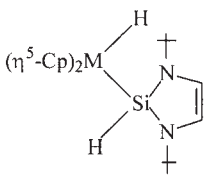


62 **63** **64**

V. Complexes of Silicon Analogues of Imidazol-2-ylidenes

Silicon analogues of imidazol-2-ylidenes are stable as the parent compounds and are characterized to some extent by aromatic stabilization (96JCS(D)1475, 00JCS(CC)1427, 02JOM(643)272). The synthesis, structure, and properties of the silicon (94JA2691, 94JA6641, 94JA10813, 94JCS(CC)33, 94JCS(D)2405, 96JCS(CC)2657, 96MI1, 96PAC785, 98EJIC1067, 98JA12714, 98OM2352, 00ACR704, 00OM4726) and germanium (92AGE1485, 98AX(C)1830 analogues have been studied. 1,3-Di-*tert*-butyl-1,3,2-diazasilol-2-ylidene reacts with $[(\eta^6\text{-Mes})Cr(CO)_3]$, $[Fe_2(CO)_9]$, and $[Ni(CO)_4]$ to yield stable carbene complexes (94JCS(CC)33, 96MI3, 96PAC785). The same ligand with $[(\eta^5\text{-Cp})_2MH_2]$ (M = Mo, W) gives **65**

(M = Mo, W) (99OM2615), which results from the insertion of the ligand into the M–H bond. Interaction with $[(\eta^5\text{-Cp})_2\text{Mo(PEt}_3)]$ in a typical ligand substitution reaction is followed by the formation of carbene complex **66**. The product can add water to yield **67**. Photochemical reaction with $[\text{M(CO)}_6]$ (M = Cr, Mo, W) gives the bis-carbene complexes *trans*-$[\text{M(CO)}_4\text{L}_2]$ (M = Cr, Mo, W) (01JOM(636)17). With $[\text{Fe}_2\text{(CO)}_9]$ in THF, the product is $[\text{LFe(CO)}_5]$, while with $[\text{Ru}_3\text{(CO)}_{12}]$ in THF $[\text{L}_2\text{Ru(CO)}_3]$ is formed. The data show that the M–Si bond in these species is weaker than the M–C bond in the corresponding imidazol-2-ylidene complexes in accordance with theoretical calculations (98OM5801). 1,3,-Di-*tert*-butyl-1,3,2-diazasilol-2-ylidene with $[(\{\text{Cy}_2\text{P(CH}_2)_4\text{PCy}_2\}\text{ClRu}(\mu\text{-Cl})_3\text{Ru}\{\text{Cy}_2\text{P(CH}_2)_4\text{PCy}_2\}(\text{N}_2)]$ gives the η^1(Si)-coordinated species **68** (02OM534). Other illustrative examples with a bulkier ligand include complexes **69**, **70** (98OM5599), and **71** (00OM3263).



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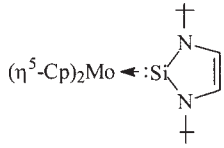

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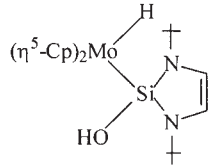

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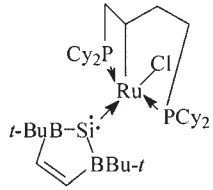

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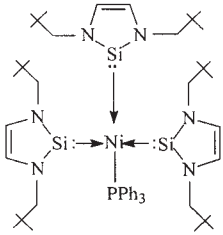

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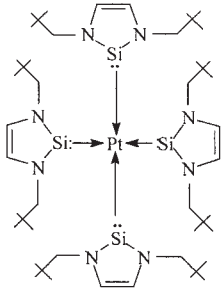

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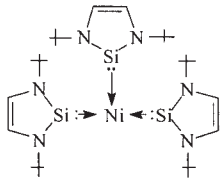
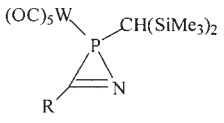


71

VI. Complexes of Azaphospholes

Conjugative stabilization of the phosphorus lone pair in the P- and also the As-analogue of benzimidazole with the π-system is less than in the parent benzimidazole (89JOM(373)49, 89JOM(373)57. In a series of 1,3-azaphospholes, 1,2,4-diazaphospholes, and 1,2,3,4-triazaphospholes, aromatic stability increases with the number of the nitrogen atoms in the heteroring (89MI1, 90MI3, 92JA9080, 92JCP623, 94TOC307, 95JMS(T)55, 96MI2, 96MI3, 96PSS109, 01CRV1229, 01CRV3549). The same trends can be noted for the arsenic analogues of azaphospholes (95JMS57). In the analogues of imidazol-2-ylidene the reaction site, the carbene carbon atom, is replaced by a phosphorus–chlorine grouping (96TL9025, 99EJIC41), or by P–R groups (00CEJ3414, 00EJIC369, 00EJIC2425, 01JOM(617)737).

2H-1,2-Azaphosphole complexes containing the η^1(P)-coordinated site can be obtained by thermolysis of the corresponding 2H-azaphosphirene $W(CO)_5$ species **72** (R = *p*-$MeOC_6H_4$, Ph, *p*-F_3C–C_6H_4) in dimethylacetylene dicarboxylate (95JCS(CC)2113, 97AGE1492, 97ZAAC1897, 98CEJ1542, 98EJIC2005, 99JCS(CC)2127, 99OM5627, 00EJIC1253, 00JCS(D)2495, 00OM475). The products of thermolysis are **73** (R = *p*-$MeOC_6H_4$, Ph, *p*-F_3C-C_6H_4). Nitrilium phosphane ylide complexes **74** (R = Ph, Me_2N) in dimethylaminonitrile (R = Ph) or benzonitrile (R = Me_2N) give the η^1(P)-coordinated 2H-1,3,2-diazaphosphole species **75** by 1,3-dipolar cycloaddition (97JCS(CC)2317, 98JCS(CC)1529). The product has a planar heteroring where the double bonds are localized. The 2H-azaphosphirene complex bearing the pentamethylcyclopentadienyl substituent at the phosphorus atom adds dimethyl acetylenedicarboxylate in benzonitrile at elevated temperature to give complex **76**, which undergoes further [4+2] cycloaddition of the acetylene derivative with elimination C_5Me_5 to yield **77** (99EJIC1567). Complexes similar to **76** have instead of a phenyl group a piperidino moiety. Instead of a cyclopentadienyl substituent there are Me or Ph groups attached (00AGE3686). Complexes of type **72** [R = Ph, instead of $W(CO)_5$-$M(CO)_5$, M = Cr, Mo, W] react with 1-piperidinonitrile and TCNE to yield in toluene **78** (M = W; R = 1-piperidino) and yield **78** (M = Cr, Mo, W) (00CEJ3997) without solvent. With TCNE in benzo- or acetonitrile, the tungsten precursor gives **78** (M = W; R = Ph, Me). A similar synthetic approach to the complexes of 2H-1,2,3-azadiphospholes was applied (00JCS(CC)1659). Thermolysis of complexes **79** (R = Me, Ph) with 1-piperidino carbonitrile gives 2H-1,3,2- (**80**; R = Me, Ph) and 2H-1,4,2-diazazaphosphole (**81**; R = Me, Ph) complexes with the η^1(P)-coordination mode (01EJIC3175).



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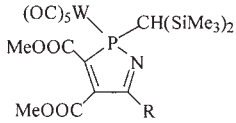

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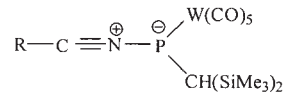

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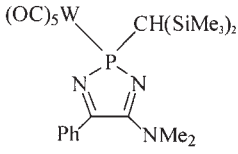

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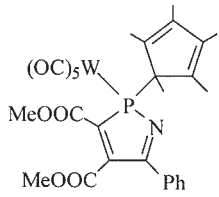

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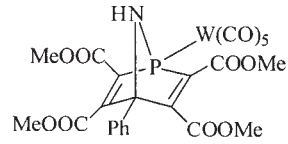

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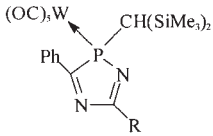

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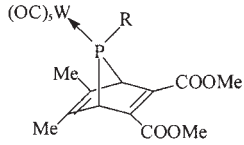

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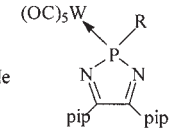

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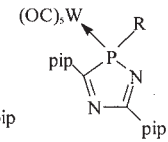
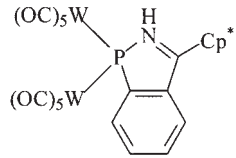


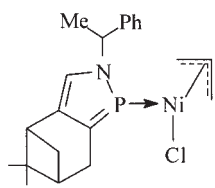
81

Benzonitrile with $[(\eta^1\text{-Cp}^*)\text{P}\{\text{W(CO)}_5\}_2]$ gives **82**, the result of migration of the phosphorus atom, insertion of the nitrile moiety into the P–C bond and further C–H bond activation (01AGE3413).



82

The 1,2-azaphosphole η^1(P)-coordinated complexes **83** and **84** follow from the corresponding ligand and $[(\eta^3\text{-allyl})\text{NiCl}]_2$ and [(1,5,9-cyclododecatriene)Ni], respectively (98ICA(270)273).



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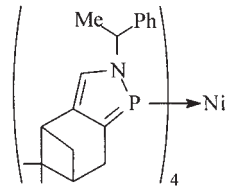
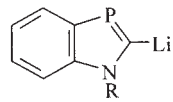


84

1,3-Benzazaphospholes are lithiated at position 2 of the P, N-heteroring to yield **85** (R = Me, Et) (82TL3643, 89JOM(373)49, 93JPC4011), a trend which is quite typical for the P, N-heterocycles (87JOM(319)49, 01JMS(T)189). While the main reactive sites for the unsubstituted 1,3-benzaphospholes are either the phosphorus or nitrogen atoms, the 2-lithio derivatives reveal remarkable reactivity at the C_2-center (01JCR3549, 02OM912). Thus, with [(η^5-Cp)Fe(CO)$_2$] **85** (R = Me) produces **86** and with [W(CO)$_6$]—the Fischer carbene complex **87** (02OM912). 1H-1,3-Benzaazaphospholes with [(THF)W(CO)$_5$] give the η^1(P)-coordinated species **88** [ML$_n$ = Cr(CO)$_5$, R^1 = H, R^2 = Me; R^1 = R^2 = Me; R^1 = H, R^2 = *t*-Bu; R^1 = Me, R^2 = Ph] (02JOM(646)113); with [(η^5-Cp)Fe(CO_2I] **88** [ML$_n$ = (η^5-Cp)Fe(CO)$_2$, R^1 = H, R^2 = Me, Ph, *t*-Bu]; with [(η^5-Cp)W(CO)$_3$Cl] **88** [ML$_n$ = (η^5-Cp)W(CO)$_3$, R^1 = H, R^2 = *t*-Bu].



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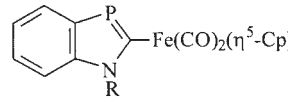

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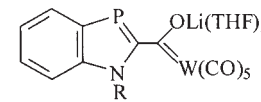

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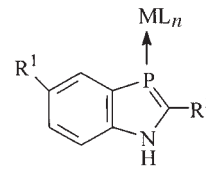
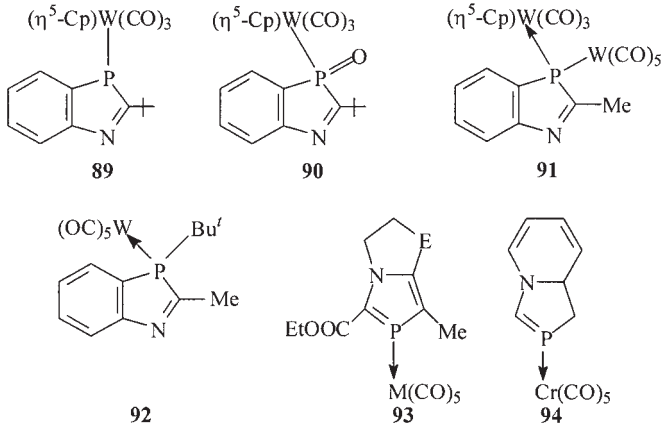


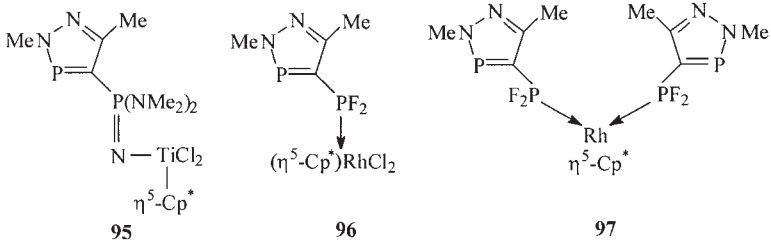
88

1,3-Azaphopspholes annulated to oxazoline, thiazoline, benzothiazole, pyridine, and pyrazine heterorings are receiving attention as new ligands in organometallic compounds (78TL441, 82PS259, 90JOM(382)53, 90MI3, 91CB475, 94T7675, 94TOC307, 95CB259, 95JCS(CC)1541, 96CB337, 97IC1476, 99ZN(B)1244, 00JCS(CC)1637), in particular [Cr(CO)$_5$(η^1-L)], where L is 2-phenyl-1,3-benzazaphosphole-P (81ZAAC22, 86ZAAC336). The most probable donor site in these compounds is the phosphorus heteroatom of the π-excessive azaphosphole ring. 2-*tert*-Butyl-1H-1,3-benzazaphosphole can be lithiated with *tert*-butyl lithium and allowed to react with [(η^5-Cp)Cr(CO)$_3$Cl] to yield the product **89**, which is slowly oxidized in air to **90** (01EJIC2563). 2-Methyl-1H-1,3-benzazaphosphole reacts differently to yield main product **91** and side-product **92**. In another illustration, the M(CO)$_5$ species of the oxazoline- and thiazoline-annulated 1,3-azaphospholes are known, **93** (E = O, S; M = Cr, Mo, W). These compounds follow from the reaction of the corresponding ligand and [(THF)M(CO)$_5$] (99JOM(577)337). Another representative is the

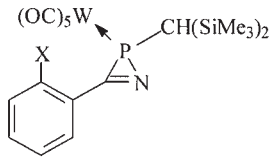
2-phosphaindolizine **94** that follows from the ligand and [(THF)Cr(CO)$_5$] (98EJIC1079).



4-(Bis(dimethylaminotrimethylsilyl)imino)(phosphorano)-2,5-dimethyl-2*H*-1,2,3-diazaphosphole (99IC1971) with [(η^5-Cp*)TiCl$_3$] forms a complex with an exocyclic mode of coordination, **95** (99IC2791). This mode is also observed in [(η^5-Cp)Ru(PPh$_3$)(L)Cl], the product of the interaction of 4-(difluorophosphino)-2,5-dimethyl-2*H*-1,2,3-diazaphosphole (L) and [(η^5-Cp)Ru(PPh$_3$)$_2$Cl] (99OM3306). The same ligand with [(η^5-Cp*)RhCl$_2$]$_2$ gives the monosubstituted complex **96** and with [(η^5-Cp)Rh(CO)$_2$] the disubstituted product **97** is formed. Although this type of coordination prevails (80JOM(185)53), exocyclic coordination is not excluded (83JOM(256)375, 88IC2612).



2H-Azaphosphirene complexes **98** (X = H, Me, OMe, NMe$_2$) with benzonitrile in the presence of ferrocenium hexafluorophosphate give rise to the 2H-1,2,4-diazaphosphole species **99** (X = H, Me, OMe, NMe$_2$) with the η^1(P)-coordination mode (02JOM(643)253). 1,2,4-Diazaphospholide ligand (L) in the species [(η^5-Cp)Fe(CO)$_2$L] is η^1(N)-coordinated (95OM581).



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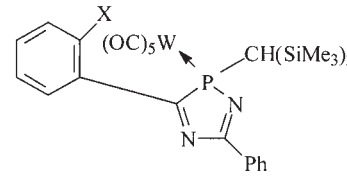
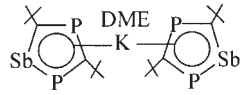


99

VII. Complexes of Di- and Triphospholes and Corresponding Phosphorus-Antimony Ligands

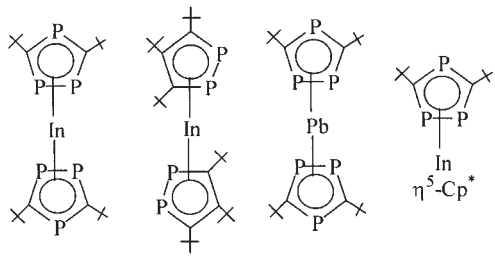
A. Non-Transition Elements

In a manner similar to that of phospholes, di-, tri-, and pentaphospholes (84CJC341, 86AGE644, 86JCS(CC)737, 87JCS(CC)844, 87JOM(323)C35, 92JOC3694, 96IC4690, 96JPC6194, 96JPC13447, 98AGE1083, 00AGE1029, 00AGE2307) as well as their arsenic and antimony analogues (81AGE33) reveal a tendency to form η^5-coordination, the products being highly reactive (80PAC1443, 87JOM(334)C35, 87MI1, 88CB443, 88CRV1327, 89POL2407, 90AGE534, 90CRV169, 90CRV191, 90MI1, 90MI2, 90MI3, 90PAC423, 90ZC41, 90ZC55, 91CB1159, 91OM2835, 92CCR(120)259, 92MI1, 93CI(L)404, 94CCR(137)1, 95CCR(145)201, 96ADOC325, 98ADOC1, 98CCR(178)771, 98CSR319, 98MI1, 99ACR751, 01EJIC891). Nevertheless, their electronic characteristics contrast to those of the cyclopentadienyl analogues (83OM1008, 89POL1135, 90IC879). In particular, the P_3C_2 ring containing two *tert*-butyl substituents at carbon atoms is more electron-withdrawing than the cyclopentadienyl counterpart (97JOM(529)375). The di- and triphospholyl anions typically include C_3–*t*-$Bu_3P_2^-$ and C_2–*t*-$Bu_2P_3^-$ (92JOM(430)C10, 93JOM(453)C16, 93POL1383, 94JCS(CC)489, 95JCS(CC)1659) and differently substituted derivatives (91JOM(415)C15, 92POL601). The anion of $P_2SbC_2Bu^t_2$ forms simple salts with lithium compounds (97JOM(527)291, 00OM1713). However, with potassium compounds, distinct complexes are formed (00OM219, 01JOM(622)61). Thus (01JOM(622)61), $KSb(SiMe_3)_2$ when reacted with $(Me_3Si)P=C(Bu^t)(OSiMe_3)$ in DME gives sandwich **100**. With tetravalent silicon and germanium compounds, SiI_4 or GeI_4 (00JCS(CC)879) and $SiMe_2Cl_2$ (01JOM(622)61), potassium complexes form the silicon- or germanium-containing cage compounds.



100

The vapor phase synthesis of sandwiches **101** and **102** involves the co-condensation of *tert*-butyl phosphaethyne and metallic indium vapor (99OM793, 00JCS(D)1715). The thallium derivative has the composition $[Tl(\mu\text{-}\eta^5\text{:}\eta^5\text{-}1,2,4\text{-}P_3C_2Bu^t_2)]$ (99JCS(CC)1731, 00JCS(D)1013, 00JCS(D)1507, 00JCS(D)3534) or $[Tl(\mu\text{-}\eta^5\text{:}\eta^5\text{-}1,4,2\text{-}P_2SbC_2Bu^t_2)]_\infty$ (98OM3826). Species $[(\eta^5\text{-Cp*})M(\eta^5\text{-}P_2SbC_2Bu^t_2)]$ (M = Sn, Pb) can be prepared similarly (99JCS(D)4057, 00JCS(CC)2027). The anion $P_3C_2Bu^{t-}_2$ with $PbCl_2$ forms the sandwich **103**, while the antimony analogue $P_2SbC_2Bu^{t-}_2$ in this reaction (as in the reaction with $FeCl_2$ (97JCS(CC)305)) gives the product of oxidative coupling in the form of the cage compound $P_4Sb_2C_4Bu^t_4$ (99JCS(D)2627). In a similar synthetic procedure, $P_3C_2Bu^{t-}_2$ with $PbCl_2$ but in the presence of $[(\eta^5\text{-Cp*})Li]$ gives the mixed sandwich **104** (E = P). The antimony analogue **104** (E = Sb) can be prepared from the relevant anion and $[(\eta^5\text{-Cp*})PbCl]$ but it is contaminated with **104** (E = P). In the reaction with $E(S_2CNEt_2)_2$ (E = Se, Te), the anion of $1,4,2\text{-}P_2SbC_2Bu^t_2$ gives $1,4,2\text{-}P_2EC_2Bu^t_2$ (E = Se, Te) (99TL3815).

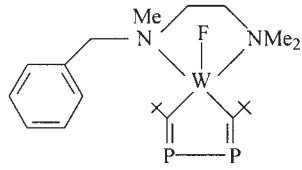


101 **102** **103** **104**

B. Chromium and Manganese Groups

Sandwich $[Cr(\eta^5\text{-}P_3C_2\text{–}t\text{-}Bu_2)_2]$ is known and its structure is unequivocal (88JOM(356)C1). The η^5-coordination is also realized in $[(\eta^5\text{-}P_2C_3\text{–}t\text{-}Bu_3)Mo(\eta^3\text{-indenyl})(CO)_2]$ (90JCS(CC)472).

Complex **105** in an atmosphere of carbon monoxide experiences rearrangement to **106**, which through C–H activation gives the final product **107** with η^4-coordiantion of the 3,4-diphosphacyclopentadienone ligand (97JCS(CC)1539).



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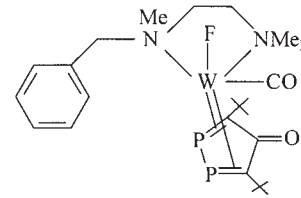

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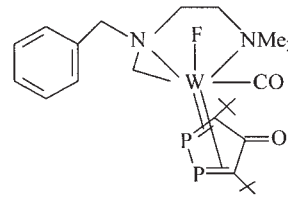
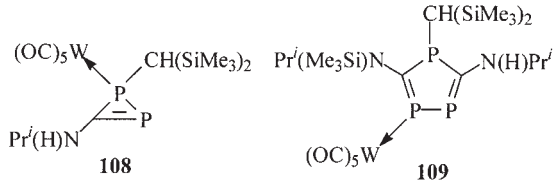


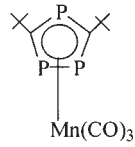
107

A 1,3,4-triphosphole complex is prepared in the thermally induced regiospecific insertion of (*i*-Pr)(Me_3Si)N–C≡P into the phosphorus–phosphorus bond of species **108** to yield **109** (01AGE2471).



108 109

1-Triphenylstannyl-3,5-di(*tert*-butyl)-1,2,4-triphosphole and [$Mn(CO)_5Br$] give the triphosphacymantrene **110** (99PSS725, 00AGE2087). The rhenium analogue is known (01JCS(D)1726). Further reaction of **110** with [$Cr(CO)_5$(THF)] gives the η^5:η^1 complex **111**. The same starting ligand with [$Mn(NSiMe_3)_2$] yields sandwich **112**.



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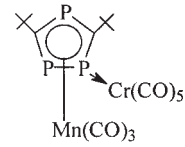

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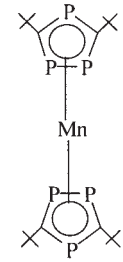
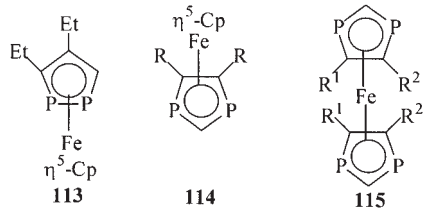
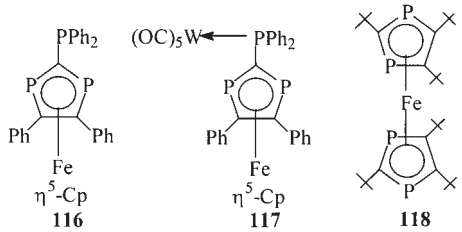


112

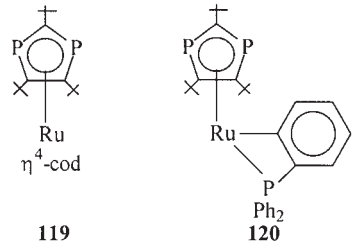
C. Iron Group

Lithium 1,2-diphospholide with [(η^6-*p*-$Me_2C_6H_4$)Fe(η^5-Cp)](PF_6) gives sandwich **113** (95AGE590). Similarly, lithium 1,3-diphospholides with [(η^6-C_6H_6)Fe(η^5-Cp)] give sandwiches **114** (R = Me, Et), and with [(η^6-1,4-xylene)Fe](PF_6)$_2$-1,1′,3,3′-tetraphosphaferrocenes **115** ($R^1 = R^2 = Me$, Et; $R^1 = Me$, $R^2 = t$-Bu) (92POL601). 2-Diphenylphosphino-4,5-diphenyl-1,3-diphospholide reacts with [(η^5-Cp)Fe(η^6-$Me_2C_6H_4$)](PF_6) to yield sandwich **116**, which retains the ligating properties and further reacts with [$W(CO)_5$(THF)] to yield the η^5:η^1 coordinated species **117** (97JOM(529)69). Reaction of K(THF)($P_2C_3Bu^t$)$_3$ with iron(II) chloride in THF gives sandwich **118** (01JCS(D)1013).



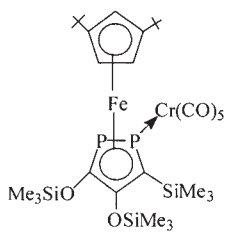


A mixture of the sodium salts of P_2C_3–*t*-Bu_3^- and P_3C_2–*t*-Bu_2^- with [(η^4-cod)$RuCl_2$]$_n$ gives the sandwich **119**, while with [(η^6-C_6H_6)$RuCl_2$(PPh_3)], the derivative **120** is formed (93JOM(462)319).



Reaction of [(η^5-1,3-*t*-$Bu_2C_5H_3$)$(OC)_2$Fe–P($SiMe_3$)P = C($SiMe_3$)$_2$] with [(cyclooctene)$Cr(CO)_5$] yields the sandwich having the η^5:η^1 coordination

mode, **121** among other products (95CB665). Thermolysis of the product in toluene in the presence of $[Fe_2(CO)_9]$ provides the pure η^5-product, **122**, which on photolysis with $Fe(CO)_5$ in *n*-pentane gives another representative of the η^5:η^1 group, **123**. Refluxing **121** in *n*-pentane in excess $[Fe_2(CO)_9]$ gives the species with the side-on-coordination of one of the iron sites, **124**. The starting complex **121** also reacts with $[Ni(CO)_4]$ and at room temperature produces the η^5:η^1 complex **125**. The other complex with the mixed η^5:η^1 coordination is $[(\eta^5\text{-}P_2C_3\text{–}t\text{-}Bu_3)Fe(\eta^5\text{-}P_3C_2\text{–}t\text{-}Bu_2)W(CO)_5]$ (92JOM(430)C10). The cyclization reaction between $[(\eta^5\text{-}t\text{-}BuC_5H_4)(OC)_2Fe\text{–}P(SiMe_3)\text{–}P{=}C(SiMe_3)_2]$ and $[(COE)Cr(CO)_5]$ gives **126** (M = Cr; $R^2 = t$-Bu, $R^1 = R^3 = R^4 = R^5 = H$) (96ZAAC543). In a similar way, derivatives **126** (M = Cr; $R^1 = R^2 = R^3 = R^4 = R^5 = Me$) (91JCS(CC)1293, 93OM731) and **126** (M = Cr; $R^2 = R^5 = t$-Bu, $R^1 = R^3 = R^4 = H$) (95CB665) can be prepared. If the reaction is started with $(Me_3Si)_2P\text{–}P{=}C(SiMe_3)_2$ and $[(\eta^5\text{-}t\text{-}BuC_5H_4)Fe(CO)_2Br]$, the η^5-coordinated diphosphaferrocene **127** ($R^2 = t$-Bu, $R^1 = R^3 = R^4 = R^5 = H$) results; this can form the η^5: η^1 species **126** (M = Cr; $R^2 = t$-Bu, $R^1 = R^3 = R^4 = R^5 = H$) on interaction with $[(COE)Cr(CO)_5]$ (96ZAAC543). This synthetic route for the diphosphole sandwiches can be used for **127** ($R^1 = R^2 = R^3 = R^4 = R^5 = H$) (91JCS(CC)1659). A similar sandwich **127** ($R^2 = R^5 = t$-Bu, $R^1 = R^3 = R^4 = H$) photolyzes with $[M(CO)_6]$ (M = Mo, W) to yield the η^5:η^1 coordinated products **126** (M = Mo, W; $R^2 = R^5 = t$-Bu, $R^1 = R^3 = R^4 = H$) (96ZAAC543). Photolysis with $[(\eta^5\text{-}MeC_5H_4)Mn(CO)_3]$ gives the η^5:η^1 product **128**. Reaction with $[Co_2(CO)_8]$ in turn gives the trinuclear species **129**.



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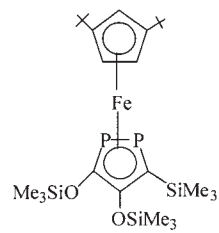

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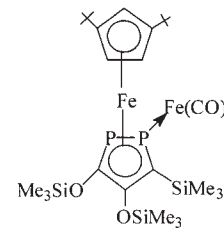

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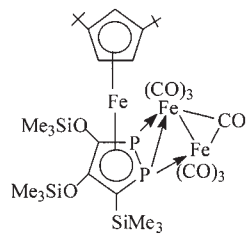

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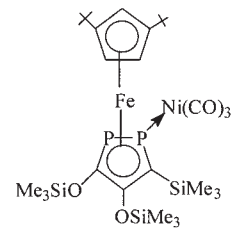

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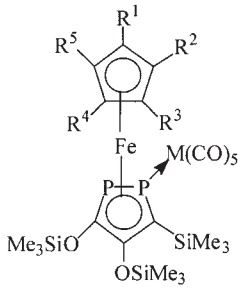

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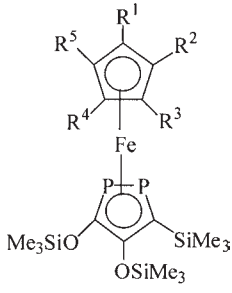

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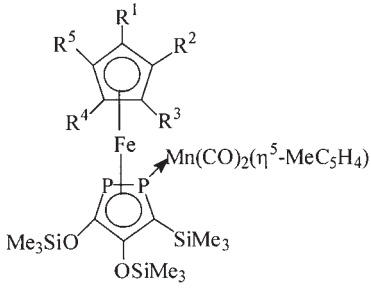

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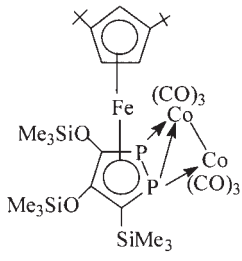
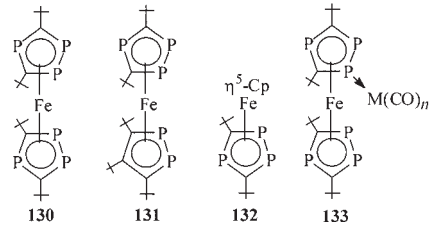
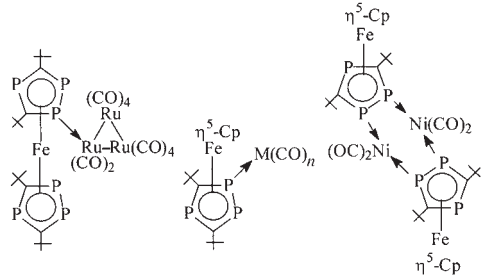


129

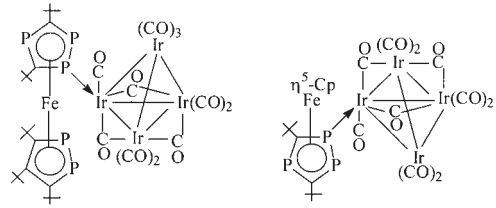
Sandwiches $[Fe(\eta^5\text{-}C_3Et_2HPAs)_2]$ (93BSCF521), $[Fe(\eta^5\text{-}P_3C_2\text{–}t\text{-}Bu_2)_2]$ (87JCS(CC)1146, 97CCCC309, 99CEJ3143, 99JOM(584)87) and the $\eta^5{:}\eta^1$ coordinated species $[(\eta^5\text{-Cp})Fe(\eta^5\text{-}C_2\text{–}t\text{-}Bu_2AsP_2)W(CO)_5]$ (94JOM(480)45) are known. Sandwiches **130** (87JCS(CC)1146), **131** (87JCS(CC)1146, 94JOM(479)C28), and **132** (88JOM(340)C37, 93JOM(453)C16) possess remarkable properties as ligands (88CRV1327, 91E49, 93CI(L)404, 96JOM(572)141). Among the illustrations of the P-coordinated species are **133** ($n = 5$, M = W; $n = 4$, M = Fe), **134** (92JOM(430)C10), and **135** ($n = 5$, M = Cr, W; $n = 4$, M = Fe; $n = 2$, M = Ni) (93POL1383). In the case of M = Ni, the product **136** is also possible. Mixed sandwich **131** with $[N(n\text{-}Bu)_4][Ir_4(CO)_{11}Br]$ in the presence of $AgSbF_6$ gives **137**, and species **132** gives an identical product **138**, which is in isomeric equilibrium with **139** (96JCS(CC)441). Further reaction of **138** with $[N(n\text{-}Bu)_4][Ir_4(CO)_{11}Br]$ in the presence of $AgSbF_6$ is unique and gives the sterically crowded complex **140**, in which two phosphorus sites are engaged in coordination. Sandwich **132** reacts with $[(\eta^5\text{-Cp*})Rh(CO)_2]$ to yield the edge-coordinated triphosphaferrocene, **141** (99JOM(584)87).



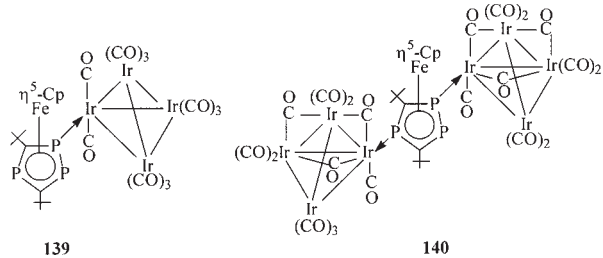
130 **131** **132** **133**



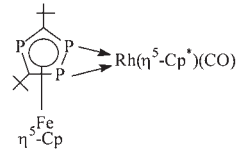
134 **135** **136**



137 **138**

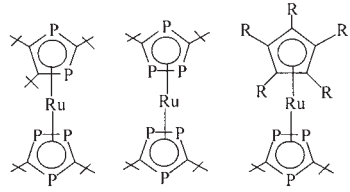


139 **140**

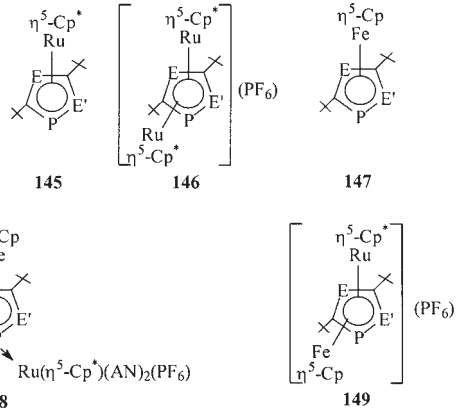


141

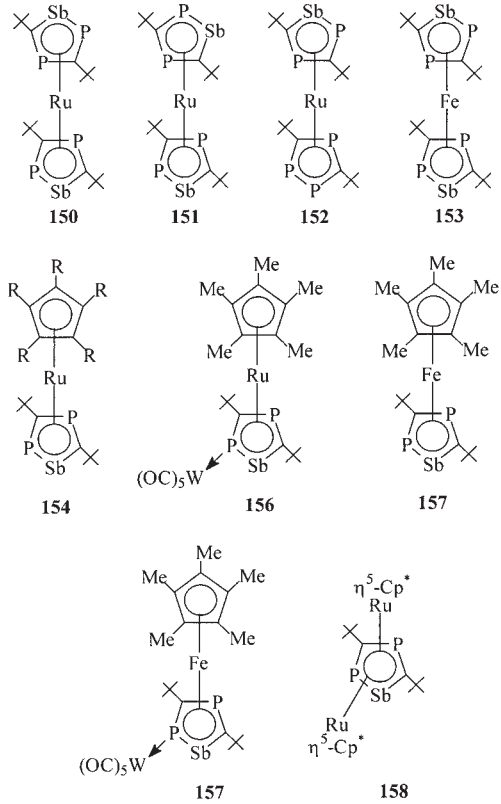
Triphospholyl anions C_2–*t*-$Bu_2PEE'^-$ (E = E′ = P; E = As, E′ = P; E = P, E′ = As) (93PSS45, 96JCS(CC)1591, 97JCS(D)4321, 97JOM(527)291) form the ruthenium cyclopentadienyl sandwiches (95JOM(490)155). A mixture of the sodium salts of P_2C_3–*t*-Bu_3^- and P_3C_2–*t*-Bu_2^- reacts with $[RuCl_2(PPh_3)_3]$ to give the mixed sandwich **142** (95JOM(490)155). The lithium salt of P_3C_2–*t*-Bu_2^- under similar conditions gives the symmetrical sandwich **143**. The same mixture of sodium salts but with $[(\eta^5\text{-Cp})RuCl(PPh_3)_2]$ gives sandwich **144** (R = H) and with $[(\eta^5\text{-Cp*})RuCl(\eta^4\text{-nbd})]$ sandwich **144** (R = Me).



With $[(\eta^5\text{-Cp*})Ru(AN)_3](PF_6)$, they first form sandwiches **145** (E = E′ = P; E = As, E′ = P; E = P, E′ = As), and then in the presence of excess ruthenium precursor, they yield the cationic triple-deckers **146** (E = E′ = P; E = As, E′ = P; E = P, E′ = As) (95OM4382). The iron sandwiches **147** (E = E′ = P; E = As, E′ = P; E = P, E′ = As) however react with $[(\eta^5\text{-Cp*})Ru(AN)_3](PF_6)$ differently, giving the η^5:η^1 species **148** (E = E′ = P; E = As, E′ = P; E = P, E′ = As). The latter are transformed to triple-deckers **149** (E = E′ = P; E = As, E′ = P; E = P, E′ = As) only on further refluxing in nitromethane. The pentamethylcyclopentadienyl analogues of **147** (E = E′ = P; E = As, E′ = P; E = P, E′ = As) react with $[(\eta^5\text{-Cp*})Ru(AN)_3](PF_6)$ straightforwardly and yield the triple-decker analogues of **149** (E = E′ = P; E = As, E′ = P; E = P, E′ = As), where the iron site is η^5-bonded to the Cp* framework.



A mixture of 1,4,2-diphosphastibolyl and 1,2,4-triphospholyl anions with $[RuCl_2(PPh_3)_3]$ give an isomeric mixture of antimony-containing sandwiches **150** and **151** as well as sandwich **152** (97JCS(D)2183). In the same conditions $FeCl_2$ produces sandwich **153** only. If $[(\eta^5\text{-}C_5R_5)Ru(AN)_3](PF_6)$ (R = H, Me) are used as organometallic precursors, the products are **154** (R = H, Me), which react further with $[W(CO)_5(THF)]$ to yield the $\eta^5{:}\eta^1$ coordinated species **155** (R = Me). The same chain of transformations takes place with $FeCl_2$ in the presence of lithium pentamethylcyclopentadienyl (**156**) and then $[W(CO)_5(THF)]$ (**157**). In excess $[(\eta^5\text{-}Cp^*)Ru(AN)_3](PF_6)$, the triple-decker **158** results.

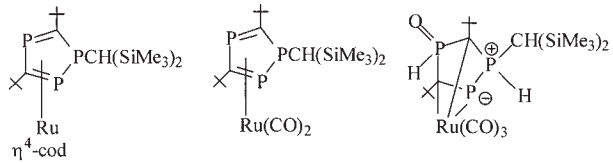


150 **151** **152** **153**

154 **156** **157**

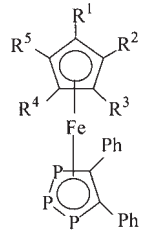
157 **158**

The 1,2,4-triphosphole ligand, $P_3C_2Bu^t_2CH(SiMe_3)_3$, displaces naphthalene from $[(\eta^4\text{-cod})Ru(\eta^6\text{-}C_{10}H_8)]$ to yield **159** (95JCS(CC)1661, 96JCS(CC)2751). Further treatment with carbon monoxide gives the dicarbonyl species **160**, the product of displacement of η^4-cod (99JOM (584)58). The latter easily reacts with water followed by **161**.



159 **160** **161**

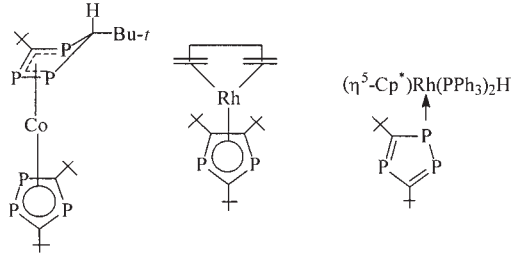
1,2,3-Triphospholyl ligands are quite rare (94BSCF397). The reaction between $[(\eta^5\text{-}1,2,3\text{-}Bu^t_3C_5H_2)(OC)_2Fe(\mu\text{-}\eta^1\text{:}\eta^1\text{-}P_4)Fe(CO)_2(\eta^5\text{-}1,2,3\text{-}Bu^t_3C_5H_2)]$ or $[(\eta^5\text{-}Pr^i_5C_5)(OC)_2Fe(\mu\text{-}\eta^1\text{:}\eta^1\text{-}P_4)Fe(CO)_2(\eta^5\text{-}Pr^i_5C_5)]$ with diphenylacetylene gives sandwiches **162** ($R^1 = R^2 = R^4 = Bu^t$, $R^3 = R^5 = H$; $R^1 = R^2 = R^3 = R^4 = R^5 = Pr^i$) (00AGE1426).



162

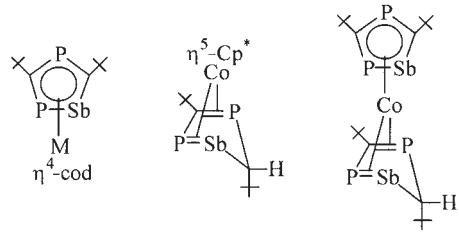
D. Cobalt Group

Sandwiches of the cobalt group are known, e.g., the one with the mixed coordination mode, **163**, prepared from the corresponding 1,2,4-triphosphole anion and cobalt(II) chloride (88JCS(CC)819), as well as the mixed-ligand species $[(\eta^5\text{-}P_3C_2\text{–}t\text{-}Bu_2)Rh(\eta^4\text{-cod})]$ (88JCS(CC)1615). Species $[(\eta^5\text{-Cp})RhH(\eta^1\text{-}P_3C_2\text{–}t\text{-}Bu_2)(PPh_3)]$ is not a frequent representative of the η^1-coordiantion of the triphospholyl ring (93JOM(462)319). A mixture of the sodium salts of $C_3\text{–}t\text{-}Bu_3P_2^-$ and $C_2\text{–}t\text{-}Bu_2P_3^-$ with $[(\eta^4\text{-cod})RhCl]_2$ and $[(\eta^4\text{-hexadiene})RhCl]$ gives products of type **164**, while $[(\eta^5\text{-Cp*})RhCl_2(PPh_3)]$ gives the P-coordinated complex **165**. Complex $[(\eta^5\text{-}P_3C_2\text{–}t\text{-}Bu_2)Rh(\eta^4\text{-cod})]$ results from a mixture of the same lithium salts and $[(\eta^4\text{-cod})RhCl]_2$ (88JCS(CC)1475).



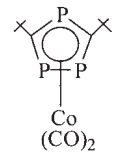
163 **164** **165**

2,4-Diphosphastibolyl anion reacts with $[(\eta^4\text{-cod})MCl_2]$ to give **166** (M = Rh, Ir) (97JOM(534)89). The same salt mixed with lithium cyclopentadienyl and $CoCl_2$ gives a mixture of two sandwiches **167** and **168**.



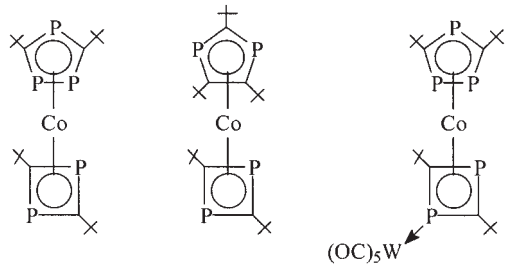
166 **167** **168**

1-Triphenylstannyl-3,5-di(*tert*-butyl)-1,2,4-triphosphole with $Co_2(CO)_8$ gives the η^5-coordinated species **169** (01OM2905). The latter enters into photochemical CO-substitution reactions with triethyl- and triphenylphosphine; one carbonyl ligand is substituted. With cyclohexylcyanide, however, a mixture of two substitution products is formed, with one and two CO ligands being substituted by CN–Cy groups, respectively.



169

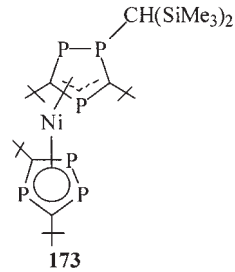
The metal-vapor technique was applied to cobalt atoms and *t*-BuC≡P (01JOM(635)212). The mixture of products that resulted includes the mixed-ligand sandwiches **170** and **171**. Further interaction of complex **170** with $[W(CO)_5(THF)]$ leads to the coordination of the $W(CO)_5$-group via the phosphorus heteroatom of the four-membered ring to yield **172**.



170 **171** **172**

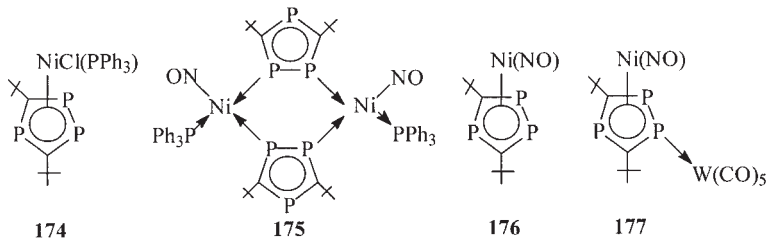
E. Nickel Group

In the nickel group, it is interesting to mention the mixed sandwich [(η^5-P_3C_2–t-Bu_2)Ni(η^5-P_2C_3–t-Bu_3)] (89JOM(373)C17). There are also the representatives of the η^1(P)-coordinated complexes, [MCl(P_3C_2–t-Bu_2)(PEt_3)] (M = Pd, Pt) (89NJC353, 93JOM(461)237), *trans*-[$PtCl_2(PEt_3)$ {P_3C_2–t-$Bu_2CH(SiMe_3)_2$}] (95JCS(CC)1661). In the latter case, the coordination is via the P^3-center. A unique case of η^5:η^2 coordination is known (97JCS(CC)1739). The η^2-coordination represents the rare edge mode, **173**. In the species [Ni($P_2C_3Bu^t_3$)]$_2$, the η^5:η^3 coordination mode is realized (95JOM(487)C21).



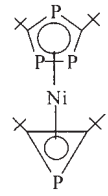
173

1-Trimethylstannyl-3,5-di-*tert*-butyl-1,2,4-triphosphole with [$(Ph_3P)_2NiCl_2$] gives sandwich **174** (00OM4283). However, the same ligand with [$(Ph_3P)_2$Ni(NO)Cl] gives the exo-bidentate species **175** with a very rare coordination mode for this type of ligands (98ZAAC399). At elevated temperatures the triphenylphosphine ligands are eliminated and the η^5-coordinated species **176** is formed in solution (00OM4283). This conclusion is based on solution data. Indirect confirmation of this possibility is found in the reaction between **176** and [$W(CO)_5$(THF)] to yield the η^5:η^1 coordinated complex **177**.



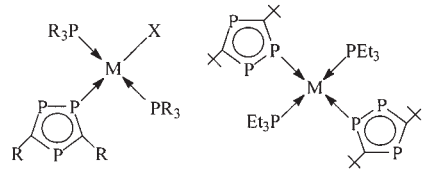
174 **175** **176** **177**

The metal-vapor synthesis, involving co-condensation of nickel vapors, t-BuC≡P, and 1,2,4-triphospholyl system leads to the mixed-ligand species **178** (94AGE2330).

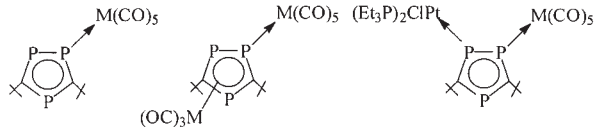


178

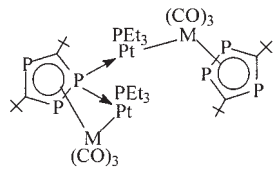
Anions $[C_2R_2P_3]^-$ (R = *t*-Bu, Ad) on interaction with *cis*-$[MCl_2(PEt_3)_2]$ give the *trans*-species **179** (X = Cl; M = Pd, Pt; R = *t*-Bu, Ad; R′ = Et) (88JCS(CC)1615). From *cis*-$[PtI_2(PPh_3)_2]$, species **179** (X = I; M = Pt; R = *t*-Bu, R′ = Ph) result. Excess $C_2(t\text{-Bu})_2P_3^-$ when acting on **179** (X = Cl; M = Pd, Pt; R = *t*-Bu; R′ = Et) gives species **180** (M = Pd, Pt). The other η^1(P)-coordinated species are known (90JCS(CC)317). Thus, treatment of the lithium salt of $P_3C_2Bu^t_2{}^-$ with $[M(CO)_6]$ (M = Cr, Mo, W) gives complexes **181** (M = Cr, Mo, W). At elevated temperatures the reaction of **181** (M = Cr, Mo, W) gives the η^5:η^1 coordinated species **182** (M = Cr, Mo, W). Treatment of **181** (M = Cr, Mo, W) with $[PtCl_2(PEt_3)_2]$ gives **183** (M = Cr, Mo, W). The latter undergo further transformation followed by the elimination of $[M(CO)_5(PEt_3)]$ to yield the dimeric clusters **184** (M = Cr, Mo, W). The η^1(P)-donor function is revealed in the compounds $[M(\eta^1\text{-}P_3C_2Bu^t_2)_2(py)_n]$ (M = Zn, *n* = 2; M = Cd, *n* = 3) (01JOM(633)143).



179 **180**



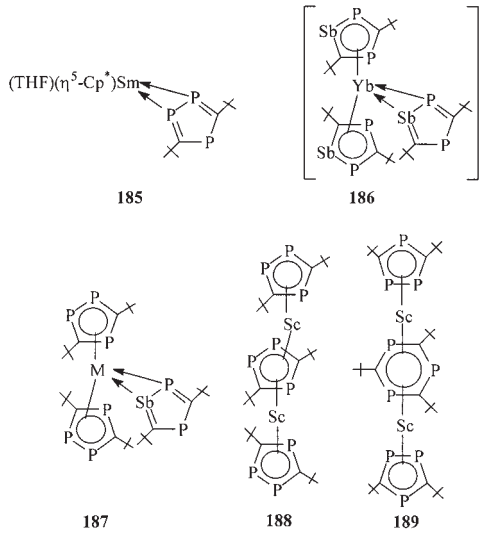
181 **182** **183**



184

F. Rare-Earth Elements

The thallium salt of 2,3-di-*tert*-butyl-1,2,4-triphosphole with [(η^5-Cp*)$_2$ Sm(THF)$_2$] gives the η^2-coordianetd species **185**, which to a certain degree is similar to the 1,2,4-triphospholyl and pyrazolyl ligands (98JCS(CC)797, 99MSF136, 00OM1713). Thallium 2,3-di-*tert*-butyl-1,4,2-diphosphastibolyl with metallic ytterbium in the presence of the lithium salt of the same anion gives the species **186** with the mixed η^5:η^2 coordination mode. The reaction of the potassium salt of 1,2,4-triphospholyl with MI_3 (M = Sc, Y, U) gives the neutral species **187** (M = Sc, Y, U) with the same coordination unit. Compound *t*-BuC≡P reacts with scandium atoms to yield the triple-decker species **188** (97JCS(CC)481). Metal-vapor synthesis also allowed the formation of mixed ligand triple-decker scandium species **189** (96JA7630).

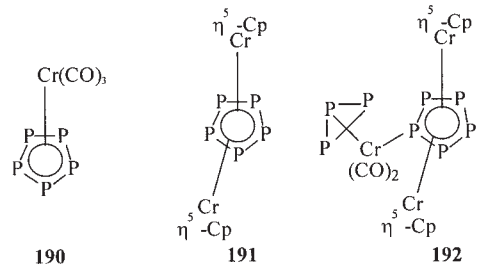


VIII. Complexes of Pentaphospholes

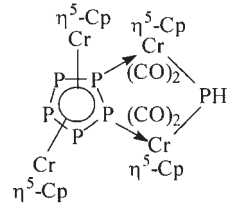
Interaction of P_4 and sodium in diglyme or P_4 and MPH_2 (M = Li, Na) in THF in the presence of 18-crown-6 gives [M(η^5-P_5)] (M = Li, Na) (85CPL352, 87ZAAC87, 89AGE485, 89CB2121, 89ZN(B)381). [K(η^5-P_5)] is also known (91AGE580).

Pentaphosphacyclopentadienyl rings manifest their ability to undergo η^5-coordination with the chromium tricarbonyl moiety, **190** (91AGE580). Chromium(0) also forms triple-decker **191**, where the equivalent P–P distances are unequivocal (85AGE351, 85AGE924, 86AGE363, 88OM1561,

89JA2030). The triple-deckers with Cr(η^5-Cp) and Cr(η^5-1,3-di-*tert*-butyl cyclopentadienyl) units follow from [(η^5-Cp′)Cr(CO)$_2$]$_2$ (Cp′ is Cp* or 1,3-di-*tert*-butyl cyclopentadienyl) and P_4 in xylene (86AGE363). The other example is the triple-decker species [(η^5-Cp*)Cr(μ-η^5:η^5-P_5)Cr(η^5-Cp*)] (94JCS(CC)163). The arsenic analogue [(η^5-Cp)Cr(μ-η^5:η^5-As_5)Cr(η^5-Cp)] follows from gray arsenic as the reactant (91OM875). The structure of the triple-decker [(η^5-Cp)Mo(As_5)Mo(η^5-Cp)] is better described in terms of the μ-η^4, η^1:η^4, η^1 coordination mode (82JA4727). The cyclopentadienyl analogue of **191** can be prepared by prolonged treatment of [(η^5-Cp)Cr(CO)$_3$]$_2$ with P_4 (89JCS(D)1951, 90JCS(D)977, 93OM888). Additionally, from the same reaction **192** can be prepared (00EJIC2585). [(η^5-Cp)(OC)$_2$Cr(μ-η^2-P_2)] with [(η^4-nbd)Mo(CO)$_4$] leads to the isolation of product **193**. Moreover, the pentaarsacyclopentadienyl-containing triple-deckers containing Cr(η^5-1,3-di-*tert*-butyl cyclopentadienyl) (89JOM(361)C11), Cr(η^5-Cp*) (90CB3), and Mo(η^5-Cp) (82JA4727) exist. The latter is the product of the interaction of [(η^5-Cp)Mo(CO)$_3$]$_2$ and $(MeAs)_5$ and is formulated as [{(η^5-Cp)Mo}$_2$(μ-η^4-As_5)], the molybdenum(II) complex.



Species [(η^5-Cp)Cr(CO)$_2$(μ,η^2-P_2)(OC)$_2$Cr(η^5-Cp)] reacts with $LiBEt_3H$ to yield a mixture of products and among them is the η^5:η^2 coordinated complex **194** (99OM2833). The crystal structure of **194** however suggests that the central ring is split into the allylic P_3 framework and P_2 moiety. Some similar developments are known (93JOM(447)259, 94PSS257, 00JCS(D)1135).

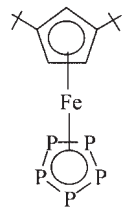


194

The reaction of t-Bu_4Sb_4 with $[(\eta^5\text{-}1,2,4\text{-}t\text{-}Bu_3C_5H_2)Mo(CO)_3Me]$ is unusual in the sense that along with the expected triple-decker species $[(\eta^5\text{-}1,2,4\text{-}t\text{-}Bu_3C_5H_2)Mo(\mu,\eta^5\text{-}Sb_5)Mo(\eta^5\text{-}1,2,4\text{-}t\text{-}Bu_3C_5H_2)]$ it gives $[(\eta^5\text{-}1,2,4\text{-}t\text{-}Bu_3C_5H_2)Mo(\mu,\eta^5\text{-}Sb_5)Mo(\eta^5\text{-}1,4\text{-}t\text{-}Bu_2\text{-}2\text{-}MeC_5H_2)]$ with replacement of one of the *tert*-butyl groups with a methyl in the second product (00AGE4148).

The potassium complex $[(\eta^5\text{-}P_5)K]$ with $[Mn(CO)_5Br]$ in DMF gives the product of metathesis, $[(\eta^5\text{-}P_5)Mn(CO)_3]$ (91AGE580).

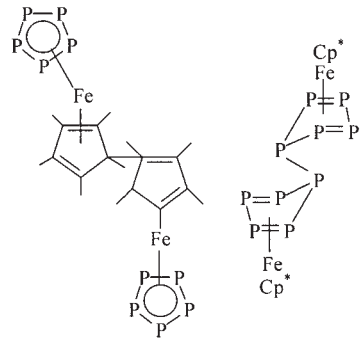
Interaction of $[Cr(CO)_5PCl_3]$ with $K[(\eta^5\text{-}1,3\text{-}t\text{-}Bu_2C_5H_3)Fe(CO)_2]$ at $-78\,^\circ C$ in THF gives the classical sandwich **195** (93AGE593, 97CB1299).



195

Thermolysis of $[(\eta^5\text{-}Cp^*)Fe(CO)_2]$ with white phosphorus (P_4) gives sandwiches $[(\eta^5\text{-}Cp^*)Fe(\eta^5\text{-}P_5)]$ (87AGE59). The electrochemical properties of this sandwich are remarkable and may be interpreted in terms of the two possible coupling processes, involving **196** and **197** (99OM1827) separately. This type of reaction for white phosphorus (P_4) and $[(\eta^6\text{-}C_5Me_4R)Fe(CO)_2]_2$ or $[(\eta^5\text{-}C_5Me_4R)Ru(CO)_2Br]$ gives mixed sandwiches $[(\eta^5\text{-}P_5)M(\eta^5\text{-}C_5Me_4R)]$ (M = Fe, R = Me, Et; M = Ru, R = Me, Et) (88CB935). Thermolysis of sandwiches **198** (M = Fe; E = P, As) with $[(\eta^5\text{-}Cp^*)M(CO)_2]_2$ (M = Ru, Os) appears to be a reaction involving the transfer of the η^5-E_5 (E = P, As) ligands in the case of M = Ru and the η^5-P_5 ligand in the case of M = Os to yield sandwiches **198** (M = Ru, E = P, As; M = Os, E = P) (95CB71). Sandwiches **198** (M = Fe; E = P, As) (89ACS458, 90JOM(387)C21, 91JOM(409)C15, 94AGE1110, 95CB635, 96PSS133, 96ZAAC1478, 00EJIC2451) serve as the ligands. There are cases of further η^1-coordination followed by the relevant η^5:η^1 species (90AGE1104).

With $[Cr(CO)_5(THF)]$, the $\eta^5{:}\eta^1{:}\eta^1$ species **199** is formed, while with $[\eta^5$-Cp)$Mn(CO)_2(THF)]$, even **200** becomes possible (89CB2049). Reaction of **198** (M = Fe; E = P, As) with the dimers $[(\eta^5$-Cp*)$M(CO)]_2$ (M = Rh, Ir) gives rise to the $\eta^5{:}\eta^2$ species **201** (E = P, As; M = Rh, Ir) with the so-called side-on coordination of the rhodium or iridium fragment (95AGE1321). Another interesting example in this respect is $[(\eta^5$-$C_5H_4Et)Fe(P_5)Co(CO)(\eta^5$-$C_5H_4Et)\{Co_2(\eta^5$-$C_5H_4Et)(\mu$-$CO)\}]$, where the coordination mode of the P_5 ring is μ-$\eta^5{:}\eta^2{:}\eta^2{:}\eta^1$ (98CEJ1910). Attempts to obtain the full sandwich of iron containing two pentaphosphacyclopentadienyl rings have so far been unsuccessful (88AGE280, 91AGE580). This might be the product of an interaction of pentaphosphacyclopentadienyl lithium with iron(II) chloride, although there is no rigorous structural confirmation (88AGE280). There are cases where the central η^5-P_5 ligand is cleaved (94AGE1110, 97JOM(529)379), for example, in the reaction of $[(\eta^5$-Cp*)$Fe(\eta^5$-$P_5)]$ with $[(\eta^5$-Cp*)$Ta(CO)_4]$ followed by the splitting of one of the P–P bonds.



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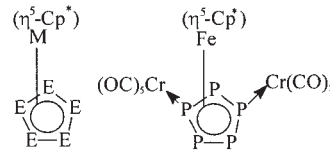
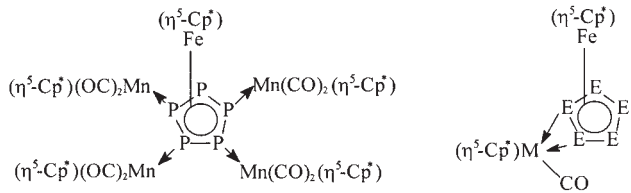
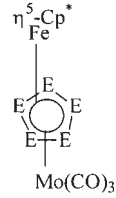


198 199



200 201

Sandwiches [(η^5-Cp*)Fe(η^5-E_5)] (E = P, As) serve as the starting materials for the triple-deckers **202** (E = P, As) that follow from their reaction with [$(OC)_3Mo(AN)_3$] (92MI2). The stacking reaction of [(η^5-E_5)M(η^5-Cp*)] (E = P, As; M = Fe, Ru) with [$M'(CO)_3(AN)_3$] (M = Cr, Mo, W) also gives triple-deckers **202** (92CB1011).

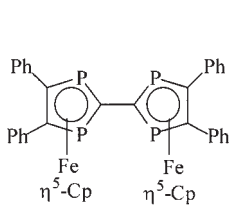


202

IX. Miscellaneous

There is some information on the analogues of azoles, which do not fall under any of the above considered ligands. These data are quite scattered and non-systematic but deserve mentioning because of their potential value.

Dilithium octaphenyltetraphosphafulvalene with [(η^5-Cp)Fe(η^6-1,4-$Me_2C_6H_4$](PF_6) gives the η^5-coordinated species **203**, which is unstable with respect to oxidants but can be stabilized by reacting with [(η^4-nbd)$Cr(CO)_4$] (92AGE1031). The latter affords the chelate complex **204**.



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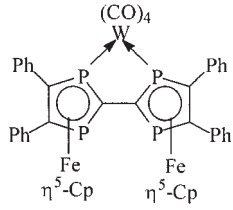
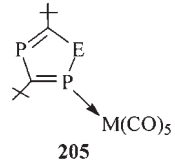


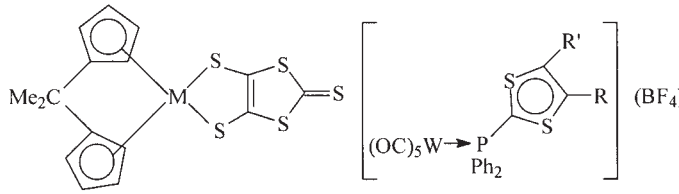
204

1,2,4-Selenadiphosphole and 1,2,4-telluradiphosphole form the η^1(P) coordinated complexes **205** (M = Cr, W; E = Se; M = W, E = Te) with [$M(CO)_5$(THF)] (99JOM(580)156).



205

Complexes with heterocycles containing two sulfur heteroatoms may be of interest in materials chemistry (95IC4979, 98CEJ1714, 98JCS(D)483). One such ligand is dianionic 4,5-disulfanyl-1,3-dithiole-2-thionate (99OM1834). The interaction of the disodium salt of this ligand with $[Me_2C(\eta^5\text{-}C_5H_4)_2MCl_2]$ (M = Mo, W) gives products **206** (M = Mo, W) with a rare dithiolene coordination. Further oxidation of the complexes obtained with $TCNQF_4$ gives $[\mathbf{1}]_2(TCNQF_4)$ with a highly organized layered structure. Protonation of $[W(CO)_5(PPh_2)(CS_2CHRC{\equiv}CR')]$ (R = H, R′ = CH, N; R = Me, R′ = N) with tetrafluoroboric acid gives 1,3-dithiolium tungsten complexes **207** (R = H, R′ = Me, NH_2; R = Me, R′ = NH_2) (01OM2604). Interaction of the product **207** (R = H, R′ = NH_2) with Ph_3CBF_4 gives **207** (R = H, R′ = $NHCPh_3$).



206 **207**

Another interesting aromatic anion **208**, which is well within the group of cyclopentadienyl and pentaphospholyl species, is a possible ligand (01AGE3173).

208

X. Conclusions

1. The di- and triborolyl ligands tend to η^5-coordination in sandwich-forming reactions. There is a clear-cut tendency for stacking processes followed by the formation of multidecker species and often stabilization of the unusual oxidation states of the transition metals. The route to the linked sandwich and multidecker complexes is attractive for materials chemistry. Thia- and azaborolyl organometallic chemistry follows the same trends, although in the azaborolyl complexes the η^3-rather than η^5-coordination is sometimes realized. Moreover, coordination via the boron atom is known. In the B, N, Si-heterocycles, the heteroring is η^4-coordinated.

2. Silicon analogues of imidazole-2-ylidenes are stable carbenes that form adducts where the metal–silicon bond is relatively weaker than that between metal and carbon atoms.
3. Azaphospholes where heteroaromaticity is regarded as appreciable, however, act mainly as η^1(P) ligands, and often the P-donor carries two coordinated organometallic moieties.
4. Di- and triphospholyl ligands are in sharp contrast with the corresponding azoles tending basically to the η^5-mode. Although there are cases of η^4- or η^1(P)-coordination, the trend is striking, sandwich ions based on the P_2 and P_3 heterorings possess noteable reactivity leading to numerous η^5:η^1(P) cases along with the η^5:η^2 side-on coordination of the complicated organometallic molecules, and variety of η^5:η^1:η^1 coordinations. One such combination resembles endo-bidentate coordination in pyrazole chemistry, which however requires preliminary η^5-sandwich formation. Finally, stacking reactions followed by triple-decker complexes appear possible.
5. Pentaphospholyl organometallic chemistry is in development again in sharp contrast to that of N_5, which is still considered by theoreticians as a possible ligand. The main trend is η^5-sandwich-formation and further stacking reactions although sometimes the islands as donor sites (η^3:η^2 instead of η^5) are postulated and the cases of cleavage of the η^5-ligand exist. As for di- and triphospholyl ligands, the reactivity of sandwiches and multideckers is remarkable and cases of η^5:η^1 and η^5:η^2 (side-on) mixed coordination are typical.
6. Some ligands by being analogues of azoles (condensed diphospholyls, SeP, TeP, SS, and S_2N_3) are occasionally examined but no systematic study of their organometallic chemistry exists.

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Heterocyclic Mesomeric Betaines and Analogs in Natural Product Chemistry. Betainic Alkaloids and Nucleobases

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I. Introduction

A. The Terms "Zwitterion" and "Mesomeric Betaine"

In principle, the relationship between positive and negative charges in molecules can be simplified and categorized as shown in Fig. 1 (99JOC9499). In salts **I**, positive and negative charges are localized on discrete cations and anions, whereas the charges on zwitterions and mesomeric betaines are in the same molecule. An interrupted conjugation between the charged parts of the molecule, for example by one or more sp^3-hybridized carbon atoms, results in zwitterions **II**. Polyheterocyclic molecules, however, can form zwitterionic ground states as shown in **III**, in which both the negative and the positive charges are delocalized within a common π-electron system, although at least one uncharged covalent structure can be drawn (93JOC6976, 93H1055, 91TL4473). As a consequence of the weighted average of all the canonical formulae highly polar entities are formed. In contrast to these kinds of zwitterions, mesomeric betaines **IV** are neutral compounds that can *exclusively* be formulated as dipolar structures, in which the positive and negative charges are delocalized within a common π-electron system. They possess an *even* number of positive and negative charges and no uncharged covalent structure can be drawn (85T2239). Betaines with an *odd* number of charges form a distinct class of compounds (98JOC4636, 98H865, 99H2119, 00MI2, 01H827, 02JHC949, 02OL1375).

Representatives of all these distinct categories of charged or charge-separated species have been isolated from natural sources. Salts of cationic alkaloids are widespread in nature, among them pyridinium, quinolinium, and isoquinolinium alkaloids. Examples of monocationic alkaloids are Cryptaustoline (**1**) (*Cryptocarya*) and the antitumor active Avicine (**2**)

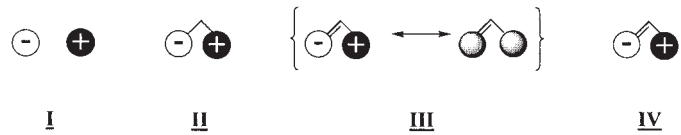
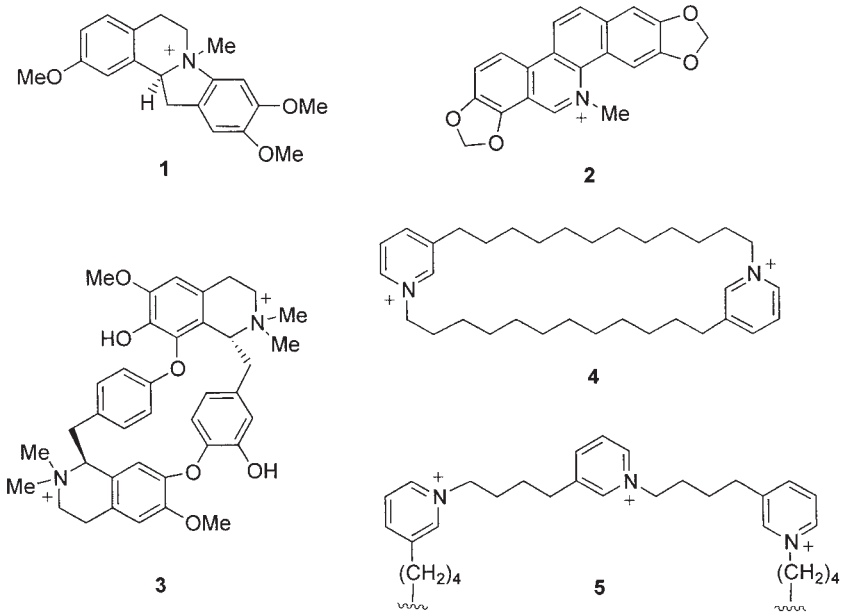


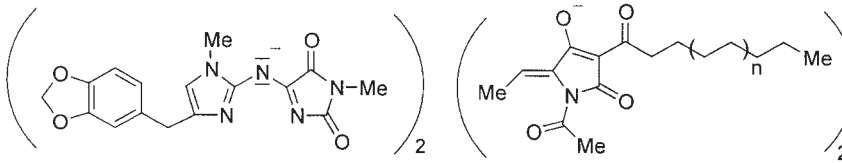
Fig. 1

(93P1449, 85CPB4139) shown in Scheme 1. The former mentioned alkaloid has a sp^3 hybridized quaternary nitrogen atom and is an ammonium salt. Alkaloid **2** is a heteroarenium salt as it has a quaternary sp^2 hybridized nitrogen atom. There are a number of highly biologically active natural products which bear more than one charge. Tubacurarine (**3**) and Cyclostellettamine (**4**) (94TL3967, 96T10849) are examples of dicationic alkaloids, whereas the oligomeric pyridinium-alkaloid **5** is a multicationic species (93JOC5925).



Scheme 1

Negatively charged alkaloids are rare. The isolation of the zinc salt Clathridin (**6**) (Scheme 2) from the marine sponge *Clathrina clathrus* was reported in 1990 (90T4387). Other examples are bis(isonaamidinato) A Zinc

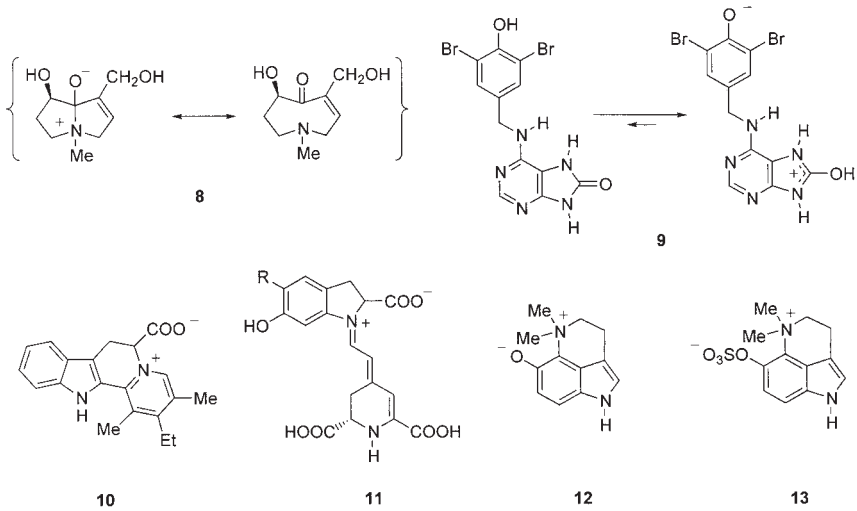


Scheme 2

(II) and G from *Leucetta* species (95HCA1178) and zinc containing alkaloids from *Leucetta* cf. *chacosensis* (98JNP384). Magnesidine (**7**) ($n = 0, 1$) is produced by the marine bacterium *Pseudomonas magnesiorubra* (74TL983) and *Vibrio gazogenes*.

The combination of positive and negative charges within the same molecule causes a more complicated situation, which obviously has not been well-defined to date. A quite large number of pyrrolizidine alkaloids are related to Otonecine (**8**) (Scheme 3). Spectroscopic investigations show that these alkaloids exist in the nonionized form in $CDCl_3$, and in the zwitterionic form in D_2O (00JNP857, 71TL3421). The dipolar structure is the result of an intramolecular interaction between a nucleophilic and an electrophilic center.

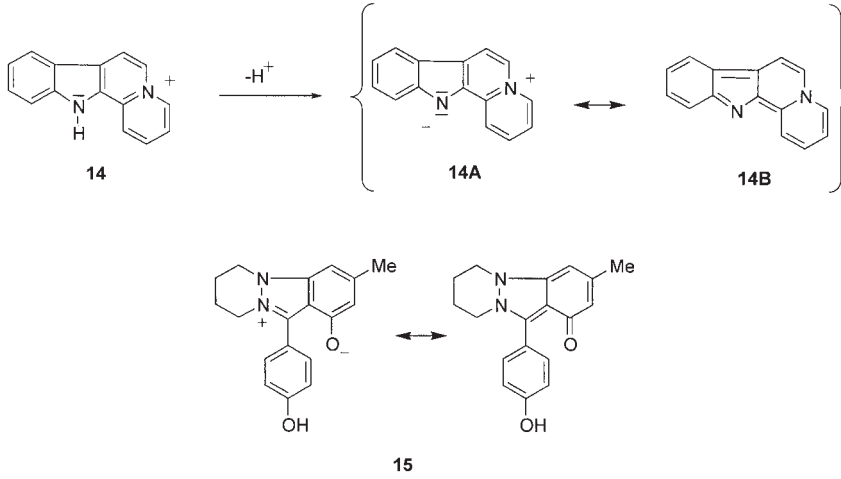
In contrast to this, the zwitterion Aplidiamin (**9**), which was isolated from *Ascidiae* living in the Ningaloo Reef, exists predominantly as an inner salt in which the positive and negative charges are separated by a sp^3-hybridized carbon atom (97TL941, 92TL2597). Javacarboline (**10**) from *Picrasma javanica* (94H1413), which is used in folk medicine as febribue and as a substitute for quinine (73MI2), as well as the class of plant dyes called Betalaines (**11**) (Betanidine, Betanine) are also zwitterionic. The charge separation, however, is not due to a neutralization of acidic and basic functional groups within the same molecule, but to deprotonation of a carboxylic acid function adjacent to a quaternary nitrogen atom. As evidenced by HH-COSY, HSQC and HMBC experiments as well as X-ray crystallography, Javacarboline (**10**) has a protonated indole-nitrogen atom and a deprotonated carboxy group which form a hydrogen bond in the solid state (94H1413). Interestingly, racemization of the *L*-tryptophan derived zwitterionic alkaloid occurs via a 1,2-dihydropyridinium derivative. Dehydrobufotenine (**12**) and Bufothionine (**13**), which are components of the toxin producing skin glands of toads (*Bufonidae*, *Hylidae*), are deprotonated at the hydroxy group and sulfonic acid group to form zwitterions, respectively. In **12** and **13**, the positive charge is localized outside the π-electron system.



Scheme 3

A large number of alkaloids contains the indolo[2,3-*a*]quinolizine structure increment **14** (88MI2) (Scheme 4). They are found as zwitterions with an anionic indole ring or as salts depending on their base properties (90BCJ2498). The dipolar ground state arises from deprotonation, but the positive and the resulting negative charge are delocalized within a common π-electron system which can therefore be refered to as "conjugated zwitterion". The deprotonated species can be represented by several dipolar structures and *one* neutral covalent canonical formula **14B**. The zwitterionic ground state is evidenced by its colored nature, high permanent dipole moments in the ground state and by the pH dependent UV–VIS spectra (25JCS1604, 53JA3361). The alkaloid Nigellidine (**15**) (*Nigella sativa*), which belongs to the extremly rare class of indazole alkaloids, is another example of this type of zwitterion (95TL1993). The positive and negative charges are in mutual conjugation and several dipolar structures, but only one neutral canonical formula, can be drawn. Evidently, the latter two mentioned species are related to heterocyclic mesomeric betaines and will be treated in Section III.

In contrast to the alkaloids mentioned so far, heterocyclic mesomeric betaines are defined as neutral conjugated molecules which can be represented *only* by dipolar structures in which both the negative and the positive charges are delocalized within the π-electron system (38JCS824, 85T2239). The first heterocyclic mesomeric betaine was prepared unknowingly by Emil Fischer (1882LA316). The real structure remained unknown



Scheme 4

until 1969 (69JCS(CC)1356, 69JCS(CC)1240, 70JA1965) when it was formulated as the mesoion tetrazoliumthiolate which is the valence tautomer of the originally proposed structure. For decades the nomenclature as well as the adequate representation of these structures were controversal (55CIL521). This is examplified by the flood of acronyms such as mesoion (49JCS307, 55CIL910), ylide, paraion (80JA3971), sydnone (46JCS591, 64CRV129), münchnone (64AG185, 70CB2581), mesoionic 4$n\pi$-heterocycle (80ZN1002, 83H23), mesoionic malonyl heterocycle, inner salt, and anhydro compound. In addition, the symbols ψ and $\pm$ were used for the dipolar representation of these compounds. After the first systematizations of heterocyclic N-oxides and N-ylides by Katritzky (71MI2), Ochiai (67MI2), Johnson and Petrovanu (66MI1, 76MI1), heterocyclic mesomeric betaines were classified in 1977 by Ramsden on the basis of their type of conjugation (77JCS(CC)109). The first comprehensive classification was published eight years later by Ollis, Stanforth and Ramsden (85T2239). All mesomeric betaines can be divided into four major classes, conjugated (CMB), cross-conjugated (CCMB), pseudo-cross-conjugated (PCCMB) heterocyclic mesomeric betaines, and conjugated heterocyclic N-ylides, the later are closely related to CMB. Today, the term mesoion is exclusively restricted to five-membered conjugated heterocyclic mesomeric betaines and thus includes the well-known sydnones, münchnones and derivatives (55CIL521, 85T2239). It has been demonstrated that these four major classes can be subdivided into four additional categories on the basis of their isoconjugate relationships to odd/even, alternant/nonalternant hydrocarbon

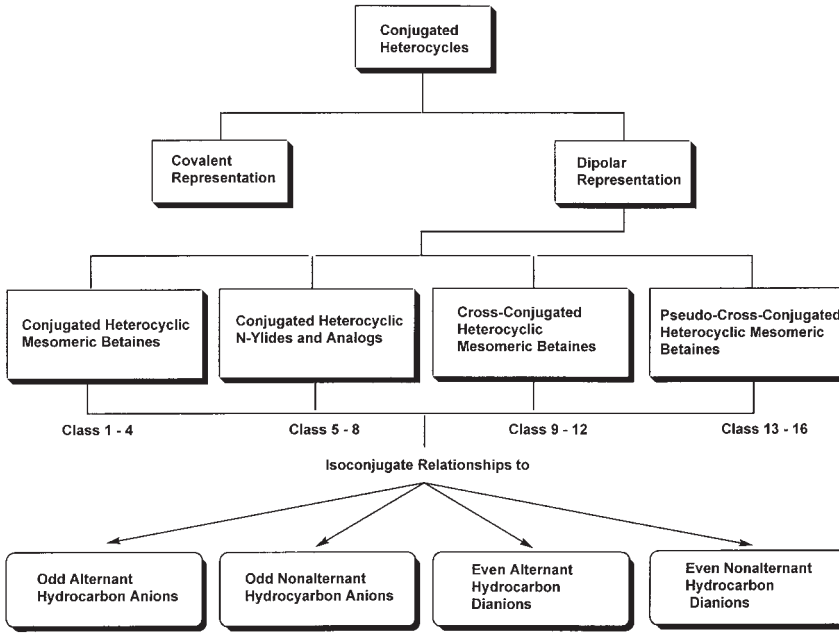


Fig. 2

anions/dianions, respectively. In summary, at least 16 distinct classes of heterocyclic mesomeric betaines can be differentiated (85T2239) which is examplified in Fig. 2. The chemistry of mesoionic heterocycles of type A and B (02CHE681, 76AHC1, 79MI4, 82T2965), heteropentalenes (77T3203, 84CHEC1027, 77MI3, 77H1319, 78AHC183, 75ACR139, 78JOC3893), and conjugated mesomeric betaines isoconjugate with alternant hydrocarbon atoms (80AHC1) have been reviewed.

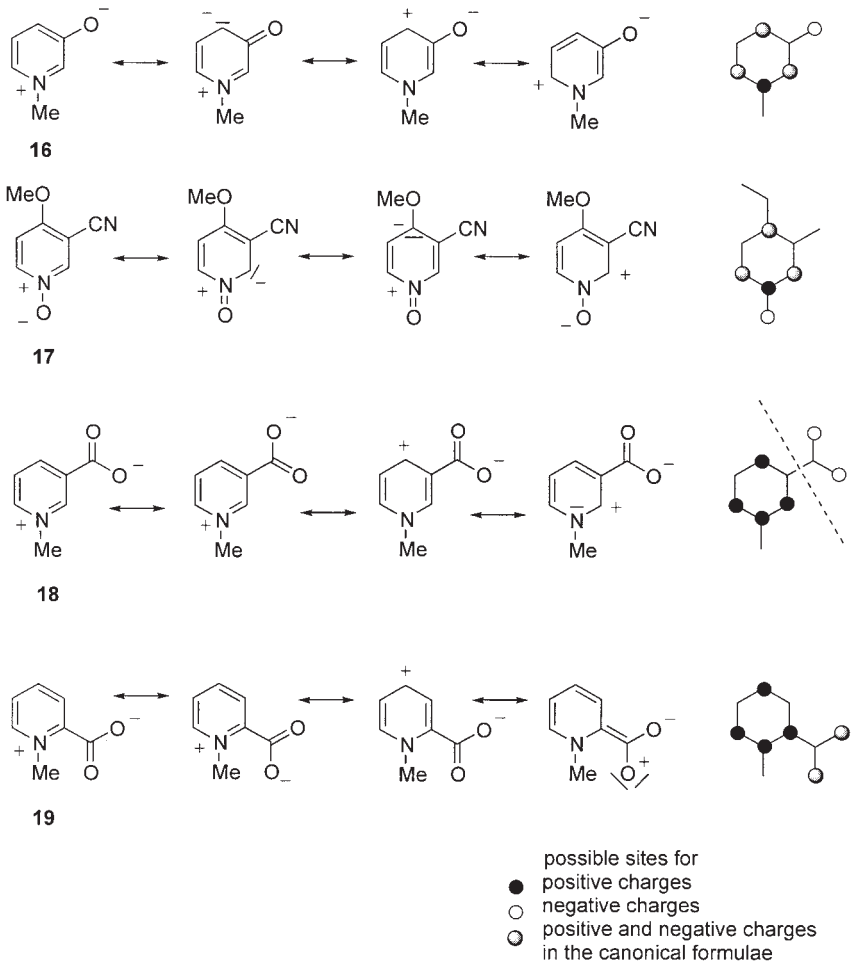
B. Classification and Characteristic Features of Heterocyclic Mesomeric Betaines

This review demonstrates that representatives of all four major classes of heterocyclic mesomeric betaines were isolated from natural sources. The profound differences in the electronic structures of these distinct classes can be realized by a closer look at the canonical formulae, the frontier orbital profile, the isoconjugate relationships, physico-organic properties, and the

chemical behavior. As examples, four heterocyclic mesomeric betaines are presented in Scheme 5 which are alkaloids or substructures of alkaloids. For conjugated mesomeric betaines (CMB) such as 1-methylpyridinium-3-olate (**16**) (cf. Section II.A.1), common atoms for either positive and negative charges exist in the canonical formulae. The charges are in mutual conjugation. X-ray single crystal structure analyzes show that all bonds in conjugated mesomeric betaines have double bond character (82T2965, 76AHC1, 85T2239). The same is true for heterocyclic conjugated N-ylides and relatives for which Malloapeltine (**17**) is an example (cf. Section II.B.1). They form a distinct major class, because they can satisfactorily be represented by 1,2-dipolar structures. The delocalization of the negative charge is much more important for the N-ylide stability than the delocalization of the positive charge (Kröhnke's rule) (76MI1). In 1-methylpyridinium-3-carboxylate (**18**) (the alkaloid Trigollenine, cf. Section II.C.1), however, the charges are *exclusively* delocalized in separated parts of the molecule which is characteristic for cross-conjugated mesomeric betaines. No common atoms for the delocalization of the positive and negative charge exist. Pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB) are hybrids between conjugated and cross-conjugated mesomeric betaines. As revealed by the canonical formulae of 1-methylpyridinium-2-carboxylate (**19**) (the alkaloid Homarine, cf. Section II.D.1), common atoms for the delocalization of the negative and positive charges exist. The mutual conjugation, however, involves electron sextet structures without internal electron octet stabilization. If the true structure of a molecule is to be a weighted average of its canonical formulae, there is only a very small contribution of these electron sextet structures to the overall electronic structure. Thus, the charges are effectively, but not exclusively, delocalized in separated parts of the common π-electron system. For this phenomenon the term "pseudo-cross-conjugation" was defined (85T2239).

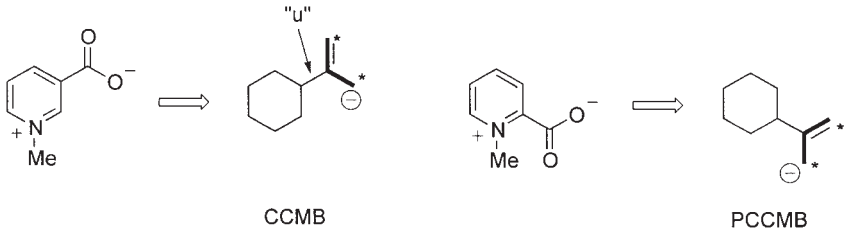
In CCMB and PCCMB the negative partial structure is joined to the negative increment through an unstarred position. This bond is called a *union* in the sense defined by Dewar (69MI3, 75MI2): union is a process in which two conjugated molecules combine in such a way that their two π-electron systems unite into a larger one (85T2239). For the case of **18** and **19**, the anionic part is isoconjugate with the propenyl anion as shown in Scheme 6.

Single crystal X-ray analyzes confirm the concept of cross-conjugation. The cationic and anionic segments of, e.g., 6-oxopyrimidinium-4-olate are unambiguously separated by single bonds without π-contributions. Delocalization and double bond character can be observed exclusively in the charge-separated segments (81JHC881).



Scheme 5

The type of conjugation is also reflected in the frontier orbital profile, the charge distribution, and the permanent dipole moments. The results of semiempirical calculations on 1-methylpyridinium-3-olate (**16**), Malloapeltine (**17**), Trigollenine (**18**), and Homarine (**19**) are presented in Scheme 7. Characteristically for the class of conjugated mesomeric betaines, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are distributed over the entire molecule as examplified for 1-methylpyridinium-3-olate. It was shown that 90% of the

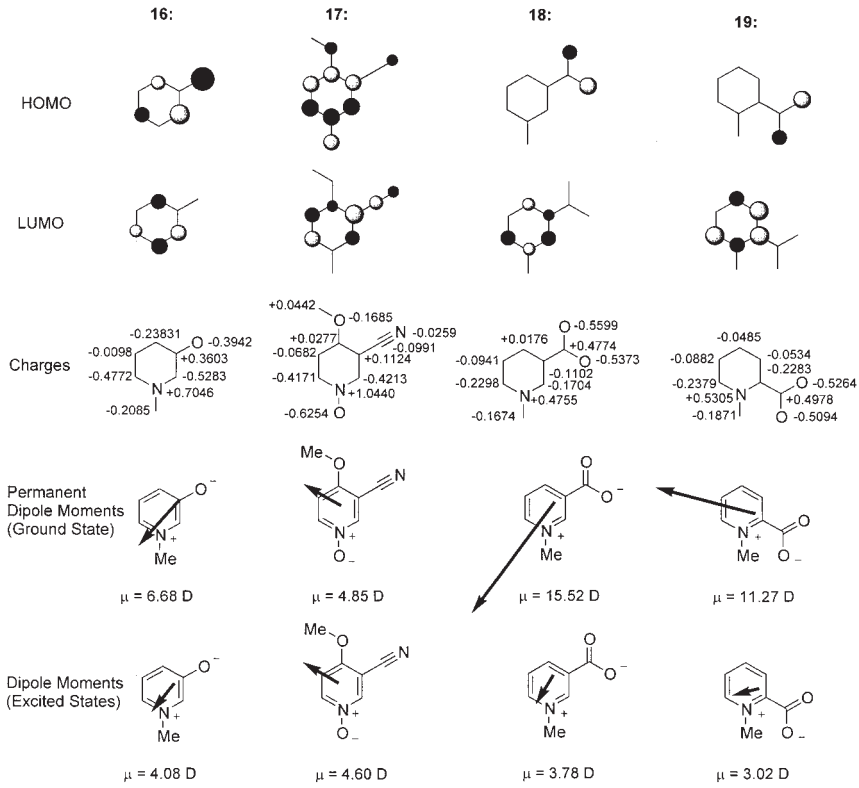


Scheme 6

charge density is located at the active positions of the HOMO (76JCS(P1)2296). The same is true for the N-ylide Malloapeltine, which is also a conjugated system. In contrast to this, the frontier orbitals of the cross-conjugated and the pseudo-cross-conjugated mesomeric betaines are located in separated parts of the π-electron system. The HOMOs of the CCMB Trigollenine and the PCCMB Homarine are essentially located at the oxygen atoms of the carboxy group, whereas the LUMOs are located in the pyridinium rings, respectively. For cross-conjugation and pseudo-cross-conjugation, the pyridinium ring is joined to the anionic partial structure by a union (69MI3, 75MI2) through a nodal position of the HOMO. Thus, the positive and negative charges are separated by an inactive position of the HOMO, which causes their isolation (88JOC2889). Consequently, the permanent dipole moments of cross-conjugated mesomeric betaines in the ground state are by far the largest as presented in Scheme 7 in correct size and direction. The zwitterionic ground state of betaines and zwitterions can be demonstrated by the effect of negative solvatochromism and Hammett correlations. Thus, all UV absorption maxima shift to shorter wavelengths with increasing solvent polarity, characterized, e.g., by the E_T^N scale by Reichardt (83LA721), or by the Z scale defined by Kosower (62MI1). This is mainly due to the decreased permanent dipole moment (Scheme 7) as a consequence of charge neutralization on HOMO–LUMO excitation (76LA125). Thus, in betainic molecules the electronic excitation is facilitated by nonpolar solvents. In addition, the zwitterionic ground state is furthermore supported by means of Hammett correlations in a specific example of a linear free energy relationship (79AG119). The spectroscopic Hammett equation may be expressed as follows:

$$(E_{T,R} - E_{T,0})/2.303\ RT = \sigma\rho_A$$

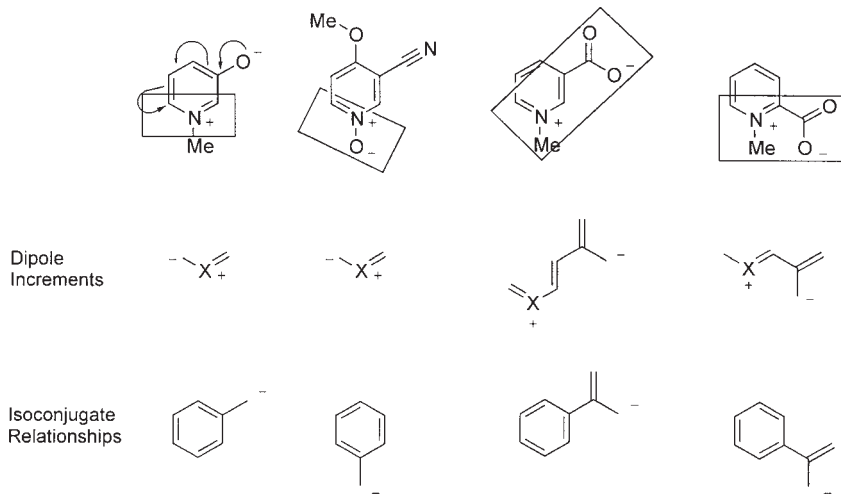
where $E_{T,R}$ and $E_{T,0}$ are the transition energies of the substituted and the reference compound (e.g., R = H), σ is the Hammett constant (73JMC1207,



Scheme 7

58JOC420, 53CRV191), R is the gas constant, T is the temperature, and ρ_A ("absorption constant") is the slope of the line. According to this equation, the energy differences $E_{T,R}$–$E_{T,0}$ are a linear function of the σ_m and σ_p constants. The substituents R^2 and R^3 in zwitterions gave negative slopes ρ_A, thus indicating an increasing charge density at the substituted ring atoms during excitation.

There are specific associations of various types of dipoles with the four major classes of heterocyclic mesomeric betaines, which have implications in providing a rational foundation for correlating the chemical reactions of these compounds (85T2239). Eight dipole types, systematically generated by *union* of the heterocations $H_2C=X^+$–H with carbanions and the heterosystem Ÿ–H, or their vinylogs can easily be identified by an inspection of the canonical formulae of a heterocyclic mesomeric betaine. The nitrile-ylide moiety, characteristic for conjugated mesomeric



Scheme 8

betaines, is present in **16** (Scheme 8). The nitrile oxide is found in the conjugated N-oxide Malloapeltine (**17**). The characteristic dipole types for CCMB and PCCMB can also easily be identified in Trigollenine (**18**) and Homarine (**19**). The complete list of dipole types for the identification of mesomeric betaines can be found in the literature (85T2239). Cross-conjugated heterocyclic mesomeric betaines undergo predominantely 1,4-dipolar cycloadditions and cycloreactions, which in some cases are thermodynamically driven by a charge neutralization (82H1083, 84H358, 83H1367, 83M227).

The isoconjugate relationships are presented in Scheme 8. 1-Methylpyridinium-3-olate (**16**) is isoconjugate with the benzyl anion, which is an odd alternant hydrocarbon anion. The terms odd and even refer to the total number of atoms, which form the conjugated molecule. The skeletal atoms of alternant hydrocarbons can be divided into two sets (starred and unstarred) in such a way that no atoms of like parity are directly bonded. The number of starred atoms is either identical or larger than the number of unstarred positions. All five-membered rings must therefore be nonalternant. The isoconjugate relationship defines 1-methylpyridinium-3-olate (**16**) as member of class 1, i.e., as a conjugated heterocyclic mesomeric betaine isoconjugate with odd alternant hydrocarbon anions (Fig. 2). Likewise, Malloapeltine (**17**) is a heterocyclic mesomeric betaine of class 5, i.e., a conjugated mesomeric N-ylide isoconjugate with odd alternant hydrocarbon anions. The cross-conjugated

Trigollenine (**18**) and the pseudo-cross-conjugated Homarine (**19**) are isoconjugate with the isopropenylbenzene anion, which is an odd alternant hydrocarbon anion. Therefore, these betaines belong to class 9 and 13, respectively.

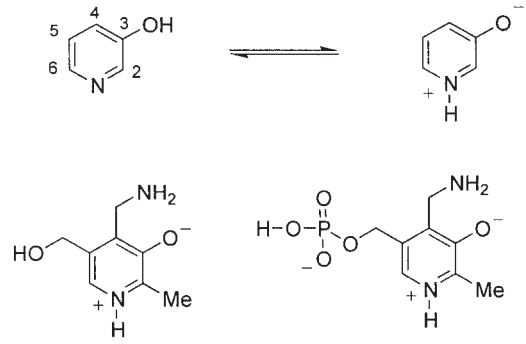
It was interesting to know which classes of heterocyclic mesomeric betaines are found in nature and to see whether there are any preferred types of conjugation. This review seeks to give an overview about isolation, characterization, known spectroscopic and chemical properties, and total syntheses of alkaloids and nucleobases, which are heterocyclic mesomeric betaines. For the sake of clarity in this review, alkaloids are categorized according to their largest cyclic π-conjugated system. Some interesting total syntheses of alkaloids via mesomeric betaines as reactive intermediates have been described. Thus, Ipalbidine, δ-Coniceine and Septicine were prepared by Padwa and coworkers employing the rhodium-catalyzed isomünchnone generation followed by 1,3-dipolar cycloaddition (97JOC438, 99OL83, 99JOC8648). Intramolecular cycloadditions of isomünchnones were applied to prepare Vallesamidine (95JOC2704), Erythrinane homologues (94JOC5518), Lycopodine (97JOC78), the frog alkaloid Pumiliotoxine C (97TL1505), and Onychine (00JOC2368). 1,3-Cycloaddition chemistry of isothiomünchnones was applied to synthesize Alloyohimbane and Tetrahydropapaverine (98TL4757, 00JOC2684). Likewise, an approach to Lysergic acid was reported (95JOC2704). As this paper is restricted to naturally occuring betainic alkaloids and nucleobases, these highly interesting aspects of the chemistry of heterocyclic mesomeric betaines are beyond the scope of this review.

II. Mesomeric Betaines

A. Conjugated Mesomeric Betaines

1. *Pyridinium-olates*

3-Hydroxypyridine is an alkaloid by itself and was isolated from the African tree *Entandophragma cylindricum* (Sapele) (71MI1). It is furthermore the structure element of the antifungal antibiotics UK-2A and UK-3A which were isolated from *Streptomyces* species (96JAN639, 96JAN1226) and whose total syntheses were described recently (98T12745). In general, 3-hydroxypyridine has been shown by ultraviolet spectroscopy to exist equally as neutral and betainic tautomers (63AHC353) in solvents of high dielectric constant (55JA2431). From the pD dependence of the ^{13}C NMR



20 **21**

Scheme 9

chemical shifts it can be concluded that neutral and betainic tautomer are present in nearly equal amounts in aqueous solution at any pD (79MI2). On the basis of NMR studies betainic structures for the vitamins B_6 Pyridoxamine (**20**) (PM) and Pyridoxaminephosphate (**21**) (PMP) in neutral aqueous solutions have been proposed (79MI2) (Scheme 9). A particular feature of the change of the UV spectrum with solvent is the appearance of a band at long wavelengths in aqueous solutions, which does not exist in alcohol. The intensity of this band, which is due to the absorption of the betainic species alone, is a measure of the tautomeric equilibrium. The tautomeric constant of 3-hydroxypyridine k_t = [betaine]/[neutral form] is 1.27. The pK_a of the OH group of 3-hydroxypyridine was determined potentiometrically in water at 20 °C to be 8.54–8.67, and of the N^+–H group 4.69–4.86 (92CJC1635). The hydroxy group of 3-hydroxy-1-methylpyridine has a pK_a = 4.96, determined under similar conditions (56JCS1294). 1-Methylpyridinium-3-olate (**16**) has absorption maxima λ_{max} at 320 nm in water, at 328 nm in EtOH, and at 356 nm in dioxane (59JCS1247), thus exhibiting the effect of negative solvatochromism, which is characteristic for betainic ground states (cf. Scheme 7). Pyridinium-3-olates proved to be photostable compounds in water (79JCS(P1)2535), although the valence-tautomerized aziridine derivative, 6-azabicyclo[3.1.0]hexene, was identified, dependening on the substitution pattern of the starting material (76JCS(P1)2338). These aziridines play key roles in the chemistry of Berberine derivatives (cf. **54**).

^{13}C, ^{14}N and ^{1}H NMR data of 3-hydroxy-1-methylpyridinium iodide have been reported (71HCA229). The chemical shift differences $\Delta\delta$ of substituted *N*-methylpyridinium iodides are mainly due to a

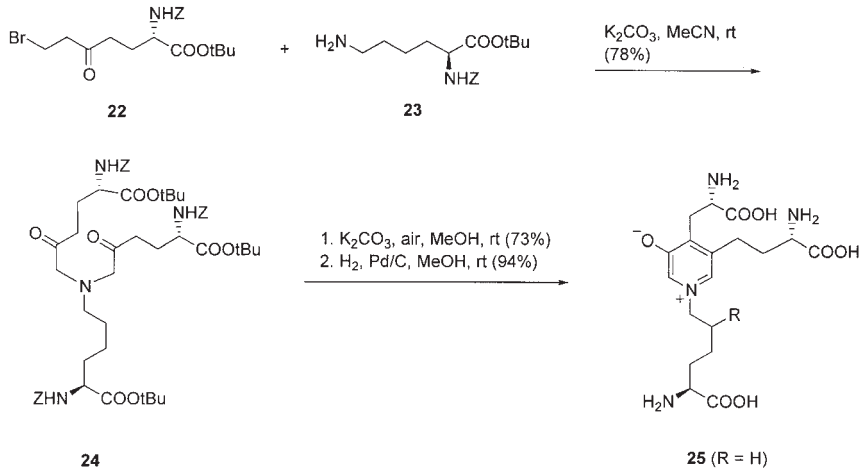
Table I. NMR Chemical Shifts of 1-Methyl-3-Hydroxypyridinium Iodide and FP_1 **26a**

	16 · HI			**16**	FP_1 **26a**	
Atom	^{1}H NMR[a]	^{13}C NMR[b]	^{13}C NMR[c]	^{1}H NMR[d]	^{1}H NMR[e]	^{13}C NMR[e]
2	8.03, d, $J = 1.9$ Hz	134.58	136.05	7.37, s	8.50, dd, $J = 2/1$ Hz	133.5
3	–	157.36	167.62	–	–	158.8
4	7.50, d, $J = 8.7$ Hz	132.73	134.57	7.12, m	7.94, ddd, $J = 9/2/1$ Hz	132.8
5	7.65, dd, $J = 5.6/8.7$ Hz	129.59	128.66	7.17, m	7.88, dd, $J = 9/6$ Hz	129.3
6	8.00, d, $J = 5.9$ Hz	138.01	130.32	7.18, m	8.48, dt, $J = 6/1$ Hz	136.2

[a] In DMSO-d_6.
[b] In D_2O at pD 2.
[c] In D_2O at pD 8.
[d] In $CDCl_3$.
[e] In CD_3OD.

charge transfer from the substituent through the π-electron system of the heteroaromatic ring to the *N*-methyl group. The $^1J_{CH}$ coupling constant of the *N*-methyl group increases with decreasing nitrogen charge density. It is interesting to note that in contrast to $CDCl_3$ the ^{1}H and ^{13}C NMR values determined in D_2O shift considerably to lower field with increasing concentration, whereas the ^{14}N resonance frequencies remain unchanged. An association constant of 2.3 in water was reported for 3-hydroxy-1-methylpyridinium iodide (56JA2537), so that the formation of ion pairs is probably the reason for this observation. Table I presents the ^{13}C NMR chemical shifts determined in D_2O at pD 2 and pD 8. Other reported values are slightly different (76JA8237). The peak assignment of C-4 and C-5 were assigned from the coupling constants (79MI2) and contrasted to literature values (73OMR551).

Although derivatives of 1-alkylpyridinium-3-olates are well-known in heterocyclic chemistry, seemingly only few representatives of this betainic system exist in nature. Deoxypyridinoline (**25**) (R = H) and Pyridinoline (R = OH) are cross-links of the mature form of collagen and were isolated from bones (96MI1) (Scheme 10). They are biochemical markers of collagen turnover correlated with biochemical diseases such as osteoporosis, bone cancer and arthropathies (96MI2, 97MI1). Deoxypyridinoline was synthesized starting from the bromo ketone **22** and the protected

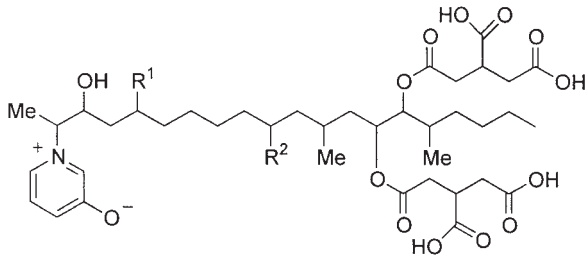


Scheme 10

L-lysine **23** to give the rather unstable amine **24** which was cyclized to a protected deoxypyridinoline. Hydrogenolysis followed by treatment with TFA finally gave the target molecule as a white crystalline monotrifluoroacetate monohydrate (99JCS(CC)559). On protonation of the betaine the ^{1}H NMR resonance frequencies of the α-pyridinium hydrogen atoms shift from $\delta = 7.57$ and 7.48 [CD_3OD] to $\delta = 8.69$ and 8.62 [D_2O], respectively.

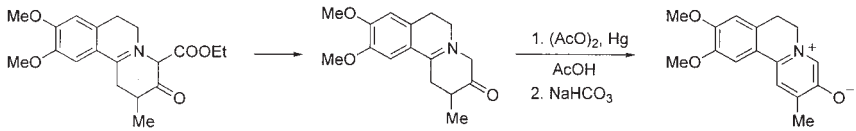
1-Substituted 3-hydroxy-pyridines were identified in a new series of fungal toxins known as Fumonisins (**26**) after acidic work-up with 0.1% formic acid (Scheme 11). These toxins are produced by several species of *Fusaria*, most notably *F. moniliforme*. Characteristically for 3-hydroxy pyridinium salts, the UV spectra of the new compounds show a UV maximum at 289 nm in 0.1 N HCl with a shift to 322 nm under basic conditions (0.1 N NaOH) (96JNP970). In general, fumosinines, which are found in corn and corn products (93MI1, 93MI2) and cause a variety of deseases (90MI1, 91MI1), possess an aminopolyol eicosane backbone and two tricarballylic acid esters (88JCS(CC)743). The NMR data presented in Table I are in accordance with the isolation of FP_1 in protonated form.

In the course of studies directed towards the structure elucidation of Rotundine from *Stephania rotunda* LOUREIO, the β-piperidone **28**, which is available starting from the keto ester **27**, was treated with mercuric acetate in 10% acetic acid solution. Basification yields the betaine **29** as colorless prisms (Scheme 12).



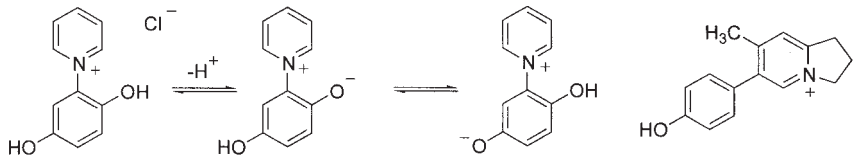
26a: FP_1: $R^1 = R^2 = OH$
26b: FP_2: $R^1 = OH$, $R^2 = H$
26c: FP_3: $R^1 = H$, $R^2 = OH$

Scheme 11



27 **28** **29**

Scheme 12



30 **31A** **31B** **32**

Scheme 13

2. *Pyridinium-phenolates*

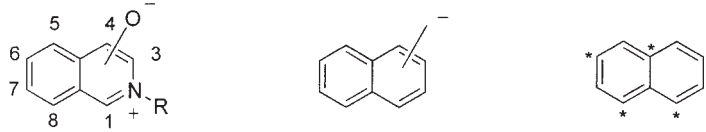
An unusual phenolic alkaloid **30** was isolated as pyridinium chloride from the leaves of *Punica granatum* (94P1175) (Scheme 13). As an aqueous solution of this compound has pH 4.5, this alkaloid exists as a mixture of cation **30** and mesomeric betaine **31** (02UPI1). It is interesting to note that deprotonation of the 2-hydroxy group resulted in a conjugated mesomeric betaine **31A**, whereas the formation of a 4-olate group gave a cross-conjugated mesomeric betaine **31B**. Mesomeric betaines that are interconvertible between two classes are rare (99H237). On addition of

hydrochloric acid to the aqueous solution, the color changes from yellow (pH 4–5) to green yellow (pH 1–3) and on addition of aqueous sodium hydroxide the color changes to red (pH 8). At higher pH, decomposition via pericyclic ring cleavage to amino pentadienals accompagnied by a color change to brown (pH 10) and finally reddish black (pH 11) is observable by ^{1}H NMR spectroscopy. The mesomeric betaine either produced from the cation with Amberlite IRA-410 or with sodium carbonate is negatively solvatochromic. The UV absorption maxima λ_{max} shift from 505 nm in chloroform (E_T^N 0.259) to 400 nm in water (E_T^N 1.000) (02UPI1). By means of HH-COSY experiments the unambiguous assignments of the hydroxy groups resonance frequencies were possible. A ^{1}H NMR titration of **30** with 1,8-bis(dimethylamino)naphthaline (DMAN, proton sponge) clearly showed that in DMSO-d_6 the 4-hydroxy group is the more acidic one. At higher ratios of the base, a rapid equilibrium between CMB and CCMB is observable.

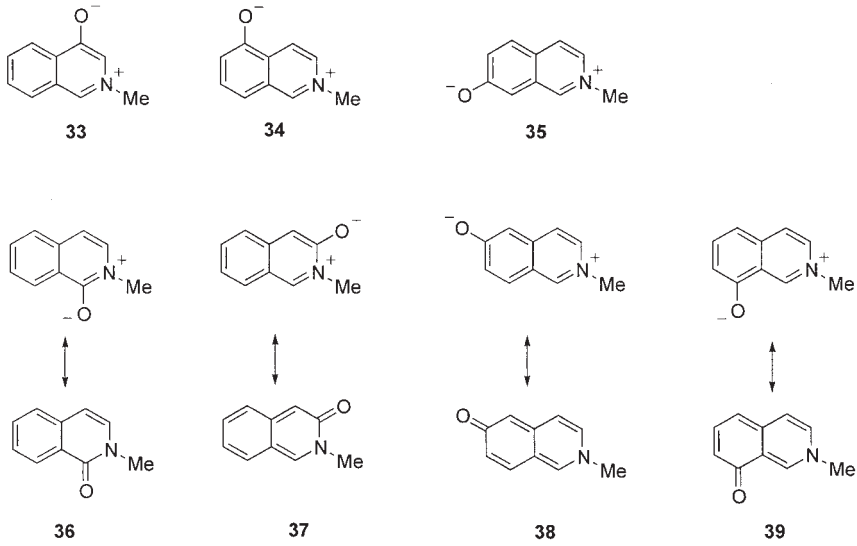
This compound had already been prepared by treatment of hydroquinone with pyridine and iodine (1901G256) or bromine (80IJC(B)718), or by vigorous reaction between benzoyl chloride, quinone, pyridine and copper (31CB1045) before it was identified as a natural product. Furthermore, a reaction of *p*-quinone with pyridine in the presence of water and hexachlorocyclotriphosphazatriene was described (70MI2). The formate and acetate were synthesized on reaction of *p*-benzoquinone with pyridine in the presence of formic acid and acetic acid, respectively (37CB2339). On deprotonation with sodium carbonate, the betaine forms (37LA51). The inolizine Ipohardine (**32**), the aromatic derivative of Ipalbidine, is an Ipomoea alkaloid isolated from *Ipomoea violacea*. The seeds of this plant are used as hallucinogens (79JCR(S)1, 86JOC3915). It is mentioned here, because of the structural relationship to **31B**, although deprotonation resulted in a cross-conjugated mesomeric betaine.

3. *Isoquinolinium-olates*

2-Substituted isoquinolinium-olates are isoconjugate with the methylnaphthalene anion as shown in Scheme 14. Joining negative structure elements—the olate function—to unstarred positions of the isoconjugate



Scheme 14



Scheme 15

heteroaromatic of the naphthalene anion results in heterocyclic mesomeric betaines. In all other cases covalent structures can be drawn.

Thus, *N*-alkylated isoquinolinium-4-, 5- and 7-olates **33**, **34** and **35** are mesomeric betaines, whereas the corresponding 1-, 3-, 6- and 8-derivatives **36**–**39** are lactams or ketones which may or may not adopt zwitterionic ground states (Scheme 15). The main question in view of heterocyclic mesomeric betaines in nature is whether the isoquinolinium derivatives exist as cationic species possessing a hydroxy group, or as betainic species with an olate function. The UV spectra of a wide range of *N*-heteroaromatic hydroxy compounds have been measured and it was found that tautomerism to the betainic forms is general amongst the nonalkylated monoaza hydroxy compounds. The concentration of the betainic form increases with conjugation between the oxygen and the nitrogen atoms and with the addition of fused benzene rings. By a comparison of the hydroxy compounds with the corresponding *N*-methyl derivatives it was concluded that the compounds with a hydroxy group α or γ to the ring-nitrogen atom tautomerize predominantly to the amide form in organic and aqueous solutions. The compounds with hydroxy groups neither in an α nor in a γ-position show a change of spectrum on changing the solvent from an organic solvent to an aqueous solution. The changes are due to the displacement of a single equilibrium process as the absorption curves taken in continously changing solvent mixtures of alcohol–water or

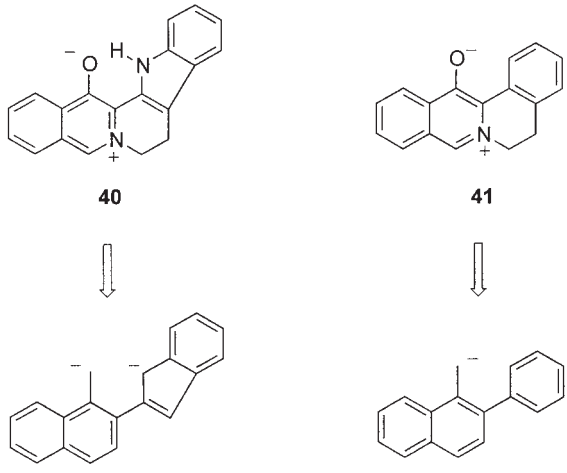
dioxane–water show a single set of isosbestic points. The conclusion is, the betainic and the neutral forms exist in equilibrium in solvents of high dielectric constant.

In general, the *N*-methyl derivative of a given compound absorbs at longer wavelengths than the O-methyl derivative. The intensity of a band which appears in aqueous solutions beyond the maximum absorption in alcohol and which is due to the absorption of the betainic species alone, is a measure of the tautomeric equilibrium. The pK_a value of the 2-methyl-hydroxyisoquinolinium chlorides increase in the order 4-hydroxy (4.93), 8-hydroxy (5.81), 6-hydroxy (6.02), 5-hydroxy (6.90), and 7-hydroxy (7.09 in water at 25 °C, respectively) (57JCS5010). Thus, 2-methyl-4-hydroxyisoquinolinium chloride is the strongest acid. The UV spectra of 2-methyl-isoquinolinium-5-olate (**34**) and 2-methyl-isoquinolinium-8-olate (**39**) were also presented (61BCJ533) and the formation of a quinoid structure of 2-methyl-isoquinolinium-6-olate (**38**) can also be detected by means of UV-spectroscopy.

a. Isoquinolinium-4-olates. Isoquinolinium-4-olate **33**, a structure element of some betainic alkaloids, was prepared as hygroscopic yellow needles on ion-exchange of 4-hydroxy-2-methylisoquinolinium iodide with Amberlite IRA-401 (72JCS(P1)2054). Under slightly basic conditions at pH 8.5, 4-hydroxy-2-methylisoquinolinium iodide has absorption maxima at $\lambda_{max} = 364$ (9660), 320 (3670), and 248 nm (9180). The tautomeric constants k_t = [Betaine]/[neutral form] of unsubstituted 4-hydroxyisoquinoline is 3.76 (57JCS5010, 58JCS674).

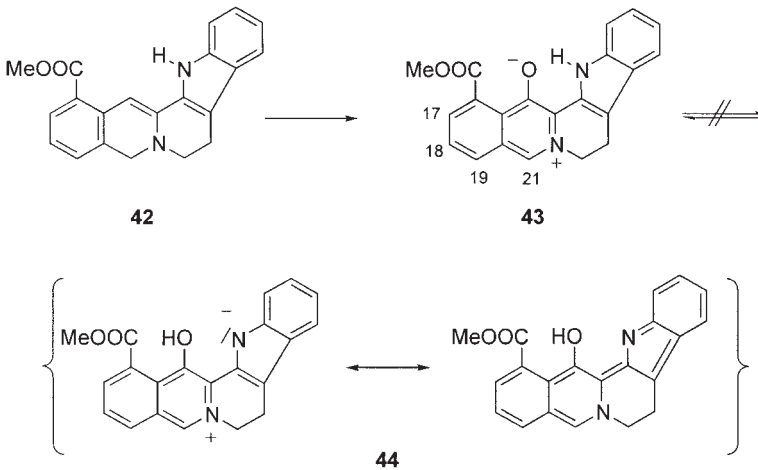
The alkaloids isolated from natural sources or derived by simple reactions from natural material possess the isoquinolinium-4-olate moiety as a partial structure of larger conjugated ring systems. In some alkaloids, the 3-position is substituted by an indole, forming the indolo[2′,3′:3,4]pyrido[1,2-*b*]isoquinolininium-14-olate ring system **40** (Scheme 16). Others possess the isoquino[3,2-*a*]isoquinolinium-13-olate ring system **41**. This substitution pattern enlarges the delocalization of the positive as well as of the negative charge. The ring system **40** is isoconjugate with the 2-(1*H*-inden-2-yl)-1-methyl-naphthalene dianion, which is an even nonalternant hydrocarbon dianion, so that these alkaloids belong to class 4. The ring system **41** is isoconjugate with the 1-methyl-2-phenyl-naphthalene anion and the 5-methyl-benzo[*a*]anthracene anion which are odd alternant hydrocarbon anions, respectively. They are therefore natural representatives of class 1 of heterocyclic mesomeric betaines.

Neooxygambirtannine (**43**) shown in Scheme 17 is an example of a heterocyclic mesomeric betaine belonging to class 4. This alkaloid, which is red in color, was found in Gambir and is a tanning material produced by



40 **41**

Scheme 16

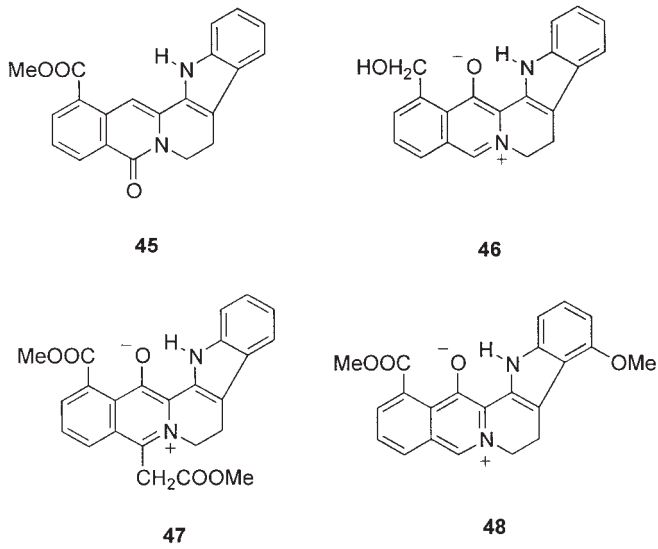


42 **43**

44

Scheme 17

evaporation of the aqueous extract of leaves and stems of the south-east Asian Rubiaceae *Uncaria gambier* (67T3129). Betaine **43**, which apparently is an oxidation product of Gambirtannine (**42**), is easily formed from Gambirtannine on alumina, when a hexane–acetone mixture is used as eluent. It is an isomer of Oxogambirtannine (**45**) and resembles Neooxyberberine (**52**), whose UV spectrum is quite similar. It is interesting to note that the indolic NH of **43** was unambiguously confirmed by a ^{1}H NMR resonance frequency at $\delta = 11.62$ ppm which is not exchangable



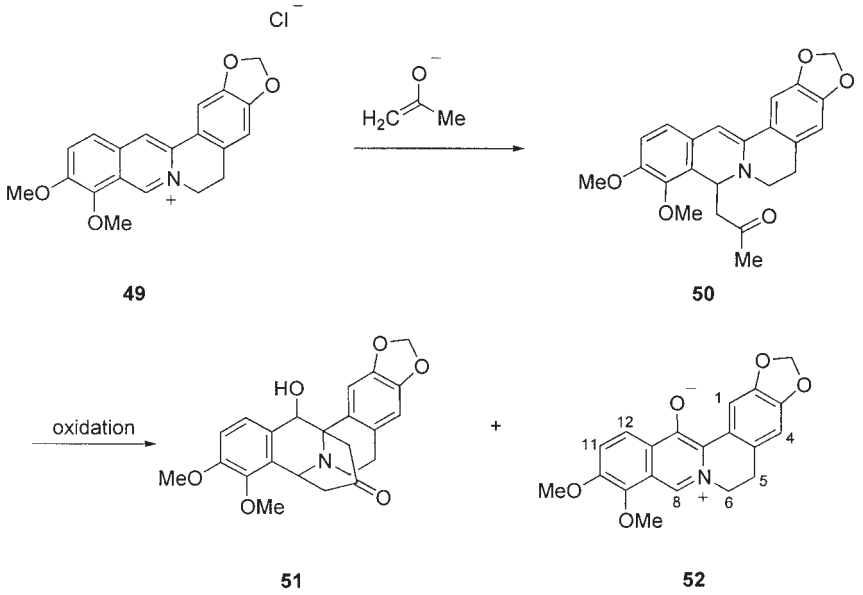
Scheme 18

with excess trifluoroacetic acid. Therefore, the zwitterionic structures **44** shown in Scheme 17 were excluded from consideration, although β-carboline alkaloids are known to adopt zwitterionic ground states (cf. Section III.E). The 21-H is strongly deshielded in ^{1}H NMR taken in $CDCl_3$ by the charged vicinal nitrogen atom ($\delta = 8.32$). 17-H appears at $\delta = 7.95$ with ortho and meta splittings. 18-H and 19-H form a multiplet at $\delta = 6.98$ ppm. The UV–VIS absorption maxima λ_{max} in 95% EtOH ($\log \varepsilon$) were found at 227.5 (31,900), 250 (26,100), 299 (9940), 394 (14,780), 403 (15,200), 490 (12,900) nm.

Two other alkaloids **47** and **48** were isolated in addition to Neooxygambirtannine **44** (67T3129). Anhydroalstonatine from *Alstonia venenata* is a closely related structure (77IJC(B)183) (Scheme 18).

Derivatives of Berberine (**49**), a protoberberine alkaloid, are widespread in nature and berberine-containing plants are used in virtually all traditional medicines (Ayurvedic, Chinese) dating back at least 3000 years (Scheme 19). Berberine (**49**) was isolated from *Hydratis canadensis* (''goldenseal''), *Coptis chinensis* (''goldenthread''), *Berberis aquifolium* (''Oregon grape'') and *Berberis vulgaris* (''barberry'') and others. Some mesomeric betaines derive from simple reactions starting from natural alkaloids.

The yellow–orange Neooxyberberine (**52**) (9,10-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoquino[3,2-*a*]isoquinolinium-13-olate; ''phenolbetaine of Berberine'', ''13-hydroxyberberinium phenol-betaine'') was already



Scheme 19

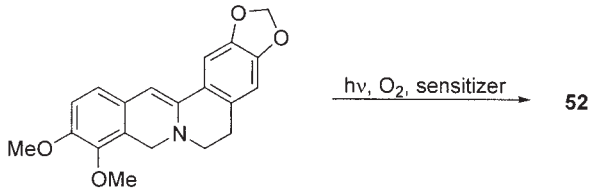
prepared in 1911 (11JCS1690, 65CB2566). Treatment of Berberine (**49**) with acetone anion results in the formation of ketone **50** (''Berberine acetone'', 8-acetonyldihydroberberine), a crystalline solid, which on oxidation with potassium permanganate yields Neooxyberberine–acetone (**51**) and Neooxyberberine (**52**) (73TL2795). The mesomeric betaine **52** is available in pure form by reaction of **50** with osmium tetroxide. Protonation gives the corresponding phenol (66JPJ534) and treatment with iodomethane and iodoethane yields the 13-methoxy and 13-ethoxy derivative, respectively (76CCC3654). The UV absorption maxima are as follows: λ_{max} (MeOH) = 236 (4.48), 258 sh (4.24), 312 (4.05), 365 (4.02), 444 (4.16) nm (84CPB2230). Neooxyberberine (**52**) has antimalarial (88JMC1084) and antimicrobial activities (98MI1). ^{1}H NMR data are presented in Table II (84CPB2230). The peak assignments for 11-*H* and 12-*H* are obviously incorrect in the original literature.

Dihydroberberine (**53**) is converted by irradiation in the presence of oxygen and Rose Bengal in 80% yield into Neooxyberberine (**52**) (Scheme 20). Applying the same reaction conditions without sensitizer yielded Berberine (77H953). Alternatively, reaction of dihydroberberine with *m*-chloroperbenzoic acid gave Neooxyberberine (75JOC644). The betaine can be used to synthesize a spirobenzylisoquinoline and methoxyberberal (77H1981).

Table II. NMR Chemical Shifts of Neooxyberberine **52** and the 8-Methoxyberberinephenolbetaine **58**

	^{1}H NMR[a]	
Atom	**52**	**58**
1	9.01, s	8.80, s
4	6.65, s	6.58, s
5	3.03, t, $J=6$ Hz	2.90, t, $J=6$ Hz
6	4.38, t, $J=6$ Hz	4.58, t, $J=6$ Hz
8	7.76, s	3.90, s (OMe)[b]
9	4.02, s (OMe)[b]	4.02, s (OMe)[b]
10	4.05, s (OMe)[b]	4.02, s (OMe)[b]
11	7.39, d, $J=9$ Hz	7.40, d, $J=9$ Hz
12	8.37, d, $J=9$ Hz	8.42, d, $J=9$ Hz
–OCH_2O–	5.97, s	5.91, s

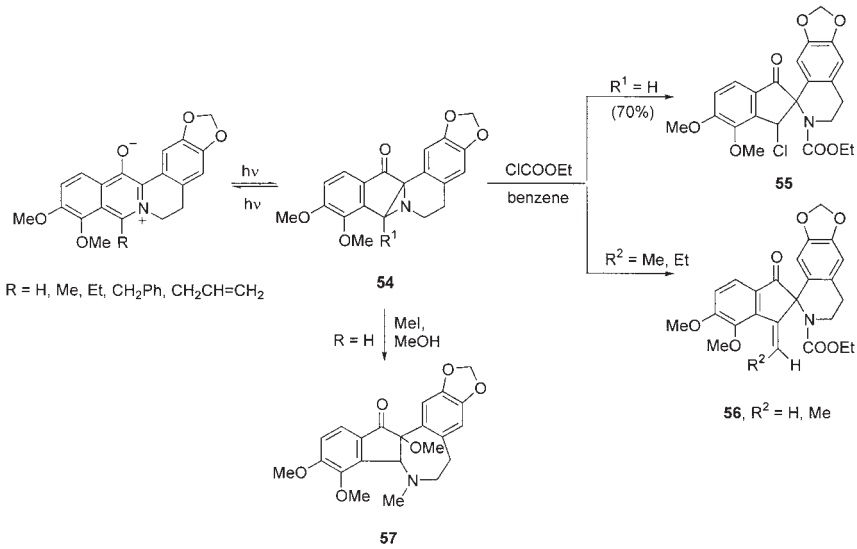
[a]In $CDCl_3$.
[b]Peak assignments exchangeable.



53

Scheme 20

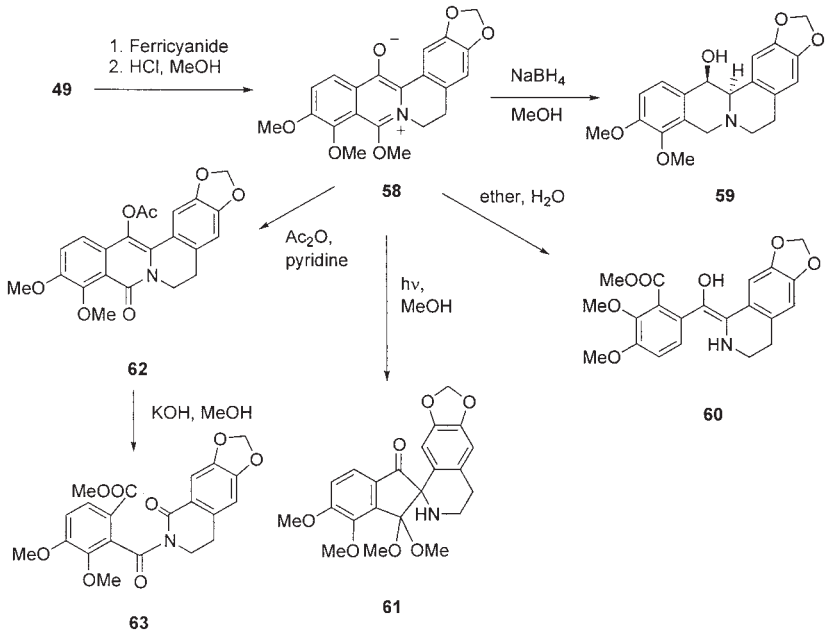
On irradiation of Neooxyberberine derivatives in methanol through a Pyrex filter in a stream of nitrogen 8,14-cycloberbines **54** were formed in 70% yield (Scheme 21). The ring system is unexpectedly stable as conrotatory ring cleavage of the aziridine is thermally disallowed. Irradiation without Pyrex filter yielded the orange-colored starting material in 55% yield through a photochemically allowed disrotatory ring opening (84CPB2230). Ethyl chloroformate in benzene converts **54** into spirobenzylisoquinoline **55** (R = H, 70% yield), methylidene-spiroisoquinolinine (R = Me, 100%), a mixture of *E*- and *Z*-ethylidene-spiroisoquinoline and an oxazolidinone derivative (R = Et). Methylation of the unsubstituted derivative gave the benzindenoazepine **57** in 60% yield, whereas the methyl- and ethyl derivative were converted into spiro compounds similar to **55** and **56** (*N*-methyl instead of *N*-COOEt).



Scheme 21

The orange colored 8-methoxy derivative of Neooxyberberine (**58**) (8,9,10-trimethoxy-5,13*a*-dihydro-6H-[1,3]dioxolo[4,5-*g*]isoquino[3,2-*a*] isoquinolium-13-olate, "8-Methoxyberberinephenolbetaine") was formed on ferricyanide oxidation of Berberine (**49**) and subsequent treatment with methanolic hydrogen chloride (76JA6714). The 8-ethoxy derivative was prepared similarly (79JOC4337). The UV absorption maxima λ_{max} in EtOH ($\log \varepsilon$) of **58** were found at 235 (4.22), 262 (4.15), 317 (4.13), 362 (3.92), 377 (4.12), 464 (4.13) nm (83CPB947) and are in good agreement with a structure related to **52**. The ^{1}H NMR values are presented in Table II (77H895). Reported NMR data in the literature are obviously incorrect.

Scheme 22 presents the synthetic potential of this mesomeric betaine. The alkaloid Ophiocarpine (**59**) was formed from the betaine on reduction with sodium borohydride. Treatment of the betaine with wet diethylether, a solvent in which it is only slightly soluble, resulted in the formation of the dehydronorhydrastine methyl ester **60** in 80% yield. Methyl anhydroberberilate (**63**) was formed in a two-step-procedure on treatment of the betaine **58** with acetic anhydride in pyridine. The resulting 13-acetoxyoxoberberine (**62**), which was formed in 95% yield, gave the target alkaloid on addition of methanolic potassium hydroxide (79JOC4337). Irradiation of the betaine effects a valence isomerization to give an aziridine derivative as an intermediate, which undergoes ring

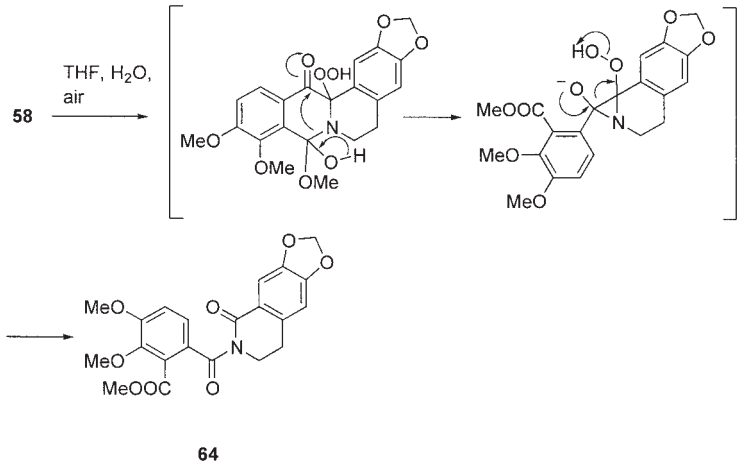


Scheme 22

cleavage to the spiro compound **61**. This is a model compound for spirobenzylisoquinoline alkaloids (84CPB2230).

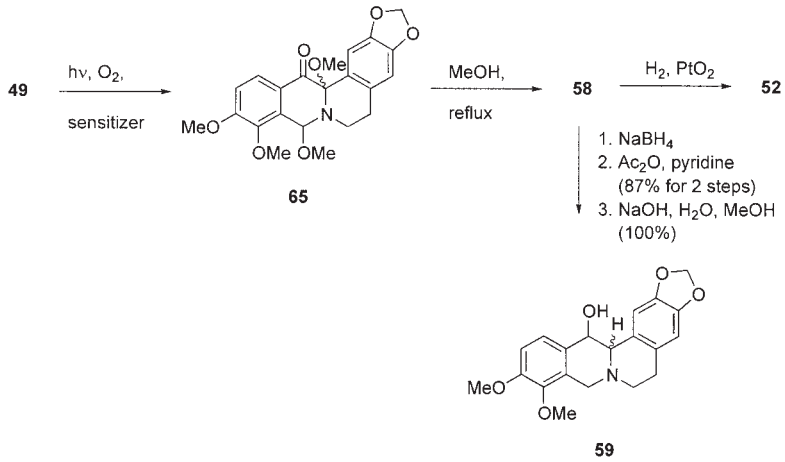
In contrast to the reaction of the betaine **58** in wet diethylether, wet THF, in which the betaine is better soluble, gives the methyl isoanhydroberberilate **64** in 71% yield. The mechanism seemingly involves an unusual carbon to nitrogen acyl migration as shown in Scheme 23. Hydration and air oxidation of the betaine to the peroxide leads to the formation of an aziridine intermediate and loss of a hydroxide anion (77TL3787).

Irradiation of Berberine (**49**) (400W high-pressure Hg lamp, Pyrex filter) in methanol in the presence of Rose Bengal and sodium methoxide in a stream of oxygen gave the methoxy derivative **65** in 59% yield (Scheme 24). Recrystallization from methanol gave the orange-colored 8-methoxyberberinephenolbetaine (**58**) in quantitative yield. A possible mechanism for this transformation involving the initial attack of methoxide ion on a 8-methoxydihydroberberine, and reaction of the resulting enamine moiety with singlet oxygen to form an oxetane was discussed (83CPB947). Here, betaine formation is a consequence of aromatization. The phenolbetaine was converted into racemic Ophiocarpine (**59**) as shown in Scheme 24 (77H895). Betainic azaberbinones were also described (70JCS(CC)1601, 87H1841).



64

Scheme 23

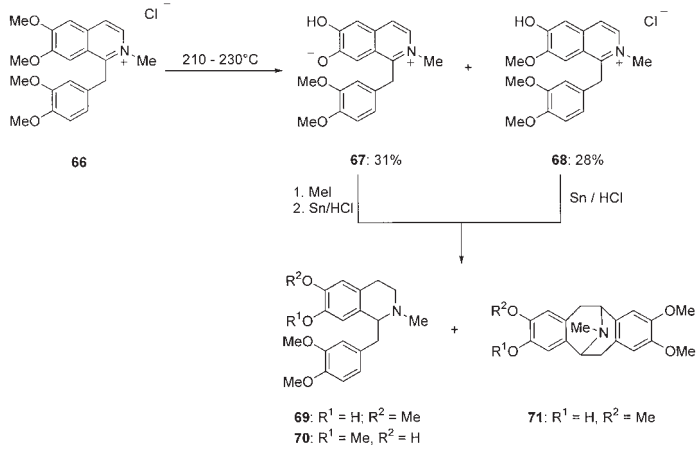


Scheme 24

b. Isoquinolinium-7-olates. 2-Methyl-7-hydroxyisoqinolinium iodide (**66**) in methanol exists as a mixture of neutral and cationic species, as evidenced by a complex absorption of seven peaks in the UV spectra (61BCJ533) (Scheme 25). In general, formation of a phenolate group causes a red shift which is enlarged by protonation of the nitrogen atom. The shift for the π_1-band is the largest. As UV spectroscopy is an important method for the detection of betaines, the characteristic features are mentioned here. The absorption maxima of 2-methyl-7-hydroxyisoquinolinium iodide in

66

Scheme 25



66 **67**: 31% **68**: 28%

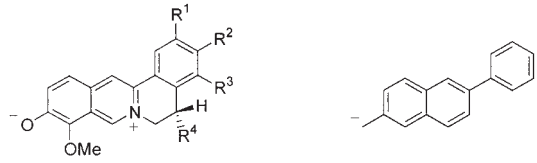
69: R^1 = H; R^2 = Me
70: R^1 = Me, R^2 = H
71: R^1 = H, R^2 = Me

Scheme 26

methanol/0.1 N HCl are found at λ_{max} ($\log \varepsilon$) = 217 (4.48), 243 (4.71), 280/367 (3.72/3.54), whereas in methanolic 0.1 N NaOH the maxima are observable at λ_{max} ($\log \varepsilon$) = 217 (4.39), 265 (4.64), 308/424 (3.86/3.38), corresponding to π_3, π_2/π_1, respectively. Obviously, bathochromic shifts are characteristic for betaine formation from salts.

On heating Papaverinium chloride (**66**) beyond its melting point for some minutes a separable mixture of Protopapaverinium betaine (**67**) and Norpapaverinium chloride (**68**) was formed (Scheme 26). The dipolar 6,7-dihydroxyisoquinolinium **67** can form a conjugated mesomeric betaine (7-olate form) or a zwitterionic species (6-olate) (cf. Section III). It can be converted into its methyl derivative by methyl iodide in a sealed tube. The reduction gave Codamine (**69**), Pseudolaudanine (**70**) and Argemonine (**71**). By this work the structure of Argemonine, first isolated from the desert poppy *Argemone hispida* (44MI1), was elucidated (66TL1177).

Dehydrodiscretamine (**72**), Thalifedine (**73**), Thalidastine (**74**), Fissisaine (**75**), Stepharanine (**76**), and Dehydrocorydalmine (**77**) are additional examples of alkaloids, which possess the 7-hydroxy-isoquinoline moiety which on deprotonation yields conjugated mesomeric betaines (Scheme 27). In either case, the π-electron system is extended by substitution

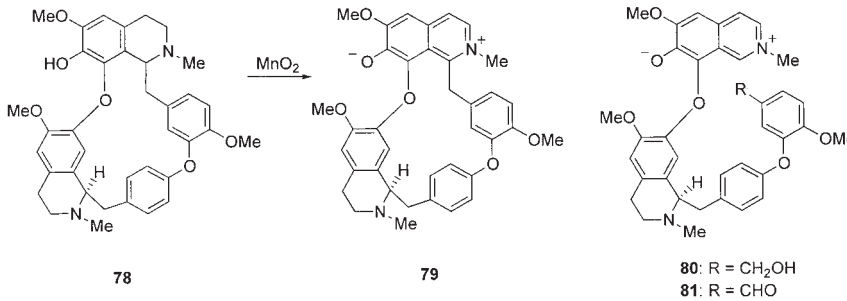


72: R^1 = OMe, R^2 = OH, R^3 = R^4 = H
73: R^1-R^2 = -O-CH_2-O-, R^3 = R^4 = H
74: R^1-R^2 = -O-CH_2-O-, R^3 = H, R^4 = OH
75: R^1 = R^2 = OMe, R^3 = OH, R^4 = H
76: R^1 = OH, R^2 = OMe, R^3 = R^4 = H
77: R^1 = R^2 = OMe, R^3 = R^4 = H

Scheme 27

of the 3-position by an additional aromatic substituent. These six alkaloids represent members of class 1 of mesomeric betaines as they are conjugated heterocyclic mesomeric betaines isoconjugate with the 2-methyl-6-phenyl-naphthalene anion, which is an odd, alternant hydrocarbon anion.

The protoberberine alkaloids Dehydrodiscretamine (**72**), Fissisaine (**75**), and Columbamine (not a mesomeric betaine) were found in the twigs of the Chinese and Vietnamese climbing shrub *Fissistigma balansae* in 1998 (98P367). Extraction was performed with 3% HCl, but final purification was accomplished by column chromatography using chloroform, methanol, and ammonia (100 : 5 :1). In the spectra of Fissisaine (**75**), seemingly, no OH-group was observed in the ^{1}H NMR spectra, however, the authors report a band at 3400 cm^{-1} in the IR spectrum for the hydroxyl group. On addition of alkali the typical bathochromic shifts of phenolic berberine-type betainic alkaloids are observable (72MI1). As no anion is described in the original literature, the existence of these alkaloids as betaines or salts in the natural material remaines unanswered. Dehydrodiscretamine (**72**), however, was isolated earlier as an orange colored chloride (*Corydalis tashiroi* MAKINO) (81MI2). On investigating the natural products contained in *Thalictrum foliolosum* DC., a herb indigenous to the temperate Himalayas which is used for the treatment of flatulence, jaundice and visceral obstructions, 11 alkaloids were isolated (83P2607), among them Dehydrodiscretamine (**72**), Thalifendine (**73**), Thalidastine (**74**). The alkaloids were isolated as chlorides after treatment with the anion exchange resin in its Cl^- form (83P2607). The formation of a betainic species from Dehydrodiscretamine (**72**) displays a characteristic bathochromic shift on addition of base, although deprotonation of the 6-hydroxy group would result in the formation of a



Scheme 28

neutral structure (cf. Section III.A). Thus, UV absorption maxima λ_{max} (MeOH) (log ε) of **72** were found at 434 (3.60), 346 (4.29), 273 (4.26), 263 sh (4.25), 237 sh (4.22) nm, whereas maxima were found in a mixture of methanol and sodium hydroxide at 505 (3.60), 386 (4.50), 302 sh (4.10), 278 (4.23), 255 (4.20) 235 sh (4.14) nm. Thalifendin (**73**) had already been described as a yellow phenolic alkaloid from *Thalictrum fendleri* (65TL3595) and *Thalictrum minus* var. *adiantifolium* (69MI1) before it was isolated from other species. Thalidastine chloride (**74**) was first isolated from *Thalictrum fendleri* (65TL3825). A similar bathochromic shift of the UV absorption maxima were observed on addition of base [λ_{max} (MeOH) (log ε) = 425 (3.36), 350 (4.02), 273 (4.09), 231 (4.15) nm; λ_{max} (MeOH+KOH) = 476, 378, 290] which is due to the formation of a conjugated mesomeric betaine. Stepharanine (**76**) was identified in *Stephania glabra* (67JOC3253, 80MI2, 82JNP407) and in extracts of the roots of *Tinospora capillipes*. It was isolated as an iodide after anion exchange. Methylation with dimethylsulfate gave palmatine chloride. An additional alkaloid of this series is Dehydrocorydalmine (**77**) (*Stephania glabra*).

The isoquinolinium-7-olate moiety is also part of a macrocyclic system in the orange-colored Fenfangjines D (**79**) (Scheme 28). The Fenfangjines D (**79**), H (**80**), and I (**81**) were identified in methanolic extracts of the roots of *Stephania tetrandra* (Fen-fang-ji) on plant monitoring of the inhibitory activity on angiotensine I converting enzyme (ACE). The Chinese traditional medicine Fen-fang-ji is demonstrated to have antiinflammatory, antiallergic, and hypotensive effects. Fangchinoline (**78**) was converted into Fenfangjine D (**79**) on treatment with manganese dioxide (88H1149). Fenfangjine H (**80**) and I (**81**), which are cleaved structures of Fenfangjine D (88H1149), showed hydroxyl groups at 3408 and 3412 cm^{-1}, respectively, in the IR spectra, so that the protonated form was formulated as a hydroxide salt. However, no aromatic OH group of Fenjangjine H and I were detected in ^1H NMR in $CDCl_3$ and no elemental analyzes were presented to confirm

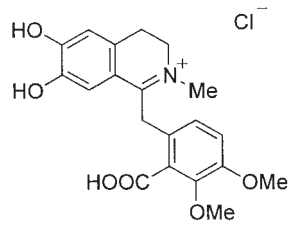
Table III. NMR Chemical Shifts of the Isoquinolinium Moiety of Dehydrodiscretamine **72**, Stepharidine **76**, and the Fenfangjines D **79**, H **80**, and I **81** (Isoquinoline Numbering)

	72[a]	**76**[b]	**79**[c]	**80**[c]		**81**[c]	
Atom	^{1}H NMR	^{1}H NMR	^{1}H NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
1	9.50, s	> 9.00[d]	–	8.59, s	134.7	8.66, s	134.3
3	–	–	7.86, d, $J=6.6$ Hz	7.42, d, $J=6.4$ Hz	126.8	7.43, d, $J=6.4$ Hz	127.6
4	8.53, s	8.50, s	7.75, d, $J=6.6$ Hz	7.40, d, $J=6.4$ Hz	121.8	7.36, d, $J=6.4$ Hz	121.5
4a	–	–	–	–	126.8	–	126.3
5	7.93, m	7.93, m	6.53, s	6.81, s	100.8	6.85, s	100.7
6	7.93, m	7.93, m	–	–	165.6	–	166.0
7	–	–	–	–	158.6	–	159.3
8	–	–	–	–	132.4	–	132.5
8a	–	–	–	–	122.1	–	122.3

[a]As chloride in a mixture of $CDCl_3$, CD_3OD, TFA.
[b]As iodide in TFA.
[c]In $CDCl_3$.
[d]Spectrum terminated at $\delta = 9.00$.

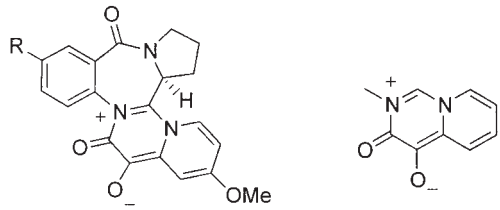
the existence of an anion (98H311). In addition, a comparison of the chemical shifts with the series of NMR experiments published for the alkaloid PO-3 (**129**, Section II.A.8) strongly hint at a mesomeric betaine instead of a cationic species. This is furthermore confirmed by a comparison of the resonance frequencies of the Fenfangjines **80** and **81**, Dehydrodiscretamine (**72**), and Stepharanine (**76**) are presented in Table III. The spectra of **72** and **76** were determined in the presence of TFA so that the cationic species were measured. Thus, Table III presents a ^{1}H NMR spectoscopic comparison between cationic and betainic molecules. The signals of the Fenfangjines appear considerably upfield and unambigously prove the existence of mesomeric betaines. A considerable upfield shift of all the protons of the isoquinoline moiety is obviously characteristic for betaine formation.

Leptopinine **82** possesses the 3,4-dihydro-isoquinolin-7-ol moiety without further conjugation and was isolated as yellow powder from *Hypecoum leptocarpum* after several extractions with hydrochloric acid so that this alkaloid was finally isolated as a chloride (Scheme 29). The formation of a mesomeric betaine from this dihydroisoquinoline derivative is unlikely because on addition of base no significant changes of the UV spectra were observed (99P339). A similar structure is Pycnarrhine (*Pycnarrhena longifolia*), which was isolated as a hydroxide (81P323).



82

Scheme 29

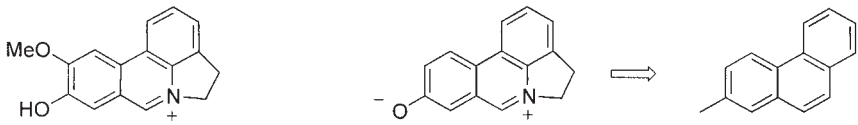


83: R = OMe
84: R = H

Scheme 30

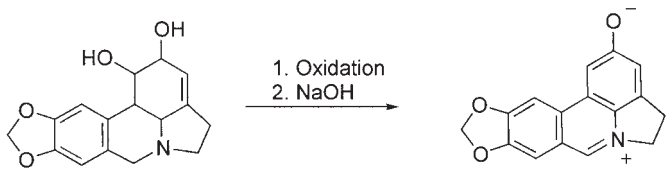
4. *3-Oxo-pyrido[1,2-c]pyrimidinium-4-olate*

Circumdatin A (**83**) and B (**84**) were isolated as red–orange solids from a culture of the fungus *Aspergillus ochraceus* (99JOC1689) (Scheme 30). These highly unusual structures belong to the class of benzodiazepine alkaloids and represented the first betainic naturally occurring benzodiazepines. The structure proposals are based on $^{1}J_{CC}$-INEPT2-INADEQUATE in combination with $^{1}J_{CC}$-HMBC-INADEQUATE experiments. The UV absorption maxima λ_{max} of Circumdatin A in ethanol were found at 357 (3.30), 290 (shoulder, 3.33), 238 (shoulder, 3.84), and of Circumdatin B at 358 (2.76), 284 (shoulder, 2.73). The ^{1}H and ^{13}C NMR data of the isolated alkaloids are presented in the original literature. The parent 3-oxo-pyrido[1,2-*c*]pyrimidinium-4-olate moiety, however, seemingly is without precedent in the chemistry of heterocyclic mesomeric betaines so that the unambiguous structure elucidation of Circumdatin A and B still await confirmation by a total synthesis or at least by the preparation of model compounds for spectroscopic comparison (02UPI2). Recently, an interesting N-oxide was isolated from this fungus (01JAN911).



85

Scheme 31



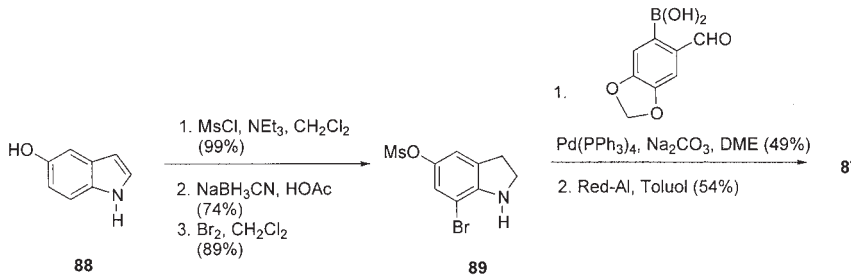
86 **87**

Scheme 32

5. *Phenanthridinium-olates*

8-*O*-Demethylvasconine (**85**) (9-methoxy-5-methyl-phenanthridin-8-olate) presented in Scheme 31 was found in *Crinum kirkii* (95P1291) (Amaryllidaceae). Although published as cation, no information about the anion of this alkaloid is given. Its relationship to other alkaloids of this class, however, makes a betainic structure more than likely and this is confirmed by a comparison of the ^{1}H NMR data of **85** with the cationic and betainic alkaloids presented in Table III. This betaine is isoconjugate with the 2-methylphenanthrene anion and thus defined the alkaloid as a member of class 1 (odd alternant hydrocarbon anions). Whereas substitution of the isoconjugate phenanthridinium moiety at the 1-position with an anionic fragment results in zwitterions (cf. Section III.D), the phenanthridinium-2-olate is a mesomeric betaine.

The betainic structure of the pyrrolophenanthridinium alkaloid Ungeremine (**87**) (*Amaryllidaceae*) (86P2399) is unambiguous (Scheme 32). The parent 1-methyl-quinolinium-6-olate moiety has been known since 1891 (1891JPR522). It was first identified in *Ungernia minor* in 1965 (65MI1, 96MI3, 92P2139, 70MI1), but was already synthesized as early as 1955 (55JA5885): A dark red compound was obtained on oxidation of the alkaloid Lycoporine (**86**) by selenium dioxide, *t*-butyl hypochlorite, pyridine perbromide hydrobromide, or *N*-bromosuccinimide, to which the structure of Ungerimine was assigned. In the protonated form the pK_a value is 7.15 in



Scheme 33

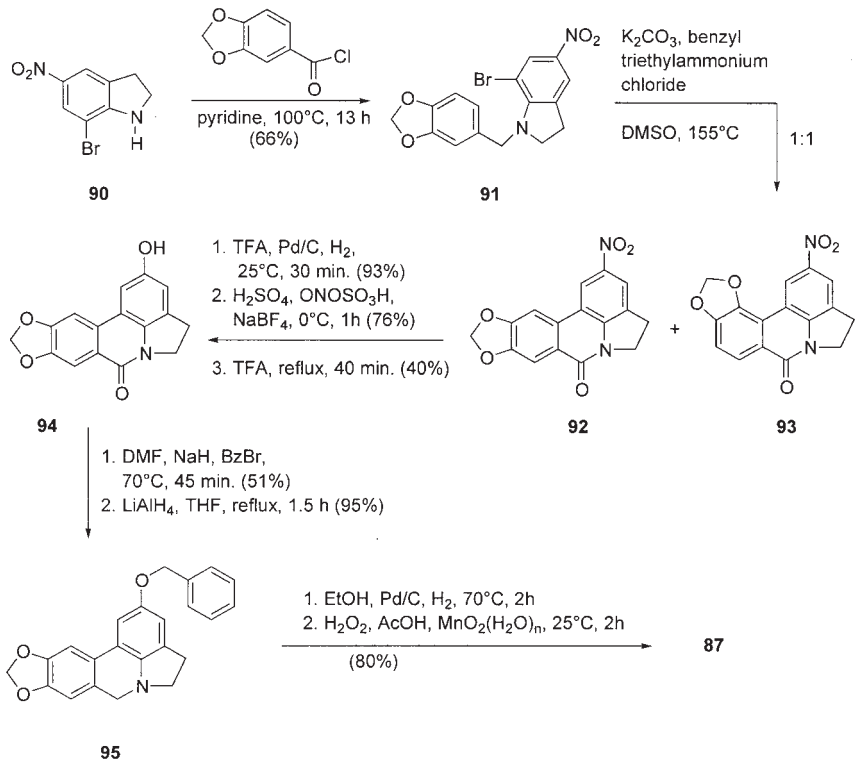
water at 20 °C. As expected, the UV absorption maxima of Ungerimine shift bathochromically on addition of base. Thus, λ_{max} values were found at 360 and 258 nm in methanol plus 0.1 M HCl, and at 408 and 262 nm in methanol plus 0.1 M NaOH.

Later, Ungerimine (**87**) was isolated from *Crinum americanum* (86P2399), *Crinum asiaticum*, and *Zephyrantes flava*. It has aroused considerable interest due to its anti-cancer activities (97MI2, 89MI1, 88MI2, 87MI1, 83MI1, 81MI1, 80MI1, 78JMC199) especially against human ovarian and stomach cancers (97MI3, 82MI1). In general, this class of alkaloids attracted considerable attention due to its anti-leukemia (78JMC199) and other pharmacological activities (91TL65, 90TL1523).

The first total synthesis of **87** was published in 1990 (90TL1523). 5-Hydroxyindole (**88**) was mesylated and then reduced with sodium cyanoborohydride to give an indoline which was brominated to afford the bromoindoline **89** in good yield (Scheme 33). Cross-coupling with *ortho*-formyl boronic acid under Suzuki conditions, followed by air oxidation of the resulting cyclized product, followed by reduction of the lactam formed with excess Red-Al gave the target compound **87**.

In 1991, another total synthesis of **87** was described (91TL65). Starting from the indoline **90**, amidation with benzo[1,3]dioxole-5-carbonyl chloride gave the precursor **91** for a radical cyclization which is the key step of the synthesis (Scheme 34). On treatment with potassium carbonate and benzyl triethylammonium chloride in DMSO at elevated temperatures a nitrophenyl radical is formed which is quenched by reaction with an adjacent phenyl group. The resulting 1:1 mixture of **92** and **93** was separated by fractional crystallization to give 27% of pure **92**. Diazotization, phenol formation to **94**, subsequent reduction of the amide function to **95** and oxidation gave the target compound Ungerimine (**87**).

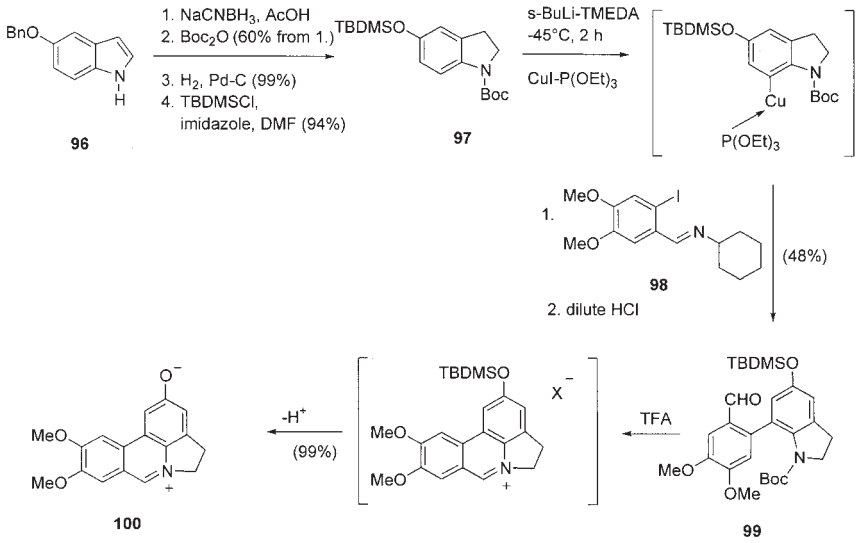
Criasbetaine (**100**) was isolated from *Crinum asiaticum* (98MI2, 90P805, 86P1975, 86JCR(S)112, 56JA4145). Syntheses of Ungerimine and



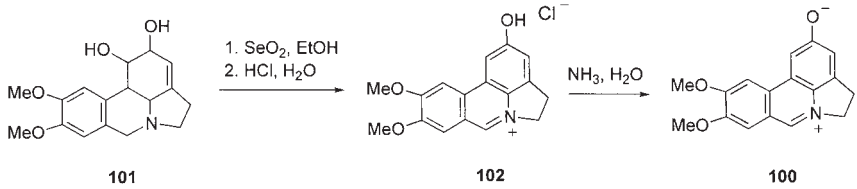
Scheme 34

Criasbetaine were published in 2000 (00JOC3227). Starting from 5-benzyloxyindole (**96**), reduction to the corresponding indoline, protection as a *t*-BOC carbamate and deprotection using hydrogen and palladium catalyst gave the starting material 1-BOC-5-hydroxyindoline (Scheme 35). Protection as *tert*-butyldimethylsilyl (TBDMS) ether to **97**, the lithiation—transmetalation—Ziegler–Ullmann coupling sequence with the iodoarylimine **98** was applied to result in the formation of **99**. Refluxing trifluoroacetic acid over a period of 16 h promoted the BOC removal, cyclization-dehydration, a desilylation sequence to Criasbetaine (**100**) which was finally obtained as a trifluoroacetate. A similar reaction sequence led to Ungerimine (**87**).

In 1956, the alkaloid Methylpseudolycorine (**101**) isolated from the King Alfred daffodil (*Narcissus pseudonarcissus* L.) was oxidized to the pale yellow chloride with selenium dioxide (Scheme 36). Conversion into the betaine was accomplished by aqueous ammonia to give yellow prisms of the trihydrate of Criasbetaine (**100**) (56JA4145, 56JA4151). The UV absorption



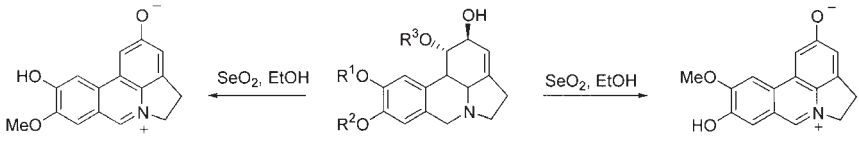
Scheme 35



Scheme 36

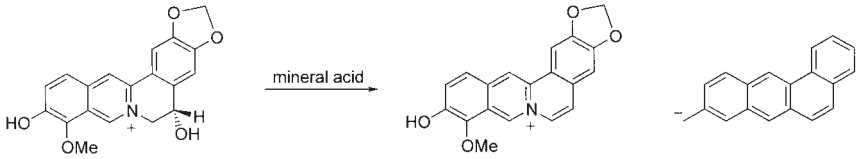
maxima are shifted to higher wavelengths on conversion of the cationic species **102** into the betaine.

Another 2-oxyphenanthridinium betaine-type alkaloid is Zefbetaine (**103**), isolated from the Egyptian sea lily *Pancratium maritimum* L. as an amorphous pale yellow solid (92P2139). It was first isolated from the lily *Zephyranthes flava* (86P1975), however, the reported structure proved to be incorrect. Its UV spectrum in MeOH shows absorption maxima at 409, 372, 262 nm, which is indicative of the existence of a betainic species. Zefbetaine became red when sprayed with Fast Red Salt B, a reagent for polyvalent phenols, and gave positive results when tested with 1% aqueous iron(III) chloride. The structure of Zefbetaine was established by means of ^{1}H NOE difference spectra as well as chemical synthesis. Thus, on treatment of **104** with selenium dioxide Zefbetaine (**103**) was formed in good yield (Scheme 37). On the other hand, oxidation of



103 **104**: R^1 = H, R^2 = Me, R^3 = H; **105**: R^1 = Me, R^2 = H, R^3 = Ac **106**

Scheme 37



74 **107**

Scheme 38

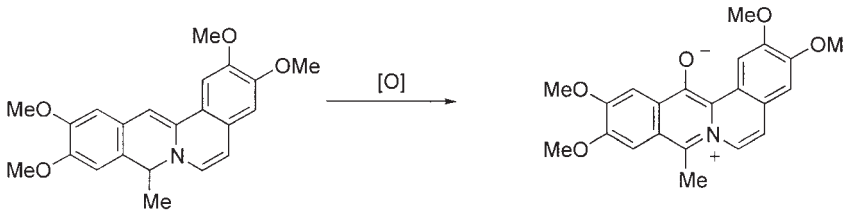
Sternbergine (**105**) form *Sternbergia lutea* Ker Gawl (84JNP1003) resulted in the formation of an isomeric species called *iso*-Zefbetaine (**106**). The ^{1}H NMR values of Zefbetaine shift downfield on changing the solvent from CD_3OD to CD_3OD–CD_3CO_2D = 3:1 which is also indicative of a betainic species.

6. *Isoquino[3,2-a]isoquinolinium-olates*

Mineral acids convert Thalidastine (**74**) into Deoxythalidastine (**107**) (60JA1145, 61JOC2231, 62JOC2213) which after deprotonation is isoconjugate with the 9-methyl-benzo[*a*]anthracene anion (Scheme 38).

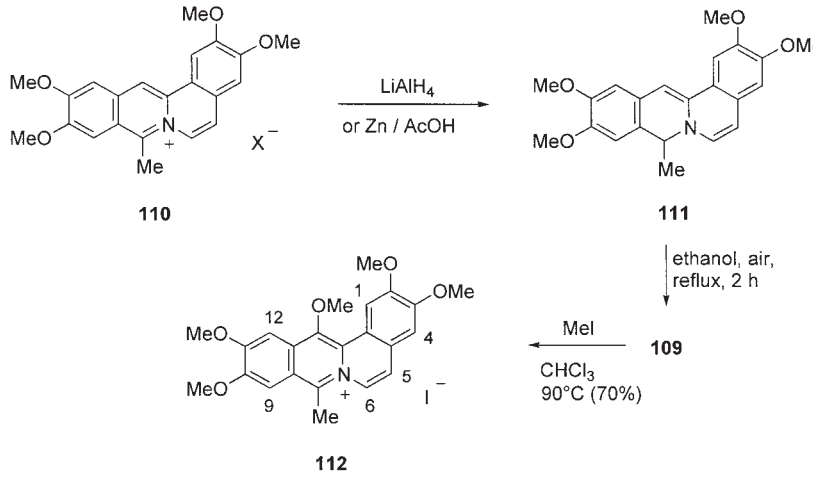
Similarly, photooxidation of dihydrocoralyne (**108**) in hot methanol at pH 8, subsequent addition of sodium methoxide and additional irradiation yielded 6,7-dimethoxyisoquinolone and 3-methyl-3,5,6-trimethoxyphthalide via the betainic intermediate **109** (77H45) (Scheme 39). It was demonstrated earlier that dihydrocoralyne is oxidized to this betaine in quantitative yields under physiological conditions (76H153). The autooxidative degradation of the mesomeric betaine was rationalized by the addition of singlet oxygen.

The coralyne salt **110** was reduced to **111**, a 5,6-dehydro analogue of dihydroberberine (Scheme 40). A solution of **111** in hot ethanol kept in the dark resulted in the almost quantitative formation of the coralyne-13-olate **109** as orange needles by autooxidation. No anion was found by elemental analysis. Treatment of **109** in ethanol with 10% hydrochloric acid resulted in



108 **109**

Scheme 39



110 **111** **109** **112**

Scheme 40

the formation of 13-hydroxy-2,3,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium chloride, which was isolated as yellow needles. As evidenced by the UV spectra, this salt is in equilibrium with the betainic form in alcohols. This is confirmed by a methylation of **109**, which was accomplished by methyl iodide to give yellow needles of 13-methoxycoralyne iodide (**112**). On methylation the absorption maximum of the betaine at $\lambda_{max} = 466-470$ nm disappears. UV and ^{1}H NMR spectroscopic comparisons of the betainic and the methylated cationic molecule are given in Tables IV and V, respectively (80JCS(P1)911). On methylation of the 13-olate function, the resonance frequencies of 4-*H*, 5-*H*, 6-*H*, and 9-*H* shift considerably to lower field, whereas the signals of 1-*H* and 12-*H* shift upfield. The shift difference $\Delta\delta$ of 6-*H* is the largest (−1.04 ppm).

Norcoralyne (**113**) was reduced with zinc in acetic acid and 1% hydrochlorid acid in 88% yield to give the 13-hydroxy-norcoralynium

Table IV. NMR Spectroscopic Comparison Between Coralyne-13-Olate **109**, 13-Methoxy Derivative **112**, and the Alkaloid **117**

	109[a]	**112**[b]	**117**[c]	
Atom	^{1}H NMR	^{1}H NMR	^{1}H NMR	^{13}C NMR
1	10.83	8.97	8.15	107.9
2	4.17 (OMe)	4.13 (OMe)	–	154.3
3	4.22 (OMe)	4.18 (OMe)	6.82	113.4
4	6.96[c]	7.57[c]	7.38	113.0
4a	–	–	–	136.6[d]
5	7.14, d, $J=9$ Hz	7.90, d, $J=8$ Hz	8.17	118.3
6	7.82, d, $J=9$ Hz	8.86, d, $J=8$ Hz	8.45	137.2
8	2.80 (Me)	2.50 (Me)	9.39	138.6
8a	–	–	–	122.2
9	6.83[c]	7.57[c]	7.66	106.6
10	3.98	3.96 (OMe)	–	152.5
11	3.98	3.96 (OMe)	7.19	119.4
12	8.17	7.81[c]	7.72	114.0
12a	–	–	–	131.7[d]
13	–	4.00 (OMe)	–	188.7
14	–	–	–	115.5
14a	–	–	–	131.4[d]

[a]In DMSO-d_6.
[b]In $CDCl_3$.
[c]In acetone-d_6.
[d]Peak assignments exchangeable.

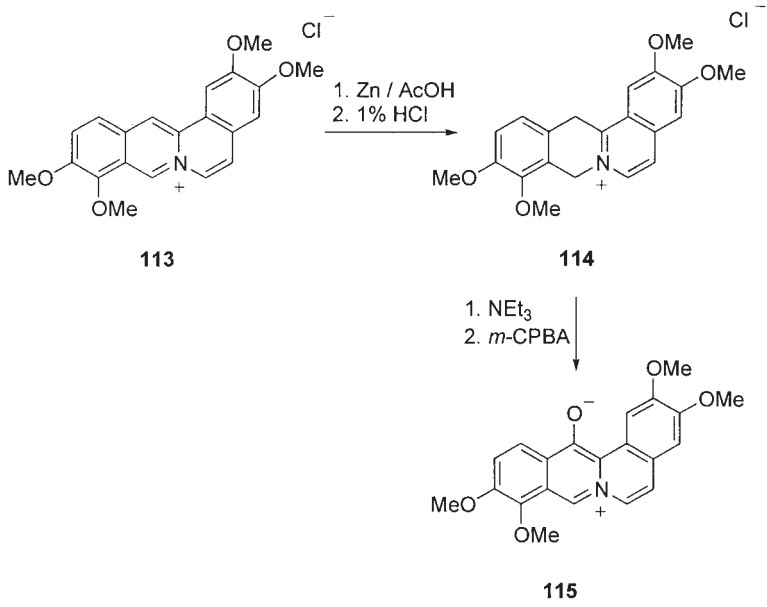
Table V. UV Spectra of Coralyne-13-Olate **109**, its Hydrochloride Salt **109** · HCl, and its Methoxy Derivative **112**

	λ_{max} [nm] (log ε)
109[a]	466 (4.15), 439 (4.09), 411 (4.00), 323 (4.24), 288 (4.37)
109 · HCl[b]	470 (3.39), 442 (4.01), 419 (3.88), 367 (3.45), 330 (4.26), 314 (4.22), 304 (4.22)
112[b]	436 (3.98), 414 (3.83), 390 (3.51), 367 (3.54), 331 (4.28), 316 (4.37), 305 (4.34)

[a]In MeOH.
[b]In EtOH, from 80JCS(P1)911.

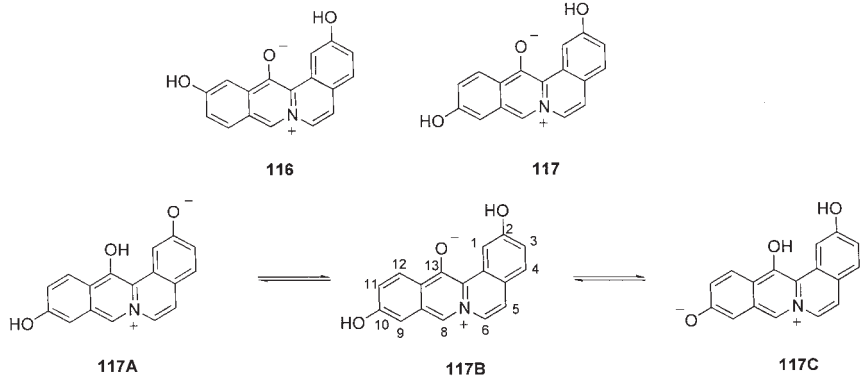
phenolbetaine (**115**) after the addition of *m*-chloroperbenzoic acid to a degassed solution of **114** in the presence of triethylamine (Scheme 41). A photochemical conversion of the partially reduced species to the betaine failed. Instead, the formation of the starting material was observed (77H959).

Despite of ^{1}H–^{1}H–COSY, ^{1}H–^{1}H–NOESY, and ^{1}H–^{13}C–COSY experiments the position of the second hydroxy group of an amorphous red



113 **114** **115**

Scheme 41



116 **117** **117A** **117B** **117C**

Scheme 42

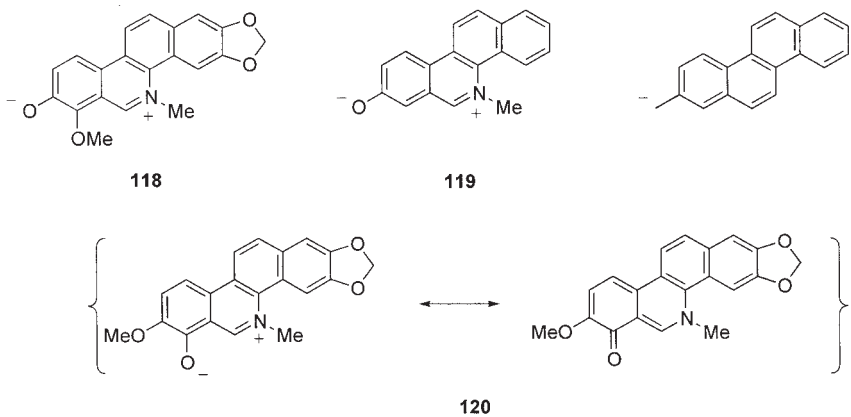
alkaloid and its glycosyl derivative isolated from *Aristolochia arcuata silvestris* could not unambigously be elucidated so that the two possible structures **116** and **117** were published (Scheme 42). As the compounds are presumably related to 8-benzylberberine and benzylisoquinoline alkaloids isolated from *Aristolochia* species, the authors suggest L-tyrosine and 4-hydroxybenzaldehyde as biosynthetic precursors. From this viewpoint the 7-hydroxyisoquinoline moiety **117** is the more likely structure (95P991).

As the alkaloid was extracted with hexane, acetone, and ethanol, subjected to column chromatography, acidified (AcOH) and then neutralized (NaOH), the cationic form was formulated as a hydroxide salt. However, only two OH groups were detectable on ^{1}H NMR spectroscopy. Only slight differences were found in the UV spectra taken in methanol [λ_{max} ($\log \varepsilon$) = 218 (4.68), 302 (4.39), 394 (4.08) nm] and methanol+NaOH [λ_{max} ($\log \varepsilon$) = 228 (4.66), 310 (4.39) nm]. Three tautomeric forms can be formulated which are shown in Scheme 42. Two of them possess the isoquinolium-7-olate moiety. The ^{1}H NMR data are presented in Table IV. They indeed unambiguously resemble the cationic species **112**.

7. *Benzo[c]phenanthridinium-olates*

Benzo[*c*]phenanthridine alkaloids are widespread in Papaveraceae, Fumariaceae, and Rutaceae. Fagaridine (**118**), the structure of which had to be revised, is a derivative of the unknown 5-methyl-benzo[*c*]phenanthridine-8-olate (**119**) which is isoconjugate with the 2-methyl-chrysene anion (Scheme 43). Thus, Fagaridine is a member of class 1 of conjugated heterocyclic mesomeric betaines, which are isoconjugate with odd alternant hydrocarbon anions.

The benzophenanthridine alkaloid Fagaridine, to which originally the structure **120** was assigned, was first isolated from the roots of *Fagara xanthoxyloides* in 1973 (73P2315), an African plant, which is used to combat diarrhoea, enteritis, and to treat wounds. Later it was identified in *Fagara tessmannii* (79MI1) and "Prickly Ash", i.e., *Zanthoxylum tsihanimposa* (77MI2), *Z. zanthoxyloides* (86MI1, 86JNP715), *Z. rigidifolium*



Scheme 43

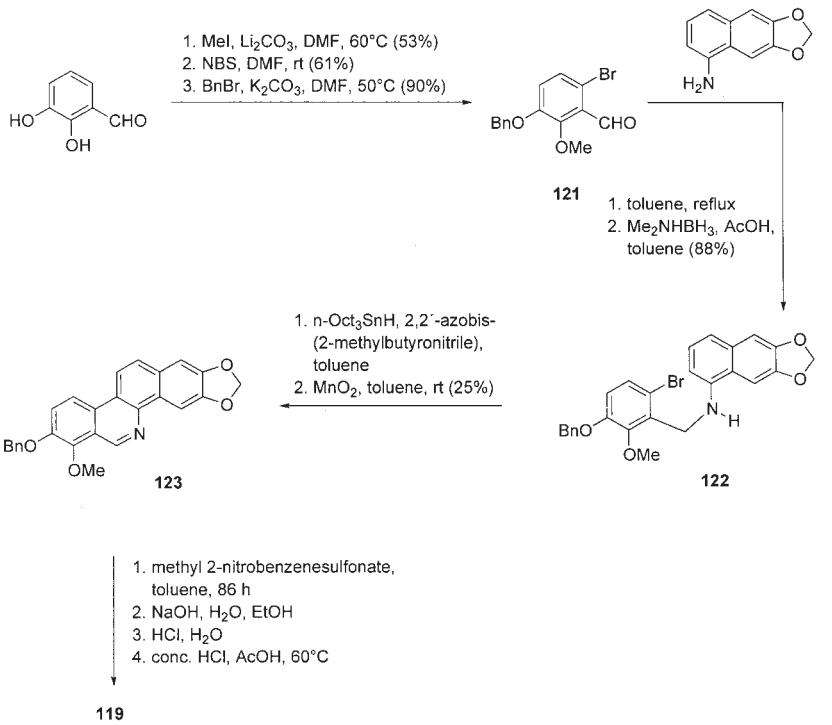
(86PHA747), and *Z. leprieurii* (87MI2). Fagaridine (called "Isofagaridine" in the original paper) was identified in the methanol extract of the southern Chinese climbing shrub *Zanthoxylum nitidum* and proved to be a strong inhibitor of topoisomerase I-mediated DNA relaxation. It stabilizes the covalent binary complex between the enzyme and the DNA (93JOC5025). Significant antitumor activities were reported in 1989 (89CA718). The hydrogen sulfate dihydrate of Fagaridine, coded NK109 (99JNP864), has undergone evaluation in clinical trials in Japan.

The originally proposed structure **120** (now called "Isofagaridine") is no mesomeric betaine, but can adopt a zwitterionic or keto form. According to the elemental analysis published in 1973, it was isolated as a phenolic hydroxide. The phenolic group was identified with $FeCl_3$ and by a broad band at 3420 cm^{-1} in the IR spectrum. As elucidated by Nakanishi and Suzuki in 1998 (98JNP1263), the spectroscopic data of Fagaridine (**119**) and Isofagaridine (**120**) are very similar, except for the UV absorption maxima. The pK_a value of the originally proposed structure is 5.3 so that the purple keto form is therefore the preferable form in dilute solution. The charged species is yellow. The revised structure of Fagaridine has been proven by a total synthesis (98JNP1263). The synthesis starts from 2,3-dihydroxybenzaldehyde, which was treated with methyl iodide in the presence of lithium carbonate to yield selectively 3-hydroxy-2-methoxybenzaldehyde (Scheme 44). Bromination and subsequent benzylation gave 3-(benzyloxy)-6-bromo-2-methoxybenzaldehyde (**121**). Condensation with the amine followed by reduction of the resulting Schiff base resulted in the formation of the key intermediate **122**, which was subjected to a radical cyclization. Subsequent aromatization with manganese dioxide, *N*-methylation with methyl 2-nitrobenzenesulfonate in toluene and debenzylation gave Fagaridine (**119**) as a hydrochloride.

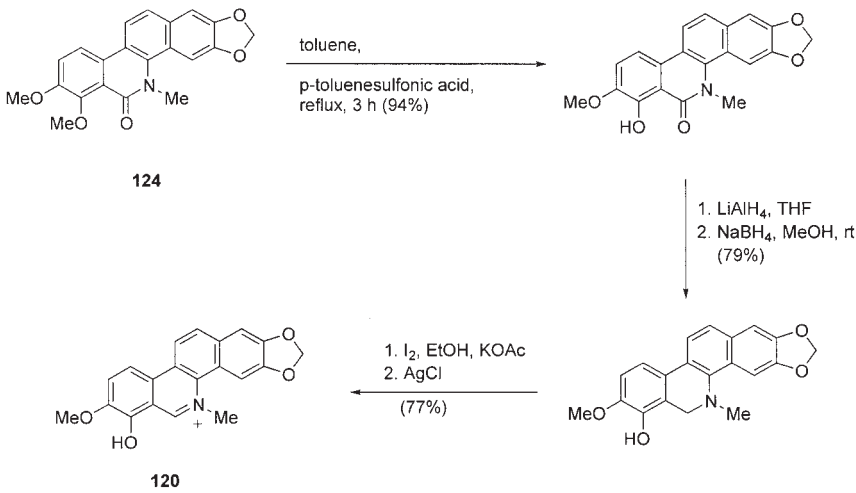
The synthesis leading to the originally proposed structure **120** starts from Oxychelerythrine (**124**) as shown in Scheme 45 (85CPB1763). The structure is not identical to the naturally occurring compounds and obviously does not occur in nature.

8. *Dibenzo[*de,g*]quinolinium-olates*

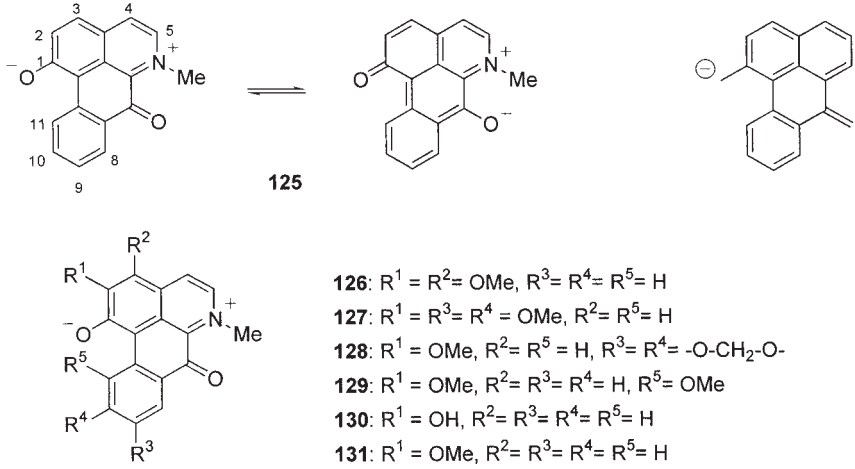
The oxoaporphine alkaloids Teliglazine (**126**), Corunnine (**127**), Nandazurine (**128**), PO-3 (**129**), *N*-Methylliriodendronine (**130**), and *N*,*O*-Dimethylliriodendronine (**131**) contain the 6-methyl-7-oxo-dibenzo [*de*,*g*]quinolinium-1-olate ring system **125** which is isoconjugate with the 1-methyl-7-methylene-7H-benzo[*de*]anthracene anion (Scheme 46). Therefore, these alkaloids belong to class 1, i.e., heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions. Another



Scheme 44



Scheme 45



Scheme 46

mesomeric form, the 1-oxo-7-olate, can be formulated with this ring system. On protonation, however, the 1-hydroxy derivative is formed (97JNP1328).

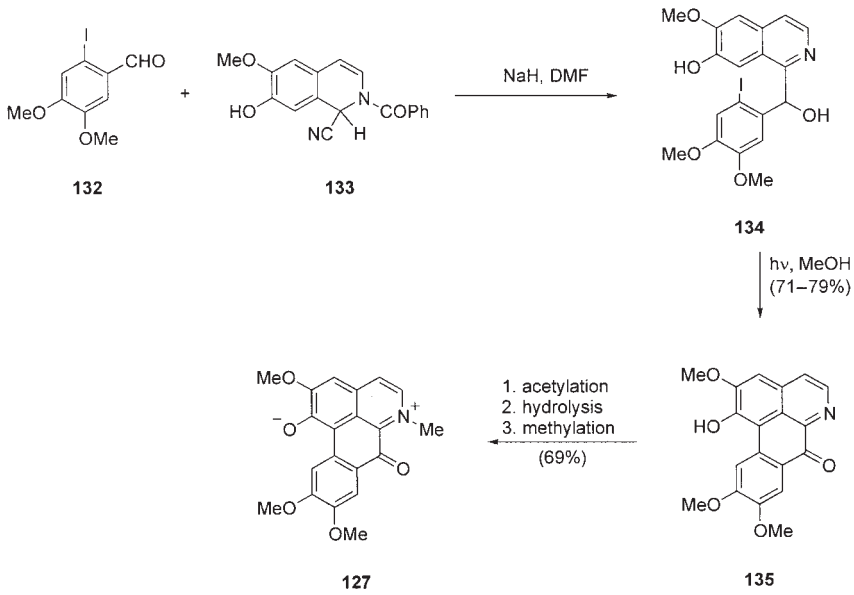
The chemistry of oxoaporphines has been reviewed in 1972 (72MI2). They are most probably derived in plants by oxidation of the corresponding aporphines. Teliglazine (**126**) was identified in *Telitoxicum glaziovii* (97JNP1328). Under acidic conditions, protonation at C(1) occurs, yielding the corresponding cation. On protonation, the color changes from green (neutral and basic conditions) to pink (acidic). All attempts to methylate, silylate, or acetylate Teliglazine failed due to the missing phenol group. A synthetic sample of Teliglazine was obtained on treatment of *O*-methylmoschatoline with excess MeI in acetone at room temperature for 18 h. The UV absorption maxima λ_{max} of Teliglazine in ethanol were determined at 246 (shoulder, 3.24), 318 (3.43), 430 (2.53), and 648 (2.55) nm, whereas the protonated form exhibits absorption maxima λ_{max} (EtOH+0.1 M HCl) at 248 (3.31), 294 (3.29), 316 (shoulder, 3.06), 378 (2.59), 520 (2.47). ^{1}H and ^{13}C NMR data are given in Table VI. The broadening of the resonance frequencies of 4-H and 5-H at 7.88 and 8.14 ppm, respectively, is indicative of a quarternary nitrogen atom. The ^{13}C NMR data were recorded through the ^{1}H-detected inverse HMQC and HMBC correlation data. The resonance frequency of C-1 could not be detected.

Corunnine (**127**) (73JCS(CC)915) was isolated as violet needles in the course of studies of Spanish Papaveraceae, i.e., *Glaucium flavum Cr*. var. *vestitum* (71TL3093). The UV absorption maxima λ_{max} of Corunnine are very similar in ethanol and hydroxide solutions and were found at

Table VI. NMR Chemical Shifts of Teliglazine **126**, PO-3 Precursors **143** and **144**, PO-3 **129**, and Nandazurine **128**

	126[a]		**143**[a]	**144**[a]	**129**[b]	**128**
Atom	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{1}H NMR	^{1}H NMR	^{1}H NMR[d]
1	–	n.d.	4.00 (OMe)[c]	4.02 (OMe)[c]	–	–
2	4.34, s (OMe)	152.3/60.9	4.08 (OMe)[c]	4.27 (OMe)[c]	3.86 (OMe)[c]	3.93 (OMe)
3	4.11, s (OMe)	143.7/61.5	7.13, s	7.89, s	7.14, s	7.14
3a	–	117.0	–	–	–	–
4	8.14, br d, $J=4.6$ Hz	117.2	7.74, d, $J=5.2$ Hz	8.90, d, $J=5.8$ Hz	7.93, m	7.96
5	7.88, br d, $J=4.6$ Hz	134.8	8.81, d, $J=5.2$ Hz	9.22, d, $J=5.8$ Hz	8.40, d, $J=5.5$ Hz	8.14
N(6)–Me	4.87, br s	51.2	–	4.82, s	4.65, s	4.50
6a	–	135.1	–	–	–	–
7	–	177.0	–	–	–	–
7a	–	130.1	–	–	–	–
8	8.48, dd, $J=8.3/1.5$ Hz	126.6	7.29, d, $J=7.9$ Hz	7.39, d, $J=8$ Hz	7.93, m	7.40
9	7.42, ddd, $J=8.3/6.9/1.5$ Hz	124.3	7.55, t, $J=7.9$ Hz	7.65, t, $J=8$ Hz	7.2–7.5	–
10	7.79, ddd, $J=8.3/6.9/1.5$ Hz	134.1	8.10, d, $J=7.9$ Hz	7.90, d, $J=8$ Hz	7.2–7.5	–
11	10.03	126.5	3.73 (OMe)[c]	3.88 (OMe)[c]	3.94 (OMe)[c]	8.32
11a	–	136.9	–	–	–	–
11b	–	105.6	–	–	–	–

[a] In $CDCl_3$.
[b] In DMSO-d_6.
[c] Peak assignments exchangeable.
[d] In TFA-d.



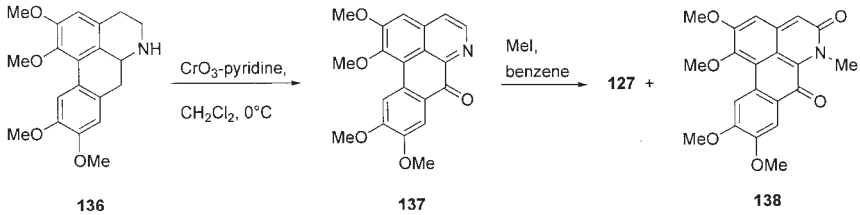
132 **133** **134** **127** **135**

Scheme 47

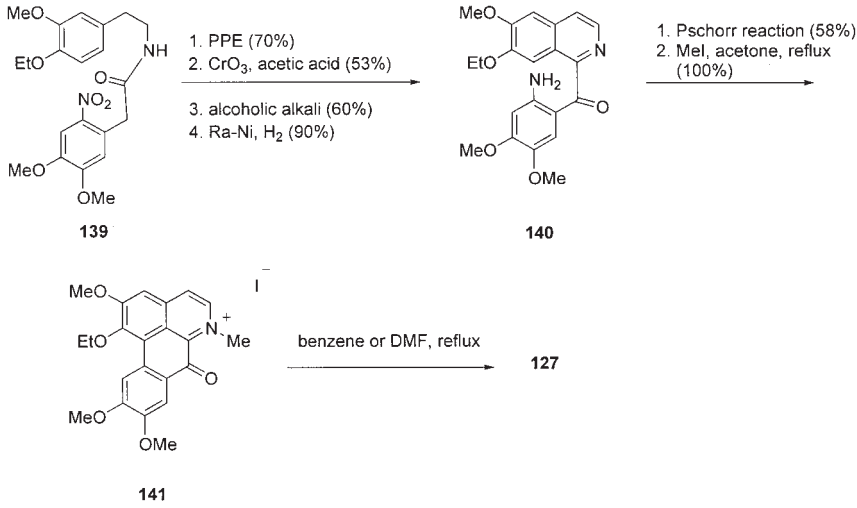
258 (4.13), 325 (4.32), 400 (3.54), 440 (3.42, sh), 630 (3.35) nm. On addition of acids, they hypsochromically shift to 256 (4.23), 295 (4.14), and 385 (3.75) nm. An oxidative photocyclization is the key step of its total synthesis, which is shown in Scheme 47. Starting from the *o*-iodoaldeyde **132** and the Reissert compound **133**, the precursor molecule for the photocyclization **134** was prepared. The authors explain the high yield of this step by the formation of the insoluble tetracycle **135** and its removal from the photolysis medium before being subjected to further photochemical transformations. Standard reactions converted **135** into Corunnine (**127**).

Oxidation of the alkaloid Glaucin (**136**) resulted in the formation of a yellow alkaloid **137**, which seemingly is contained in *Glaucium flavum* var. *vestitum* (Scheme 48). Addition of methyl iodide converted this compound via a methylation/ether cleavage sequence into Corunnine (**127**) and small amounts of Pontevedrine (**138**) which is not a mesomeric betaine (71TL3093).

Bischler–Napieralski reaction of **139** to a 3,4-dihydroisoquinoline, oxidation, dehydrogenation and reduction of the nitro to the amino function gave **140** which was subjected to a Pschorr reaction (Scheme 49). Quaternization was accomplished by methyl iodide to furnish the isoquinolininium salt **141** which underwent an ether cleavage on heating a solid sample or benzene or DMF solution to Corunnine (**127**) (73TL3617).



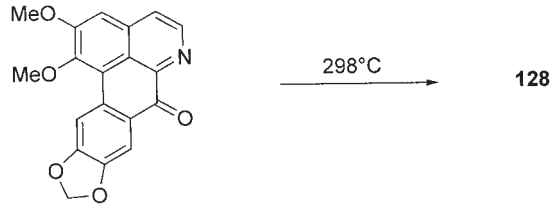
Scheme 48



Scheme 49

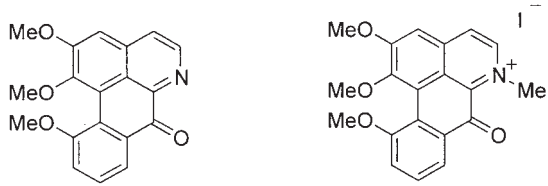
Nandazurine (**128**) was isolated from *Nandina domestica* in 1927 as a blue solid (30BCJ348). It is green in neutral or basic solvents, but yellow in acids and was also identified in *Coprydalis bulbosa* (81MI3). The structure elucidation was reported (74MI3, 74E518). The synthesis of Nandazurine was accomplished under identical reaction conditions as described for Coruninne (**127**) (73JCS(CC)915). When oxonantenine (**142**) was heated to its melting point, Nandazurine was obtained (Scheme 50).

The Apomorphine-derived alkaloid PO-3 (**129**) was isolated as violet needles after crystallization from acetone and ether from *Papaver orientale* (66MI2), but was not found in the green solutions of autoxidized apomorhine hydrochloride (62M941, 68HCA683) (Scheme 51). No anion was detected by elemental analysis. The pK_a of PO-3 is 3.88 ± 0.02 in 50% ethanol. The IR spectrum displays no carbonyl absorption between 1650 and 1700 cm^{-1} (69MI2). The UV absorption maxima of PO-3 are in agreement with the formulation of a mesomeric betaine: [λ_{max} (EtOH) = 310



142

Scheme 50



143 144

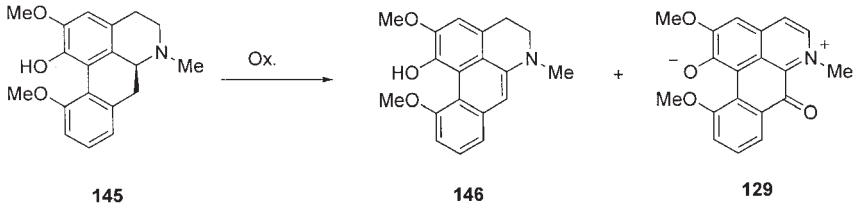
Scheme 51

(3.7), 430 (3.7), 645 (4.5) nm (values approximated from chart)]. In comparison to the nonbetainic alkaloids Cassamedine, Thalicminine, Hernandonine, Imenine, the absorption band at 645 nm seems to be diagnostic for a betainic ground-state. Table VI presents a comparison between a neutral precursor **143**, the *N*-methylated cationic molecule **144** ($CDCl_3$) (Scheme 51), and the betainic PO-3 (69MI2). On methylation of **143** to **144**, the resonance frequencies especially of 3-H ($\Delta\delta = -0.76$ ppm), 4-H ($\Delta\delta = -1.16$ ppm) and 5-H ($\Delta\delta = -0.41$ ppm) shift considerably to lower field. On betaine formation to PO-3 **129**, the chemical shift of 3-H remains virtually unchanged in comparison to **143**, 4-H shifts downfield ($\Delta\delta = -0.19$ ppm), and 5-H shifts upfield ($\Delta\delta = +0.41$ ppm).

On oxidation, Isothebaine (**145**) forms 6a,7-Didehydroisothebaine (**146**) as well as PO-3 **129**, which can be protonated to give a red substance. Both alkaloid gives Isothebain on reduction (69MI2) (Scheme 52).

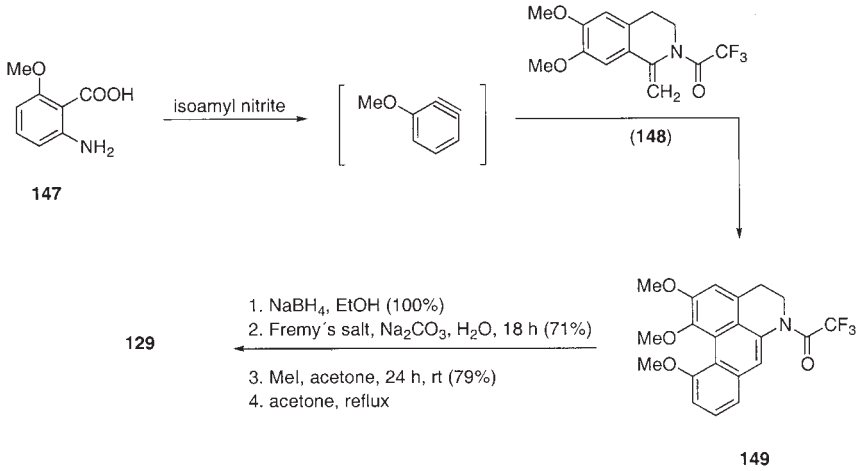
The aporphinoid alkaloid PO-3 (**129**) was also prepared by intermolecular benzyne cycloaddition between 1-methylene isoquinolines **148** and arynes derived from **147** (Scheme 53). The alkaloid was finally isolated by means of preparative thin layer chromatography (91JOC2984).

Bio-assay guided fractionation of the methanolic extract of the African climbing shrub *Stephania dinklagei* contains six bioactive alkaloids, among



145 146 129

Scheme 52



147 149

Scheme 53

them *N*-Methylliriodendronine (**130**) and *N*,*O*-Dimethylliriodendronine (**131**). The stems of this plant are used to treat infertitility of women and impotence of men; the stems are reported to possess vermifuge, analgesic, and sedative effects. *N*-Methylliriodendronine proved to be active against *Leishmania donovani* amastigotes (00MI1). 2-*N*,*O*-Dimethylliriodendronine (**131**) was also identified as a blue solid on treatment of Liriodenine methiodide (**150**) with basic alumina (80JPS1180, 76TL601) (Scheme 54). Alternatively, it was obtained as dark green needles on treatment of Liriodendronine (**151**) isolated from *Liriodendron tulipifera* with dimethylsulfate in alkaline solution. The intense absorption maximum λ_{max} at 311 nm indicated that the structure is similar to the oxaphorphine zwitterions like Corunnine. The absorption bands at 1628 and 1581 cm^{-1} correspond to carbonyl groups of the Corunnine type (77P2015). The UV absorption maxima of 2-*O*,*N*-Dimethylliriodendronine at 247 (4.03), 311 (4.29), 420 (3.46), 585 (3.44), 602 (3.44) in methanol do not change on addition of 0.005 N NaOH (77P2015). On protonation with 0.005 N HCl, however, the

150 151

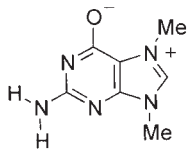
Scheme 54

UV spectrum changes dramatically. The salt causes maxima at 251 (4.16), 286 (4.16), 387 (3.56), and 473 (3.37) nm. ^{1}H NMR data for a sample in CF_3COOD were presented. It is interesting to note that the nonmethylated derivatives of **130** and **131** are present in solution above pH 6.5 as betaines, forming a protonated pyridine ring and an olate group (91MI3).

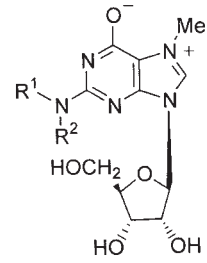
Some unnatural analogs have been synthesized and their antifungal activities have been examined (91MI3).

9. *Purines*

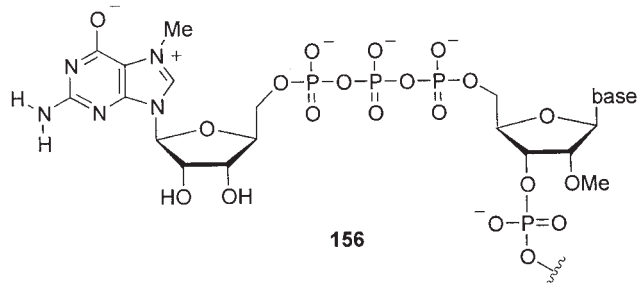
The alkaloid Herbipoline was first isolated from the giant silica sponge (*Geodia gigas*) and proved to be 7-methylguanine (**152**) (58AG80, 59CB566). This betainic purine and its derivatives were identified later as 7-methylguanosine (**153**) (m^7G) (61BBA198), 2,7-dimethylguanosine (**154**) ($m^{2,7}G$), and 2,2,7-trimethylguanosine (**155**) ($m^{2,2,7}G$) in distinct types of RNA such as *ribosomal*-RNA (89MI4, 68BBA63, 85MI3, 78JBC1101, 79MI3), archaea-, bacterial-, eucaryotic-*transfer*-RNA (61BBA198, 62JCS5281), *sn*- (69NAT1365, 91MI2, 82NAT684), *viral*- (76NAT264, 80BBR102) and *messenger*-RNA (90MI2, 83MI3) (Scheme 55). These compounds undergo nonstandard base-pairings such as $m^7G{=}G{\equiv}C$ (76NAR181, 78MI1), and unusual π-stacking interactions such as the intercalation of adenine into m^7G and G to stabilize the tertiary structures of RNA (74MI2). 7-Methylguanosine forms the 5′-capping structure **156** of eucaryotic messenger-RNA and is joined to the RNA through a unique triphosphate bridge Gp(5′-5)ppN. The enzyme guanylyl transferase adds the 7-methylguanosine. This capping structure is essential for ribosomal binding of the mRNAs and it protects the mRNAs from degradation by 5′-exonucleases. The cap-structure seems to be involved in several aspects of pre-mRNA and mRNA metabolism, in most cases related to identifying the 5′-end of the RNA. The cap-structure binds two cap binding proteins in the nucleus to form a cap binding complex which influences the splicing of the pre-mRNA. Furthermore, it may be involved in the transport of the



152



153: $R^1 = R^2 = H$
154: $R^1 = Me$, $R^2 = H$
155: $R^1 = R^2 = Me$

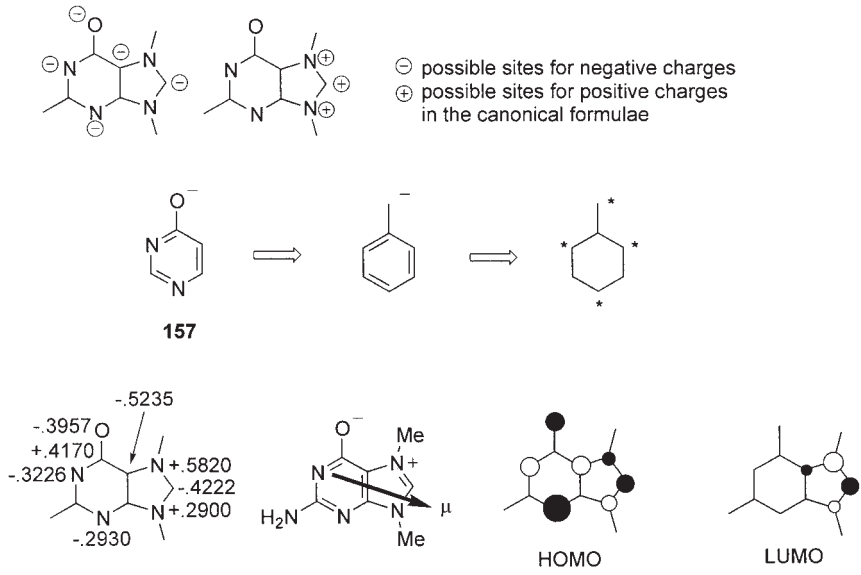


156

Scheme 55

pre-mRNA to the cytoplasm. The cap-structure, which is bound by a translation initiation factor in the cytoplasm, is important for the initiation of translation. The crystal structures of the m^7GTP and m^7GpppA initiation factor complexes have been reported. Compound **156** is sandwiched between two aromatic side chains of tryptophane. Two hydrogen bonds between the NH of m^7G and the carboxy group of glutamic acid stabilize the stacking interaction (02BJ539).

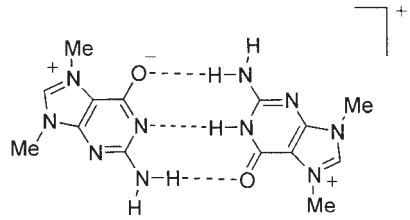
The synthesis of **152** was described (67MI3). All four compounds Herbipoline **152**, m^7G **153**, $m^{2,7}$G **154**, and $m^{2,2,7}$G **155** belong to the class of conjugated mesomeric betaines. The positive and negative charges are in mutual conjugation and are not restricted to separate parts of the π-electron system of the molecule. Correspondingly, the canonical formulae display common atoms such as C(8) for either charge which is presented in Scheme 56. This is the result of the π-connection of the negative to the positive fragment through an "active" atom, i.e., a starred position of the isoconjugated benzyl anion of the pyrimidin-4-olate moiety **157**. The 7-methylguanines **152**–**155** are members of class 4 of mesomeric betaines due to their isoconjugate equivalency with an even nonalternant



Scheme 56

hydrocarbon dianion. Semiempirical as well as *ab initio* calculations on 7,9-dimethylguanine (**152**) were perfomed (02JCS(P1)982). The HOMO [IP(PM3) = +8.19 eV] of the planar 7,9-dimethylguanine is essentially located at N(1), N(3), C(5) and O(13) of the pyrimidine moiety and in the imidazole ring, whereas the LUMO [IP(PM3) = +0.92 eV] has its largest coefficients at N(7), C(8), and N(9) in the imidazole ring and at C(5) of the pyrimidine. The calculated permament dipole moment of 7,9-dimethylguanine is 10.80 D [RHF6-31g(d)] which is presented—in addition to the net atomic charges—in Scheme 56.

The pK_a value of 7,9-dimethylguanine is 7.19 (61LA167) so that it exists as 1:1 mixture of cationic and betainic species at pH 7. This is the condition for self-complementarity and this was indeed confirmed by ESI mass spectrometry and ^{1}H NMR spectroscopy (96AG1321). Dimerization occurs between the acid and its conjugated base through three hydrogen bonds and the structure of the dimer with iodine as the anion has been elucidated by an X-ray analysis (89MI2). Similarly, N7-guanosines and guanines are self-complementary as presented in Scheme 57 (80JA5418, 82IC3216, 81JA5691, 95JCS(D)3767). 7-Methylguanosine (m^{7}G) is hepatotoxic and mutagenic (95JCS(P2)839, 97MI4), and has been identified in the liver of animals after exposure to strong carcinogens such as alkylating agents or hydrazine (80NAT596, 57CIL633, 60BJ478). Some model compounds of m^{7}G (02JCS(P1)982, 02H2231, 02CL222, 01BCJ2379, 01CL348) and other



Scheme 57

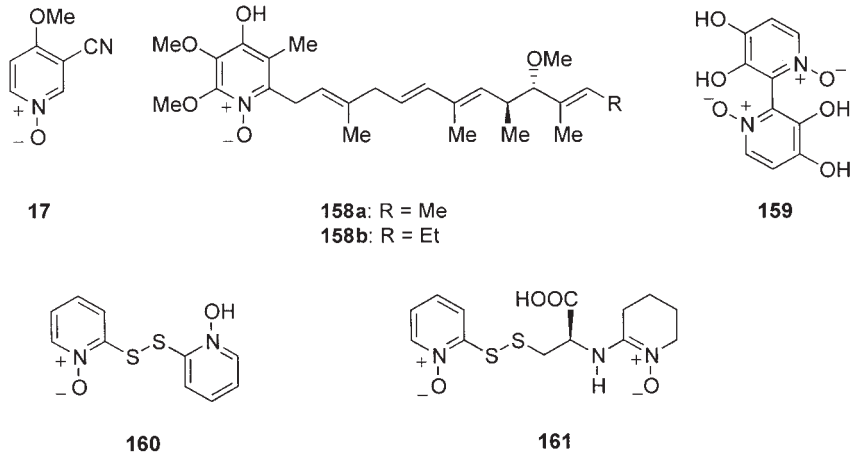
nucleobases (97JOC3910, 99JOC9499) were synthesized in order to study the dependence of the type of conjugation on the base pairing properties.

B. Heterocyclic Conjugated N-oxides

Relatively few heteroaromatic N-oxides occur in nature. The chemistry of compounds that contain the oxidized peptide bond (the so-called hydroxamic acids) and their role in iron metabolism have been reviewed (67SC1443). Another review deals with the natural occurrence of N-oxides (68MI1).

1. *Pyridine-N-oxides*

The N-oxide Malloapeltine (**17**) was extracted from the roots of *Mallotus apelta* (98P2193), which have been widely used for the treatment of chronic hepatitis in traditional Chinese medicine. Extracts of this plant containing Malloapeltine have significant anti-HIV activity (89CPB1810). The antibacterial alkaloids Piericidine B_1 N-oxide (**158a**) (91JAN1283) and Piericidine B5 N-oxide (**158b**) (93JAN564) are phosphatidylinositol turnover inhibitors and were isolated as pale yellow oils from *Streptomyces* species (Scheme 58). Reduction of **158a** with zinc powder in acetic acid gives Piercidin B_1 (91JAN1283). The UV absorption maxima of Piercidin B_1 N-oxide in methanol are seemingly not very sensitive toward the addition of 0.1 N HCl or 0.1 N NaOH. A bathochromic shift of 8–9 nm from $\lambda_{max} = 267$ nm is observable in either case, all other absorptions remain virtually unchanged (91JAN1283). Orellanine (**159**) (79TL1931) was first isolated from the mushroom *Cortinarius orellanus* (59MI2). Some syntheses (02T309, 93T8373, 88HCA957, 87E462, 87LA857, 86T1475, 85TL4903) and a study on the chirality of Orellanine derivatives have been described (02H137). The bis-pyridinium-N-oxide (**160**) and Cortamidine Oxide (**161**) were isolated from *Cortinarius* species (01JNP342). All N-oxides presented in Scheme 58 are conjugated heterocyclic ylides isoconjugate with the



Scheme 58

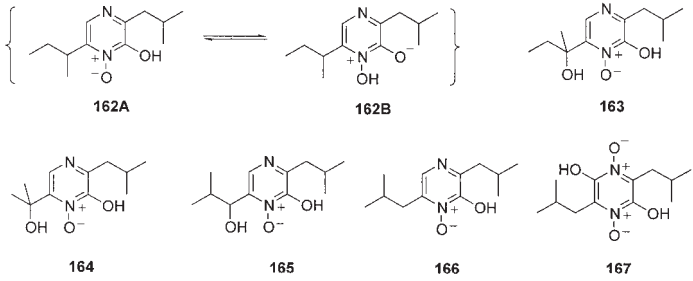
benzyl anion, which is an odd alternant hydrocarbon anion. The betaines **17** and **158**–**161** are therefore members of class 5.

2. *Pyrazine-N-oxides*

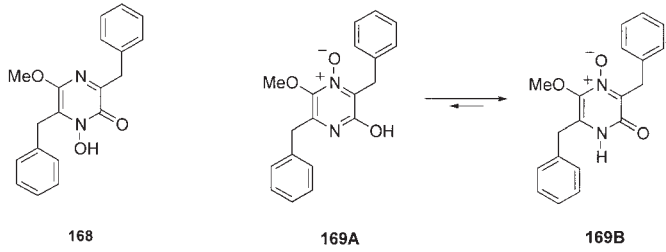
In 1943, Aspergillic acid (**162**) (6-*s*-butyl-2-hydroxy-3-isobutylpyrazine 1-oxide) was isolated from *Aspergillus flavus* (43MI1, 44JBC359, 47JBC321, 49JCS(S)126, 49JCS127, 51JCS2679). The tautomeric form of the aromatic N-oxide **162A** is a mesomeric betaine whereas a neutral covalent structure can be drawn for the olate structure **162B** (Scheme 59). It has antibiotic activity, but its toxicity prevented therapeutic use. Additional examples of aromatic N-oxides from fungi are hydroxyaspergillic acid (**163**) (*Aspergillus flavus*) (43MI2, 58JBC785), mutaaspergillic acid (**164**) (*Aspergillus oryzae*) (61MI1), neohydroxyaspergillic acid (**165**) and 3-hydroxy-2,5-diisobutylpyrazine 4-oxide (**166**) (*Aspergillus sclerotiorum*) (58MI2, 64JCS1507). Pulcherrimine is an iron(III) complex of pulcherrimic acid (**167**) (*Candida albicans*) (56JCS4133). Whereas the N-oxides **163**–**166** belong to class 5, **167** is isoconjugate with the *p*-xylene dianion, which is even and alternant (class 7).

Emeheteron (Scheme 60), to which the structure **168** was originally assigned, was isolated from a culture filtrate of the fungus *Emericella heterothallica* (88P3022) and the basidiomycetes *Albatrellus confluens* (01HCA259). The structure **169** was finally proven by a total synthesis, which is shown in Scheme 61 (90H1655).

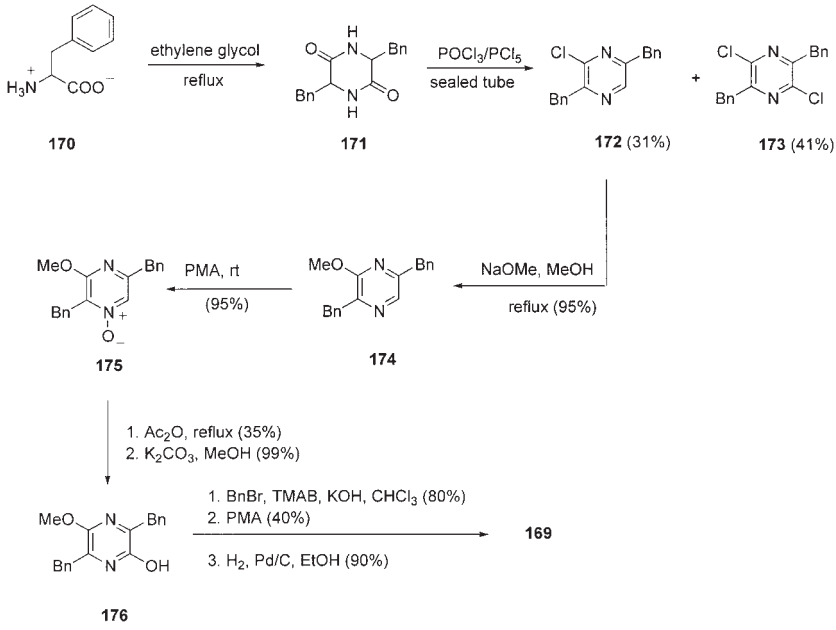
DL-Phenylalanin anhydride (**171**), readily available by heating DL-phenylalanine (**170**) in ethylene glycol, was treated with a mixture of



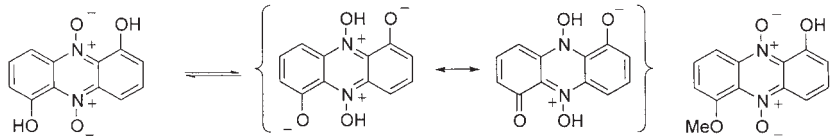
Scheme 59



Scheme 60



Scheme 61



177 178

Scheme 62

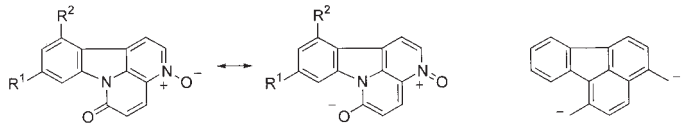
phosphoryl chloride and phosphorus pentachloride in a sealed tube to give a mixture of two chlorinated pyrazines **172** and **173** (Scheme 61). Nucleophilic substitution on **172** then resulted in the methoxy derivative **174**, which was oxidized with permaleic acid (PMA) to yield the N-oxide **175**. Subsequent acetylation, which presumably formed 6-(α-acetoxybenzyl)-3-benzyl-5-methoxypyrazine as a by-product in 55% yield, gave 2-acetoxy-3,6-dibenzyl-5-methoxypyrazine which was hydrolyzed to the hydroxy compound **176** by potassium carbonate. Benzylation and oxidation by PMA gave an N-oxide, which was then hydrogenated to yield Emeheterone (**169**). As the IR spectrum displays a band at 1640 cm^{-1}, Emeheterone is supposed to exist predominantely in the pyrazinone form **169B**.

3. *Phenazine-N-oxides*

Iodinine (**177**) (1,6-phenazindiol-5,10-dioxide) was the first aromatic N-oxide found in nature (*Chromobacterium iodinum*) (Scheme 62). It is a bis-N-oxide with antibacterial activity against gram-positive bacteria and forms a violet crystalline solid (39CA6383). Myxin (**178**) is the corresponding monomethylether from *Pseudomonas sp*. and displays additional activity against gram-negative bacteria. Methylation of Iodinine with dimethyl sulfate in the presence of alkali produced Myxin as the major product (67TL715). Care must be taken as the substance may explode on attempts to dry it. The biosynthesis follows the Shikimi-acid pathway (74TL4201). These compounds are described as aromatic molecules so that the classification as members of class 7 of heterocyclic mesomeric betaines is acceptable. The corrresponding olate tautomer, however, represent a conjugated mesomeric betaine of class 3.

4. *β-Carboline-N-oxides*

The cytotoxic 9-methoxycanthin-6-one N-oxide (**179A**) was isolated from the branches of *Picrolemma granatensis* (92P2499) (Scheme 63). It is



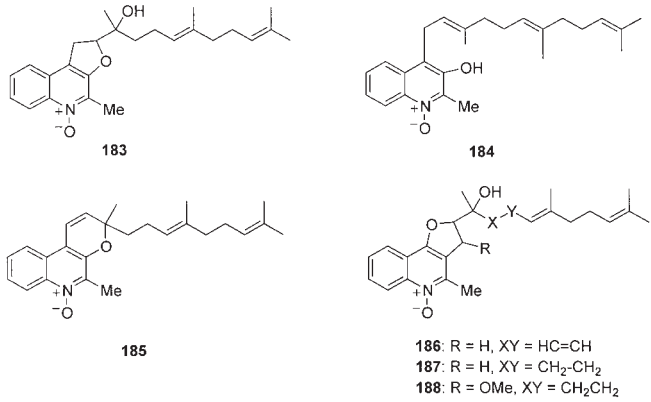
179: R^1 = OMe, R^2 = H
180: R^1 = OH, R^2 = H
181: R^1 = R^2 = H
182: R^1 = H, R^2 = OH

Scheme 63

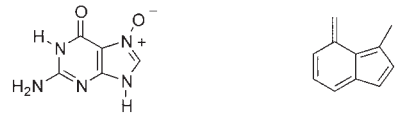
isoconjugate with the 2,5-dimethyl-1-*o*-tolyl-naphthalene anion and thus represents a member of class 5 of heterocyclic mesomeric betaines. The canonical formula **179B** signifies the close relationship between the class of N-ylides and conjugated mesomeric betaines as positive as well as negative charges are delocalized over the entire molecule and common atoms for either charge exist. In addition to 9-hydroxycanthine-6-one N-oxide (**180**) it was also found in the roots of the indonesian small jungle tree *Eurycoma longifolia* which are used as a traditional medicine for the treatment of dysentery, glandular swelling, persistent fever, and tertian malaria (91JNP1360). In the search for the biologically active substances of *Brucea Mollis* var. *tonkinensis*, which is an important drug in Chinese folk medicine and is used as a remedy for malaria and other parasitic diseases, 11-hydroxycanthin-6-one-*N*-oxide (94P1543) (**182**) was identified together with its derivative **181** which was found earlier (76CPB1532). On formation of the N-oxide **179B** from its nonoxidized derivative, the ^{13}C NMR signals in $CDCl_3$ the α/α'- and γ-positions of the pyridine moiety shift approximately 10 and 7.5 ppm to higher field, respectively (91JNP1360). Likewise, signals for the α- and β-hydrogen atoms shift upfield in ^1H NMR spectroscopy. The chemical shift differences are 0.15 and 0.43 ppm, respectively (94P1543).

5. *Quinoline-N-oxides*

Quinoline-N-oxides were found in the myxobacterium *Stigmatella aurantiaca* which is a source of the aurachins, i.e., quinoline alkaloids with a sesquiterpenoid substituent. There are noteworthy structural variations between the members of the family (Scheme 64). The following Scheme presents Aurachin A (**183**), and B (**184**), F (**185**), G (**186**), H (**187**), and I (**188**) (89GEP3520229). Aurachin A and B display antibacterial and weakly antifungal properties (87JAN258). Certain Aurachins inhibit photosynthetic electron transport by binding to quinone receptor sites in respiratory oxidases (95B1076). They also belong to class 5.



Scheme 64



Scheme 65

6. *Purine-N-oxides*

The conjugated mesomeric betaine guanin-7-oxide (**189**), isolated form natural sources (85JAN572, 85JAN972, 85JAN977, 85JAN1440), displays antitumor (87MI3), antimicrobial, and antiviral activities (85JAN1581, 86JAN1291). It is isoconjugate with the odd and nonalternant 3-methyl-4-methylene-4H-indene anion and belongs therefore to class 6 of heterocyclic mesomeric betaines (Scheme 65).

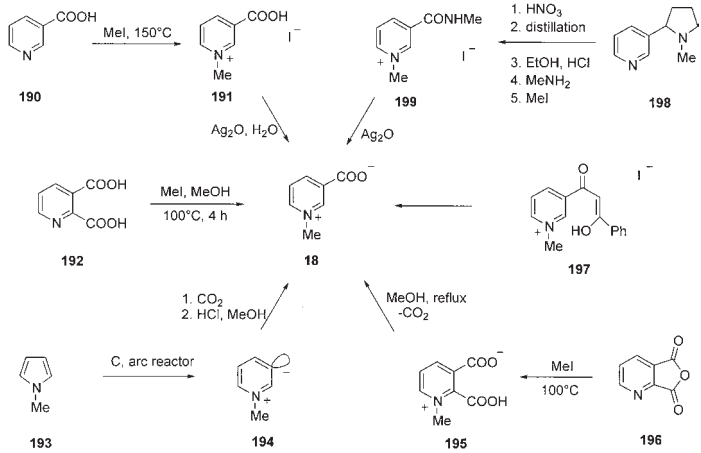
C. Cross-conjugated Heterocyclic Mesomeric Betaines

1. *Pyridinium-3-carboxylates*

The alkaloid Trigollenine (**18**), *N*-methyl nicotinate, was first identified in 1885 in *Trigonella foenum graecum* (1885CB2521). A comparison of its properties with the first synthetic sample, which was prepared by Hantzsch (1886CB32), led to its structure elucidation (1887CB2840, 1887MI). Trigollenine is wide-spread in nature. It was isolated from various plants such as lianas of *Gnetum parvifolium* (99JAN1025), *Aeschynomene indica* (99H927, 95P817), *Nothapodytes foetida* (95P383), the seeds of

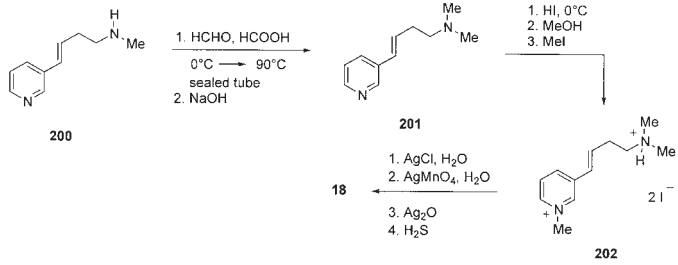
Pisum sativum (84P1837, 09ZPC174, 1894CB769, 1891ZPC145), Alfalfa (59CJC1043), *Acanthus montanus* (88P2581) and *illicifolius* (80PJC2089), *Abrus precatorius* (71P195), *Pseudolmedia laevis* and *laevigata* (91P3285), *Desmodium triflorum* (71P3312), *Calyx nicacensis* (61ZPC197), *Quisqualis fructus* (75MI1), *Arion empiricorum* (60ZPC212), *Cassia occidentalis* (70P429), potatoes (*Solanum tuberosum*) (04MI), and coffee beans (*Coffea arabica* and *Coffea liberica*) (31JPC11, 10LA242), *Astragalus wootoni* (42JOC389), *Mappia foetida* (75IJC758) the roots of *Dictamus albus* (30MI), and sugar-beet juices (60MI1). Especially, Trigollenine has been detected in many gymnosperms, several monocotyledonous and dicotyledonous plants (79P105). Trigollenine was also identified in animals (42JBC357, 67MI1) such as dogs (12MI, 26JB163) and sea urchins (31JPC11). The tail muscle of the western rock lobster *Panulirus cygnus* George contains Trigollenine as well as human urine after its ingestion (81AJC787). Trigollenine was identified as a cell proliferation regulating factor (78JA7759) and it has been shown to promote cell arrest in G2 of certain plants (74MI1). The plant hormone Trigollenine is synthesized in the leaves of *Pisum sativum* and *Glycine max*, and is translocated to the pods and seeds during fruit maturation (97P1037). Plants, when exposed to excess salt, accumulate osmoregulators such as Trigollenine to prevent water loss (97P1037). Trigollenine forms charge-transfer-complexes with $FMNH_2$. Benesi-Hildebrand plots revealed the existence of 1:1 complexes in phosphate buffer solution (66BBA459). Trigollenine is usually the most abundant molecule in pyridine metabolism for the biosynthesis of NAD. Thus, this alkaloid may have a regulatory role in NAD biosynthesis as well as in cell profileration (73MI1, 57JA4246, 82P1201). Trigollenine has been shown not to arise from tryptophane (59JBC93, 55CJC405) and the methyl group at the nitrogen atom obviously arises by transfer from *S*-adenosylmethionine (60JBC2981).

An X-ray single crystal structure analysis was performed. The unit cell contains a pair of molecules of the betaine and two molecules of water (81AJC787). The bond length between the methyl group and the pyridine nitrogen atom was determined to be 148.0(5) pm while the bond length between C(3) and the carboxy carbon is 152.8(5) pm. Thus, they are single bonds without π-contribution. The two carbon–oxygen bonds of the carboxy group were found to be 123.5(4) and 125.3(4) pm long, respectively. The UV absorption maxima λ_{max} in water were found at 264 (2700), 207 (4300). The ^1H NMR data at 400 MHz in D_2O are as follows. The resonance frequency of 2-*H* appears at $\delta = 9.10$ ppm (s, br), whereas 6-*H* is observable at $\delta = 8.80$ (d, $J = 6$ Hz). The signals of 4-*H* and 5-*H*, respectively, appear at $\delta = 8.83$ (d, $J = 8$ Hz) and 8.06 ppm (95P817). The methyl group gives a resonance frequency at $\delta = 4.42$ ppm.



Scheme 66

Hantzsch's synthesis (1886) begins with the deprotonation of nicotinic acid (**190**) with potassium hydroxide, evaporation to dryness and proceeds with the addition of methyl iodide at 150 °C for several hours (Scheme 66). Treatment with silver chloride and silver oxide gave *N*-methyl nicotinate monohydrate as long needles, which loses one molecule of water on heating at 100 °C. In 1900, Meyer prepared Trigollenine (**18**) similarly by treatment of 3-carboxy-1-methylpyridinium iodide with silver oxide in water (1900M913, 1903M195, 05M537). Starting from nicotinic acid ethyl ester, treatment with methyl iodide in a sealed tube for 3 h at 100 °C, followed by the addition of silver oxide and hydrogen sulfide to remove excess silver ions gave also Trigollenine (44CB362). Saponification can alternatively be accomplished using an anion exchange resin (Dowex, OH^- form) (84P1225, 56JA4896, 61JOC1318). Pyrolysis of nicotinic acid methyl ester also results in the formation of Trigollenine (55JPC670). Treatment of chinolinic acid (**192**) with methyl iodide in methanol gave carbon dioxide and Trigollenine; no reaction was observed under the same reaction conditions in pure MeI (1901M361). Cocondensation of *N*-methylpyrrol (**193**) with carbon and carbon dioxide at 77 K in a standard carbon arc reactor in which atomic carbon is generated by striking an arc between two high purity graphite electrodes, followed by the addition of HCl and methanol resulted in the formation of 1-methyl pyridine and *N*-methylpyridinium-3-carboxylic acid (97JA5091) which can be deprotonated to give Trigollenine. On heating to 100 °C over a period of several hours chinolinic acid anhydride **196** and methyl iodide form the corresponding pyridinium salt **195** which was converted into the colorless betaine with hot water in 80% yield. Heating in



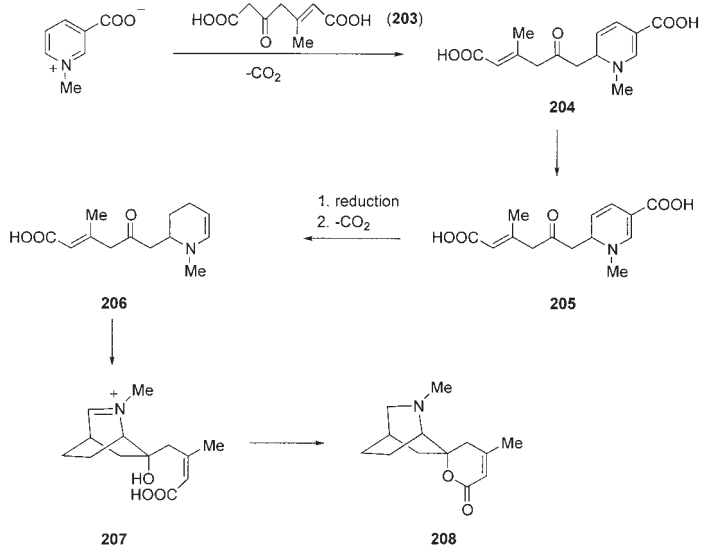
Scheme 67

methanol under reflux gives Trigollenine (**18**) in quantitative yield. When the pyridinium salt **197** was kept at room temperature with sodium methoxide in methanol, ready cleavage of the side chain occurred, giving sodium nicotinate methiodide as a monohydrate (76JCS(P1)315). Pictet and coworkers describe two syntheses of Trigollenine starting from nicotine (**198**). Methylation of nicotine to the pyridinium iodide with methyl iodide, followed by its conversion to the hydroxide with silver oxide in water, oxidation with potassium permanganate to the *N*-methyl nicotinic acid hydroxide and subsequent deprotonation with silver oxide yielded Trigollenine as colorless needles (1897CB2117). In a later publication, the formation of nicotinic acid from nicotine was described. Esterification followed by aminolysis and methylation yielded the *N*-methylnicotinamide (**199**), which gave Trigollenine on treatment with silver oxide (1898MI).

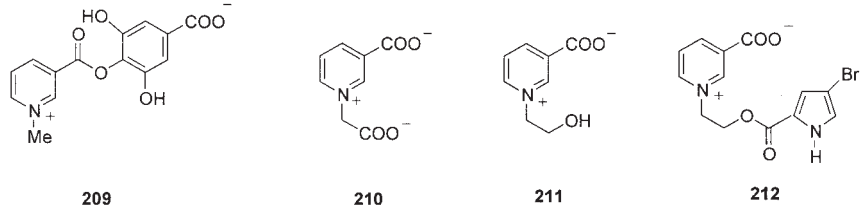
Späth and Bobenberg described a synthesis of Trigollenine starting from metanicotine (**200**), which was methylated at the side chain on reaction with formaldehyde and formic acid in a sealed tube to form **201** (Scheme 67). Hydrogen iodide protonates at the aliphatic nitrogen atom at 0 °C, whereas subsequent reaction with methyl iodide quaternized the pyridine nitrogen to give the *N*-methyl metanicotine derivative **202**. Subsequent treatment with silver chloride, silver permanganate, silver oxide, and H_2S to remove excess silver cations yielded Trigollenine (**18**) (44CB362).

In *Dioscorea hispida*, Trigollenine is incorporated into the isoquinuclidine moiety of the alkaloid Dioscorine (**208**), as proved by a feeding experiment with [*methyl*-^{14}C,2-^{2}H,^{3}H]trigollenine (88P3793). These results are consistent with the hypothesis for the biosynthesis of Dioscorine (**208**), Dumetorine and Dihydrodioscorine, which is presented in Scheme 68.

In the rosary pea *Abrus precatorius* L. Trigollenine as well as its gallic acid ester Precatorine (**209**) is found (71P195) (Scheme 69). 1-Carboxymethylnicotinic acid (**210**) was isolated as a colorless solid from the marine sponge *Anthosigmella* cf. *raromicrosclera* as a cysteine protease inhibitor (98JNP671). This compound was first synthesized in 1991. The sodium



Scheme 68



Scheme 69

salt was identified by the $m/z = 204$ amu ($M^+ + H^+$) and $m/z = 182$ ($M^+ - Na + H^+$) in FAB mass spectrometry. The alkaloid can easily be prepared on reaction of nicotinic acid with iodoacetic acid in DMF, followed by preparative HPLC on an Amide-80 column in a mixture of acetonitrile and methanol and ammonium formate buffer. The ^1H and ^{13}C NMR data are as follows (98JNP671). In contrast to the ^1H NMR values of Trigollenine, the resonance frequency of 2-*H* appears at $\delta = 8.72$ ppm, while 4-*H* and 5-*H* were detected at $\delta = 8.80$ and 8.02 ppm, respectively. The signal of 6-*H* at $\delta = 9.00$ ppm forms a broad singlet. The coupling constants are $^3J_{4-5} = 8.1$ Hz, $^3J_{5-6} = 5.8$ Hz. In ^{13}C NMR spectroscopy, C-2, C-3, C-4, C-5, and C-6 appear at $\delta = 146.8$, 168.5, 137.6, 147.0, 128.3, and 146.0 ppm, respectively. The carboxy carbon atom at C(3) of the pyridinium moiety gives a signal at $\delta = 168.5$ ppm, while the second

COOH group causes a signal at $\delta = 171.5$ ppm. The methylene group appears at $\delta = 64.2$ ppm.

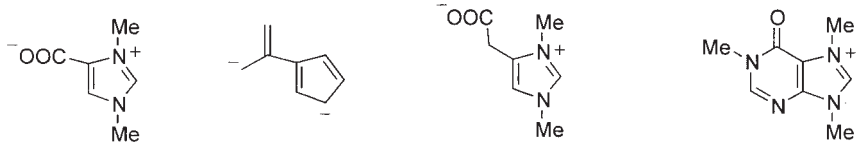
In 1998, Pyridinebetaine A (**211**) and Pyridinebetaine B (**212**) were isolated from the carribean sponge *Agelas dispar* Duchassaing and Michelotti 1860 (98JNP1171) and *Agelas conifera*, *clathrodes* and *longissima*, respectively (97BMC2283) (Scheme 69). The former mentioned species exhibited antibacterial activities against gram-positive bacteria. Pyridinebetaine A can easily be prepared on treatment of sodium nicotinate with oxirane in water at pH 7–11 (59JBC889).

2. *Imidazolium-4-carboxylates*

Norzooanemonine (**213**) (1,3-dimethylimidazolium-4-carboxylate), which may be regarded as a nor-derivative of zooanemonine (**214**), was isolated from the marine sponges *Pseudopterogorgia americana* and *Cacospongia scalaris* as a metamorphosis-inducing compound (73T3135). In addition, it was identified together with Trigollenine (**18**), which is presumably a primary metabolite, in the coralline demosponge *Astrosclera willeyana* Lister 1900 living in the Great Barrier Reef (97TL3883). This animal, termed a living fossil, is a representative of the Palaezoic and Mesozoic reef building sponges, which demonstrates the biological role of these mesomeric betaines over the last 220 million years. It is isoconjugated with the 1-isopropenyl-cyclopenta-1,3-diene dianion which is an even nonalternant hydrocarbon dianion. Thus, norzooanemonine belongs to class 12 of heterocyclic mesomeric betaines. The NMR resonance frequencies are presented in Table VII (94T13583). Note the chemical shift differences on changing the solvent. Characteristic for the proton exchange of the 2-position of dimethylimidazolium in D_2O, the signal at $\delta = 8.63$ ppm rapidly disappears on addition of ammonia vapor. Prominent peaks in the FAB mass spectra were found at $m/z = 141$ amu which

Table VII. NMR Chemical Shifts of Norzooanemonine **213**

Atom	^{1}H NMR (in D_2O)	^{1}H NMR (in DMSO-d_6)	^{13}C NMR (in DMSO-d_6)
2	8.63, s	9.22, s	140.0
4	–	–	125.9
5	7.69, s	8.27, s	128.5
COO^-	–	–	169.8
N(1)–Me	3.87	3.84	36.0
N(3)–Me	3.99	3.98	35.8



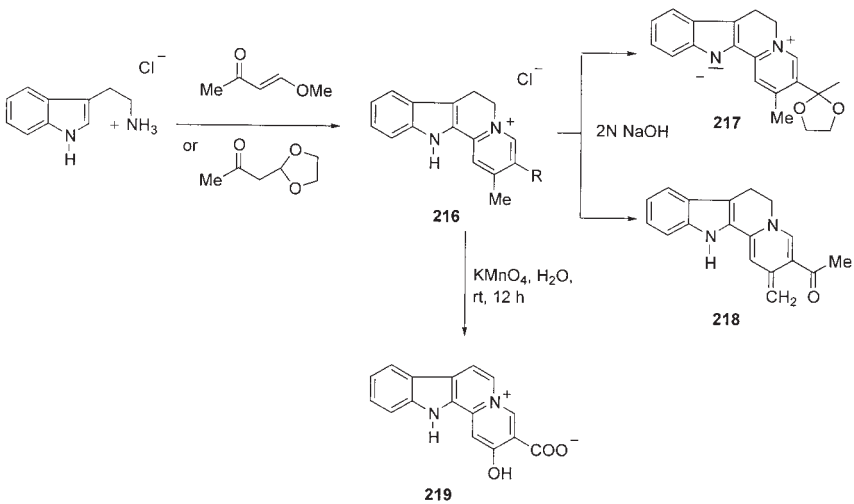
213 **214** **215**

Scheme 70

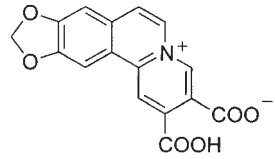
corresponds to the molecular peak, and at 97 amu which is the molecular mass minus carbon dioxide. Norzooanemonine is biogenetically related to 1,7,9-trimethylhypoxanthinium (**215**) (*Jaspis sp.*). The IR spectrum of Norzooanemonine displays a strong carboxylate ion absorption at 1640 cm^{-1} which shifted to 1710 cm^{-1} on protonation with HCl. The syntheses of Norzooanemonine can easily be accomplished by dimethyl sulfate methylation of imidazole-4-carboxylic acid using controlled amounts of NaOH to keep the pH below 9 (Scheme 70).

3. *Pyrido[2,1-a]isoquinoline-3-carboxylic acids*

It is interesting to note that the 7,12-dihydro-2-methyl-6H-indolo[2,3-*a*] quinolizinium chloride (**216**) (R = acetal) can be deprotonated to give the orange–yellow zwitterion **217**, whereas the vinylog amide **218** is formed when R = COMe (Scheme 71). This substitution pattern gives rise to the



Scheme 71



220

Scheme 72

formation of the β-enamino carbonyl chromophor. Oxidation of **216** gives the cross-conjugated mesomeric betaine **219**, but no zwitterionic species, which would result on deprotonation of the hydroxy group (88LA1111). This observation is similar to the chemistry of Neoxygambirtannine (**43**), the indolic NH of which was unambigoulsy proved by NMR spectroscopy.

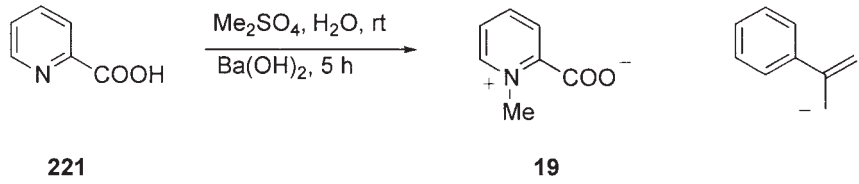
Oxidation of berberine (**49**) with hot dilute nitric acid yields berberidic acid (**220**) (58MI1) which can form a cross-conjugated and a pseudo-cross-conjugated mesomeric betaine on deprotonation as shown in Scheme 72.

D. Pseudo-cross-conjugated Heterocyclic Mesomeric Betaines

1. *Pyridinium-2-carboxylates*

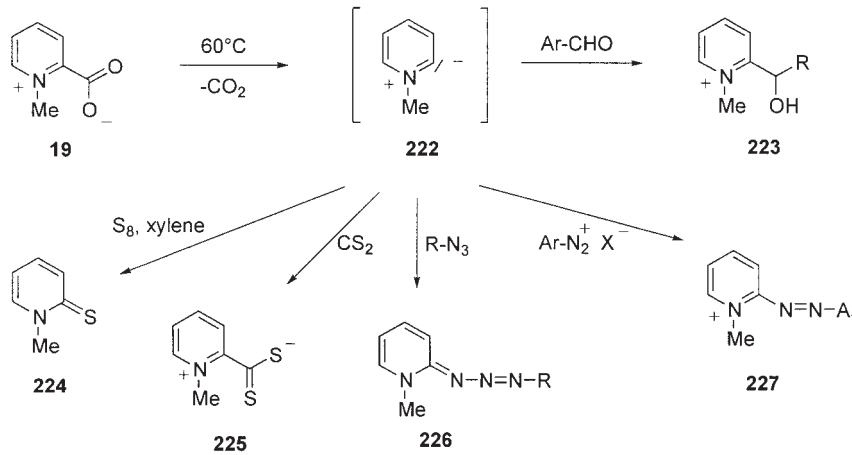
As outlined in Section I, in contrast to 1-methylpyridinium-3-carboxylate the isomeric 2- and 4-carboxylates belong to the class of PCCMB. As they are isoconjugate with the isopropenyl benzene anion (an odd alterant hydrocarbon anion), they are members of class 13 of heterocyclic mesomeric betaines. 1-Methylpyridinium-2-carboxylate (**19**) is called Homarine (33ZPC105) and was isolated from the muscles of lobsters *Homa homerus* (33ZPC45), shells *Arca noae* (33ZPC33), and *Arbatia pustulosa* (24MI), and in the groups of invertebrates *Cnidaria* (Jellyfish, sea anemones, corals), *Porifera*, *Arthropoda* and *Echinodermata* (01MI). Homarine was described as a defense or deterrent compound of *Cnidaria* (58MI3, 89MI3). It presumably affects pattern formation in *Hydractinia* (87MI4) and functions as an osmoregulator (60MI2, 95MI1) and transmethylating agent has been discussed (82JBC11971). Homarin (**19**) was obtained on methylation of picolinic acid in the presence of barium hydroxide (33ZPC105) (Scheme 73).

The ^{13}C NMR data in D_2O at pD 9 are as follows. The carbon atom of the carboxy group appears at $\delta = 165.4$ ppm, and C-2 at $\delta = 152.5$ ppm.



221 **19**

Scheme 73



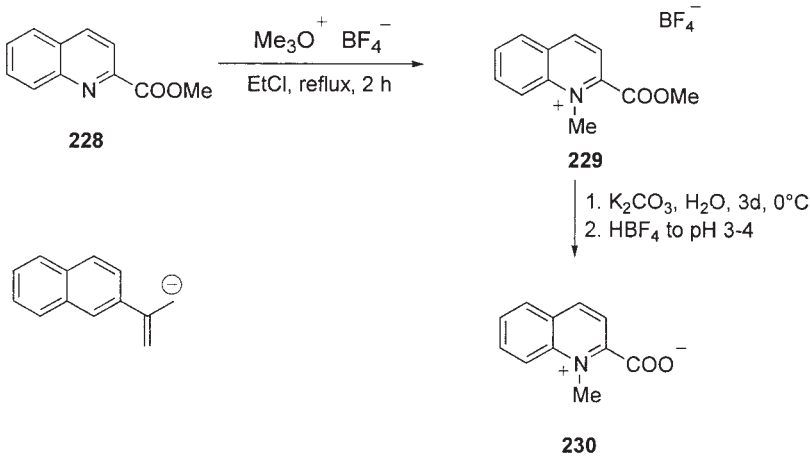
19 **222** **223**

224 **225** **226** **227**

Scheme 74

The resonance frequencies of C-3 and C-5 appear at $\delta = 127.4$ and 126.6 ppm. The atoms C-4 and C-6 give signals at $\delta = 147.7$ and 146.7 ppm in ^{13}C NMR spectroscopy (76JA8237). On saponification of the 2-carboethoxy substituent to the 2-carboxylate group, 3-H and 5-H shift 0.15 and 0.18 ppm to upper field, respectively (82JOC498). The carboxy group can be detected at 1640 cm^{-1} in IR spectroscopy (70LA64).

1-Substituted pyridinium-2-carboxylates lose carbon dioxide at 60 °C in dipolar aprotic solvents such as *N*-methylpyrrolidone, acetonitrile or benzonitrile to form an intermediate nucleophilic carbene **222** which can be trapped by electrophiles (Scheme 74). In protic solvents, pyridine forms (82JOC498). In aprotic solvents, aldehydes give alcohols like **223** (70LA43, 70LA64), sulfur gives pyridine-2-thiones **224**, carbon disulfide gives dithioacids **225** (83S149), azides gives triazenes **226**, and diazonium ions give azo compounds **227**. The decarboxylation of quinoline-2-carboxylic acid at elevated temperatures (Hammick reaction) gave rise to the postulation of nucleophilic carbenes as highly reactive intermediates (37JCS1724). It is noteworthy that considerably higher temperatures are neccesary to



Scheme 75

decarboxylate cross-conjugated mesomeric betaines such as Trigollenine (**18**) (70LA64).

Pyridine-2-carboxylic acid is a structure element of the macrocycle 1,6-bis-deacetylevonine (*Euonymus europaeus*) (02CPB199).

2. *Isoquinolinium-2-carboxylates*

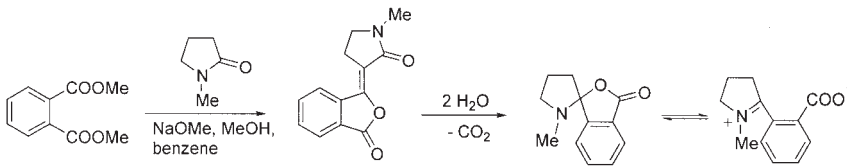
1-Methylisoquinolinium 2-carboxylate (**230**), originally prepared by Quast (70LA64), was recently identified as a defensive betaine from *Photuris versicolor* fireflies (99JNP378). It is a pseudo-cross-conjugated mesomeric betaine isoconjugate to the odd alternant hydrocarbon 2-isopropenyl-naphthalene anion which is an odd alternant hydrocarbon anion. This compound therefore is a member of class 13, which is very rare. The UV absorption maxima λ_{max} (methanol) were found at 235 (4.35), 320 (shoulder, 3.97), and 326 (3.99) nm. This compound undergoes similar reactions as Homarine **19** (Scheme 75). The NMR data are presented in Table VIII.

3. *2-Immoniummethyl-benzoylate*

Shihunine (**233**) (Scheme 76) was isolated from orchids *Dendrobium lohohense* (64CPB749), *Dendrobium pierardii* (71ACSA721), *Dendrobium lohoense* Tang and Wang (68CPB1014) which are used to prepare the Chinese drug Shi-Hu (64CPB749). The ^{1}H NMR spectra reveal that this

Table VIII. NMR CHEMICAL SHIFTS OF **230**

Atom	^{1}H NMR	^{13}C NMR
2	–	155.5
3	7.91	119.4
4	9.07	148.0
4a	–	128.6
5	8.31	130.4
6	7.99	129.7
7	8.24	136.7
8	8.40	118.4
8a	–	138.3
N(1)–Me	4.54	41.2
COO^{-}	–	166.6

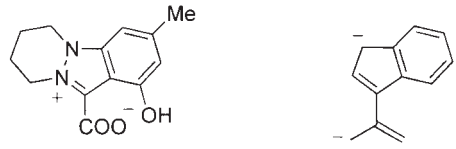


Scheme 76

alkaloid forms a racemic phthalide structure in nonpolar solvents, whereas the pseudo-cross-conjugated form is adopted in methanol or water (71ACSA721). Total syntheses have been described (75T499, 65MI4) and the biosynthesis was examined (73JCS(CC)522). In its betainic form it is isoconjugate with the 1-isopropenyl-2-vinyl-benzene anion, which is an odd alternant hydrocarbon anion.

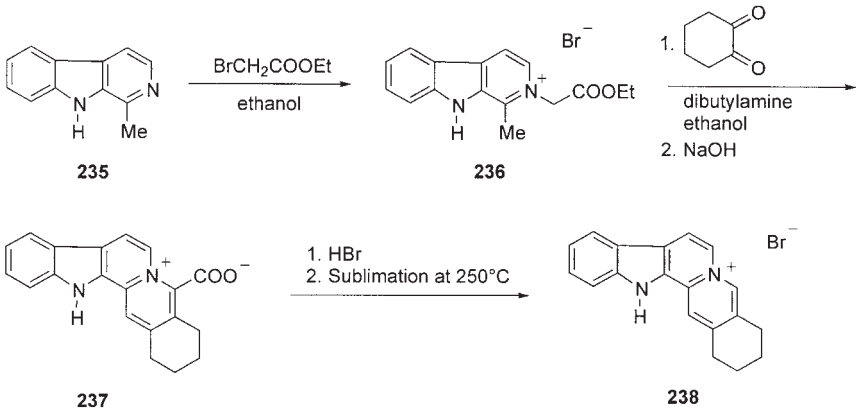
4. *Indazolium-11-carboxylates*

The alkaloid Nigellicine proved to be the pyridazino[1,2-*a*]indazolium-11-carboxylate (**234**) and forms yellow crystals (Scheme 77). It was isolated from the widely distributed herbaceous plant *Nigella sativa* L., which is used as a spice and for the treatment of various diseases (85TL2759). The structure was determined by an X-ray crystal structure analysis. The carboxylate bond distances are essentially equal (123.3 and 125.6 pm). An intramolecular hydrogen bond was found between the carboxylate oxygen atom and the hydroxy group. In mass spectrometry, the molecular peak was found at $m/z = 246$ (20) and the base peak at $m/z = 202$ which corresponds



234

Scheme 77



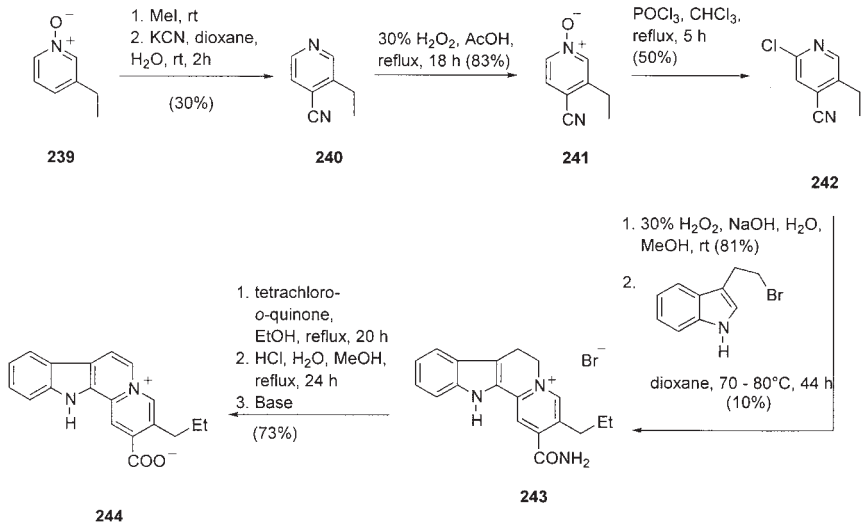
235 236 237 238

Scheme 78

to a decarboxylated species. The hydroxy group appears at 3405 cm^{-1} in an IR spectrum and additional absorptions were found at 1670 and 1650 cm^{-1} which correspond to –CH=N and C=O groups. The carboxylate group is detectable at 1406 cm^{-1}. The parent heterocyclic system is isoconjugate with the 3-isopropenyl-1H-indene dianion as shown in Scheme 77. Pyridaziniumcarboxylates are negatively solvatochromic (02UPI3).

5. *Indolo[2,3-a]quinolizinium-carboxylates*

Quaternization of harman (**235**) with ethyl bromoacetate, followed by cyclization of the pyridinium salt **236** with 1,2-cyclohexane-dione in refluxing ethanol yielded an ester which on hydrolysis gave the pseudo-cross-conjugated mesomeric betaine **237**. Decarboxylation resulted in the formation of the alkaloid Sempervirine (**238**). The PCCMB **237** is isoconjugate with the 11*H*-benzo[*a*]fluorene anion—an odd nonalternant hydrocarbon anion—and belongs to class 14 of heterocyclic mesomeric betaines (Scheme 78).

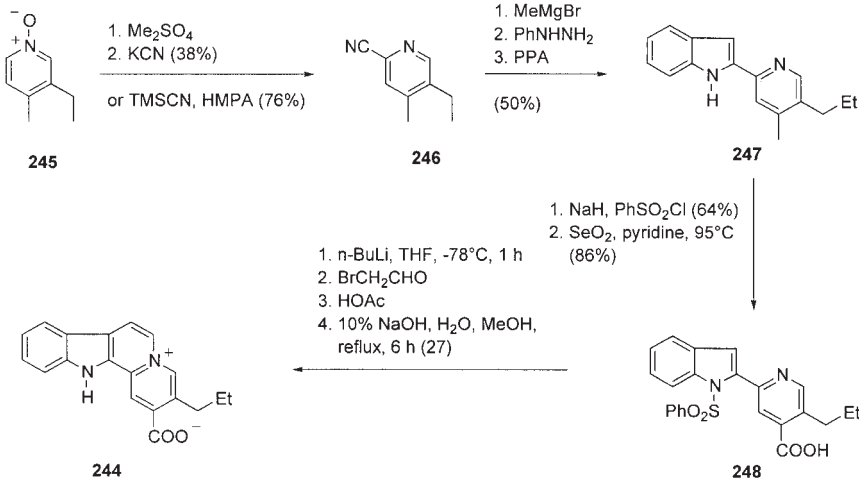


Scheme 79

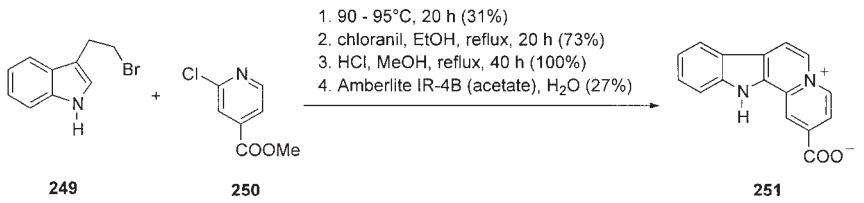
The alkaloid Flavocarpine (**244**) was isolated from the tropical plant *Pleiocarpa mutica* (62JA3393). It contains a quinolizinium-2-carboxylate, which is also known synthetically (64JCS3225). A synthesis (Scheme 79) was published by Büchi and coworkers. Starting from 3-ethylpyridine-N-oxide (**239**), methylation followed by cyanation in the γ-position yielded **240**, which was N-oxidized again by hydrogen peroxide to give **241**. Chlorination gave a mixture of the chloropyridine **242** and its isomer, which was separated by distillation. Hydrolysis to the amide and subsequent Ban-cyclization with tryptophyl bromide gave the desired tetracyclic system **243** in low yield. Aromatization and hydrolysis afforded flavocarpine (**244**) as the hydrochloride. Decarboxylation (Cu, quinoline, reflux, 20 min, 26%) gave the zwitterionic alkaloid Flavopereirine (62JA3393) (cf. Section III).

The pyridine-N-oxide **245** was converted into the cyanopyridine **246** and its isomer (Scheme 80). Grignard reaction, Fischer's indole synthesis, and N-protection gave a pyridinyl indole **247**. Selenium dioxide selectively oxidized the methyl group to give the isonicotinic acid. The synthesis of Flavocarpine (**244**) was finally accomplished by a set of standard reactions as outlined in Scheme 80 (87TL5259).

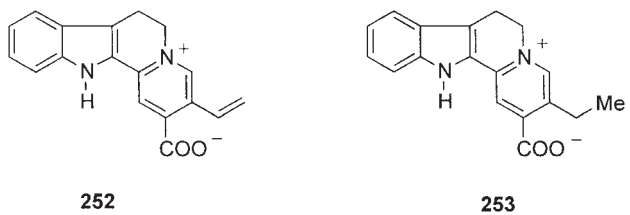
The des-ethyl derivative **251** of Flavopereirine was prepared similarly starting from 2-chloro isonicotinic acid methyl ester **250** (Scheme 81). The resulting hydrochloride was converted into the pseudo-cross-conjugated



Scheme 80



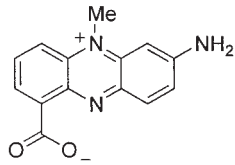
Scheme 81



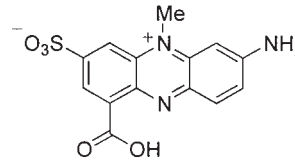
Scheme 82

mesomeric betaine by treatment with Amberlite IR-4B in water (68CPB549).

Vincarpin and Dihydrovincarpin are two additional examples of pseudo-cross-conjugated mesomeric betaines. They were isolated from *Vinca major elegantissima* (76TL4887) (Scheme 82).



254



255

Scheme 83

6. *Phenazinium-1-carboxylates*

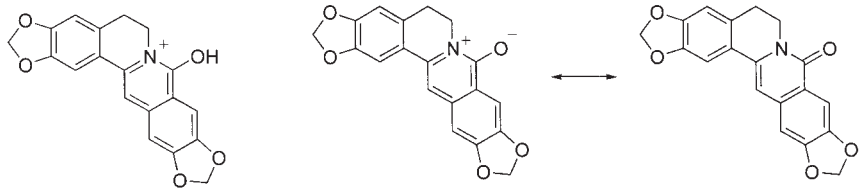
Aeruginosine A (**254**) (69JCS(C)2514) and B (**255**) (61MI2), shown in Scheme 83, are metabolites of the pyocyanine producing *Pseudomonas aeruginosa*. They are isoconjugate with the odd alternant 1-isopropenylanthracene anion (class 13).

III. Zwitterionic Alkaloids

A. 2-Substituted Isoquinolinones

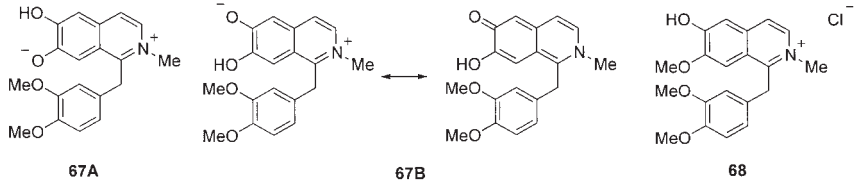
As already mentioned in Section II.A.3, substitution of the 4-, 5-, and 7-position of the isoquinolinium ring with negatively charged substituents results in conjugated mesomeric betaines. In contrast, substitution of the 1-, 3-, 6-, and 8-positions gives rise to the formulation of zwitterionic structures as well as at least one neutral canonical formula so that these compounds do not belong to the class of heterocyclic mesomeric betaines. The 1-hydroxyisoquinolinium moiety was identified in an alkaloid named 8-Hydroxypseudocoptisine chloride (**256**). It was isolated from the roots of *Thalictrum przewalskii* after treatment with 5% hydrochloric acid, extraction and basification with ammonia to pH 9–10. The existence of the hydroxy group was unambiguously proved (98MI3). Deprotonation of **256** resulted in the 2-substituted 2*H*-isoquinolin-1-one form **257**, which was not reported in the original paper (Scheme 84).

As shown in Scheme 26, Papaverine hydrochloride yields a separable mixture of Protopapaverine (**67**) and the salt norpapaverinium chloride (**68**) when heated slightly beyond its melting point for several minutes. Molecule **67** can exist as conjugated mesomeric betaine **67A** (7-hydroxy form) or as 2-substituted-2*H*-isoquinolin-6-one **67B** (6-hydroxy form) (66TL1177). Similar structures were described as zwitterionic pentacyclic

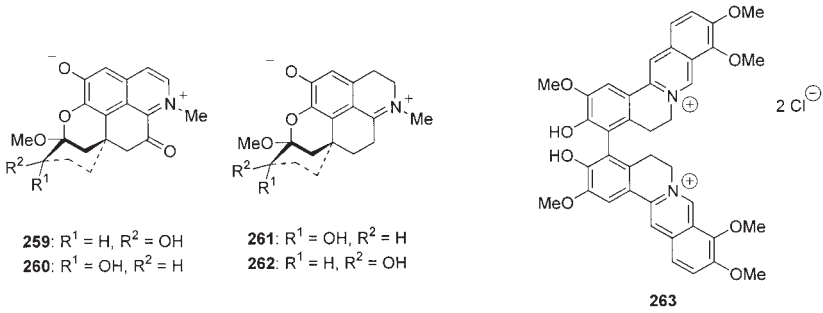


256 257

Scheme 84



67A 67B 68

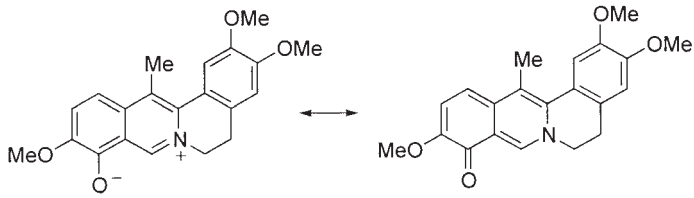


259: R^1 = H, R^2 = OH
260: R^1 = OH, R^2 = H
261: R^1 = OH, R^2 = H
262: R^1 = H, R^2 = OH
263

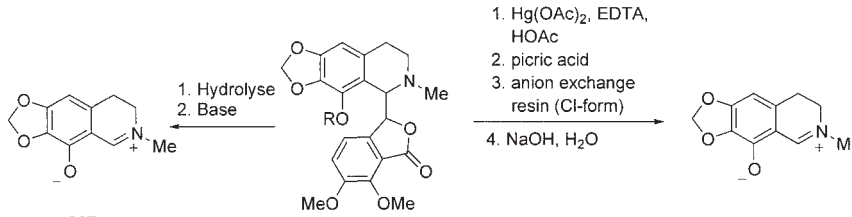
Scheme 85

homopro-aporphines. Thus, Regelinone (**259**) and Isoregelinone (**260**) from *Colchicum kesselringii* (85MI1) both possess the isoquinolinium-6-olate increment (Scheme 85). The corresponding protonated species 6-hydroxy-isoquinolinium has a pK_a of 6.02 (57JCS5010). In contrast to this, Regecoline (**261**), Isoregecoline (**262**) (85MI1) as well as the dimeric protoberberine alkaloid Bisjathrorrhizine dichloride (**263**) (*Jathrorrhiza palmata*) (72JCS(P1)327) have 2,3-dihydroisoquinoline rings. Whereas **261** and **262** were isolated as zwitterions, **263** was identified as a dichloride.

The 8-hydroxyisoquinoline moiety is present in the following alkaloids. Casadinium chloride (**264**) (9-desmethyldehydrocorydaline) gives a stable and characterizable betaine on treatment with sodium hydroxide (76TL1595) (Scheme 86). It was found in *Ceratocapnos*



Scheme 86



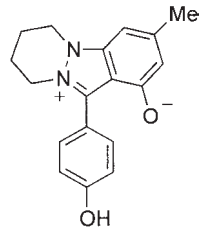
Scheme 87

heterocarpa. A bathochromic shift of the UV absorption maxima of the chloride of **264** is observable on addition of base (93P559).

The papaver alkaloid Narcotoline (**265**) can be converted into the yellow colored Cotarnoline (**267**) on hydrolysis which adopts a zwitterionic ground state (56MI1, 57MI1) (Scheme 87). The corresponding dihydro derivative was also identified in nature. The UV spectrum of the zwitterionic Tarkonine (**268**), which forms red crystals from acetone, is shifted bathochromically in comparison to the chloride. Tarkonine is a very weak base ($pK_b = 9.58$), which is well in accord with the formation of an inner salt, and Cotarnoline (**267**) is a stronger base than Tarkonine (**268**) ($pK_b = 9.15$). The pK_s values are larger than 13 (66MI3). The methylated derivative of Narcotoline is Narcotine (**266**).

B. 1,2-Dihydroindazol-4-one

The indazole alkaloid Nigellidine (**269**) (Scheme 88) which was described as a zwitterion, was detected in the seeds of *Nigella sativa* L. (Ranunculaceae) (95TL1993), which is an erect annual plant found in South Asia and is widely cultivated. The seeds are commonly believed to have carminative, stimulatory and diaphoretic properties (75PHA2759). An X-ray single crystal analysis was performed on the methyl chloride. It is



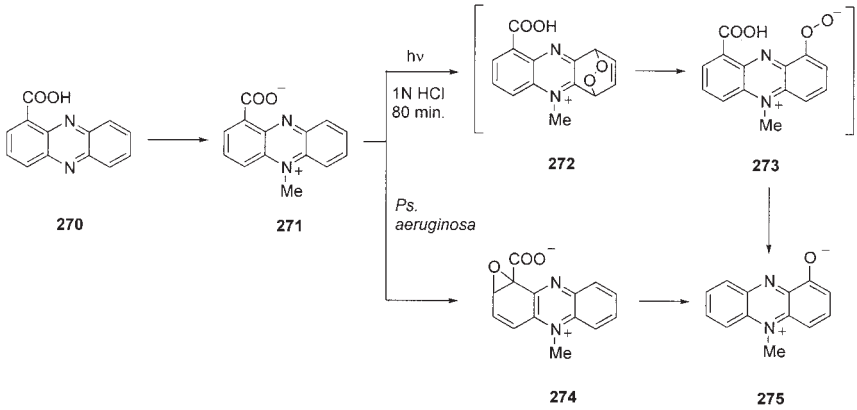
269

Scheme 88

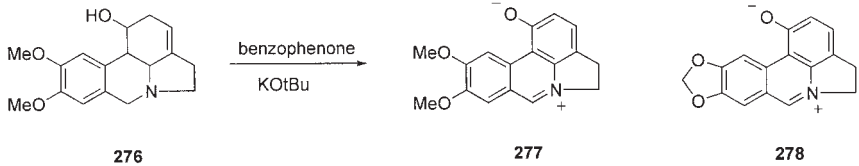
structurally related to Nigellicine (**234**) (cf. Scheme 77) which is a pseudo-cross-conjugated mesomeric betaine.

C. Phenazin-1-ones (Pyocyanines)

Pyocyanine (**275**) (cyanomycine, 5-methylphenazinium-1-olate), known for decades, is a dark-blue pigment with antibiotic activity (94MI1) which was isolated in 1972 from *Pseudomonas aeruginosa* (72JCS(P1)622), *Streptomyces cyanoflavus*, and *Bacillus pyocyaneus* (Scheme 89). It is structurally related to the heteroaromatic N-oxides Aeruginosine A (**254**) and Iodinine (**177**) (cf. Sections II.B.3 and II.B.6, respectively). Photo-oxidation of the quaternary salt **271** in hydrochloric acid gave Pyocyanine (**275**) in low yield together with 9-hydroxy- and 6-hydroxyphenazine-1-carboxylic acid and other by-products. This finding suggests a mechanism



Scheme 89



276 277 278

Scheme 90

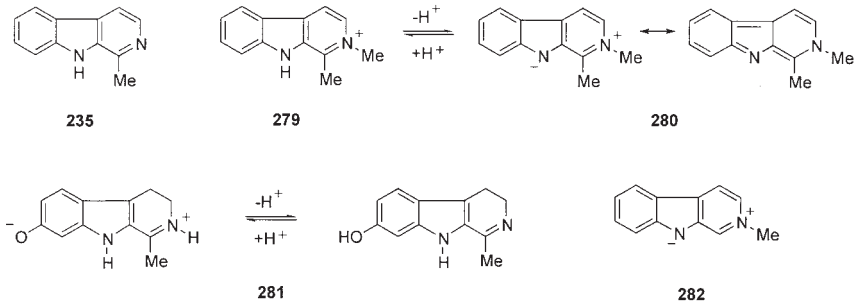
via the formation of a 1,4-endoperoxide with singlet oxygen (70TL4101). It has been shown that 1-hydroxyphenazine is not precursor of Pyocyanine (59MI1). Tracer experiments, however, have shown that phenazine-1-carboxylic acid and its 5-methyl betaine are incorporated into pyocyanine by *Ps. aeruginosa* by decarboxylative hydroxylation (72JCS(P1)622).

D. Phenanthridin-1-one

Oxidation of Pluviine (**276**), isolated from *Narcissus pseudonarcissus*, *Narcissus incomparabilis*, and *Lycoris radiata* Herb., with benzophenone and potassium *tert*-butylate yielded a red phenol-betaine **277** from which one neutral covalent form can be drawn (Scheme 90). The betaine has absorption maxima λ_{max} ($\log \varepsilon$) in a buffer at pH 10 at 240 (4.49), 325 (4.46), 360 (3.58), 380 (3.27), and 490 (3.26) nm. In dilute HCl, a salt is formed [$\lambda_{max} = 260$ (4.57), 295 (4.39), 340 (3.76), 355 (3.84), 400 (3.62) nm] (57CB363). The oxidation of the alkaloid Caranine gives a similar betaine, the 1,3-dioxolo derivative **278** (56CIL348).

E. Indole Derivatives

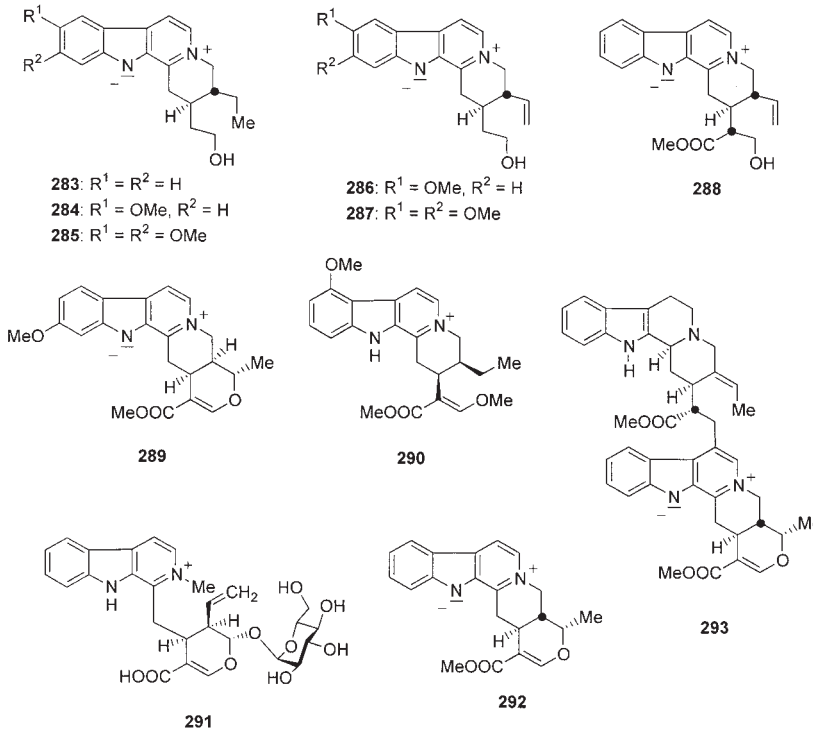
More than 1500 indole alkaloids are known today, among them β-carbolines and indolo[2,3-*a*]quinolizines which form by far the largest collection of interesting zwitterionic species in nature (88MI1). An excellent review dealing with this class of compounds appeared in 1988 so that only some representative results of the last two decades are mentioned here. The β-carboline ring is composed of a π-deficient pyridine ring fused to a π-excessive indole moiety. 1-Methyl-9*H*-pyrido[3,4-*b*]indole (**235**) (Harman, Passiflorine, Aribine, Loturine) is the structural element of numerous alkaloids from *Passiflora incarnata* and other Passifloraceae and Rubiaceae (Scheme 91). The formation of zwitterionic species in the β-carboline series on treatment of the quarternary pyridinium salts with bases is well-documented. On deprotonation, a characteristic shift of the UV



Scheme 91

absorption maxima to longer wavelengths is observed (68JOC3985). Thus, the *N*-methylated Harman (**279**), a cationic species, has UV absorption maxima in aqueous solution at $\lambda_{max} = 248$ (4.40), 303 (4.17), and 366 (3.35) nm and a fluorescence emission at $\lambda_{max} = 437$ nm. The zwitterionic form **280**—called Melinonine F (83MI4, 86MI2, 85MI2) and isolated from the stem bark of *Strychnos mellodora* S. MOORE (99P1171)—has UV absorption maxima at $\lambda_{max} = 272$ (4.20), 321 (3.82), and 357 (3.25) and a fluorescence emission maximum at $\lambda_{max} = 511$ nm (93JCS(P2)99). Dihydroharmalol (**281**) (4,9-dihydro-1-methyl-3H-pyrido[3,4-*b*]indol-7-ol) is a fluorescent alkaloid which is of considerable pharmacological interest as a hallucinogen. According to UV measurements, it exists at pH 10.2 as a mixture of the neutral ($\lambda_{max} = 340$ nm) and the zwitterionic forms ($\lambda_{max} = 431$ nm), and it is likely that the anionic and cationic species are also present. Obviously, the bathochromic shift is characteristic for the betainic form. From the flurorescence spectra it can be concluded that the zwitterionic species with the absorption maximum λ_{max} at 530 nm is present in the pH range between 6 and 12. No fluorescence of the neutral form of harmalol was detected in aqueous solutions. From the pK_a data it was concluded that the hydroxy group of harmalol is more acidic and the pyridine nitrogen atom is more basic in the excited singlet state S1 in comparison to the ground states (84MI3, 61BCJ533). Normelinonine F (**282**) (83MI2) (2-methylnorharman-hydrochloride) was also identified in plants. Recently, the brominated alkaloids 2-Methyleudistomin D and J were isolated from *Eudistoma gilboverde* (01JNP1454). They represent the simplest structures of this class of alkaloids.

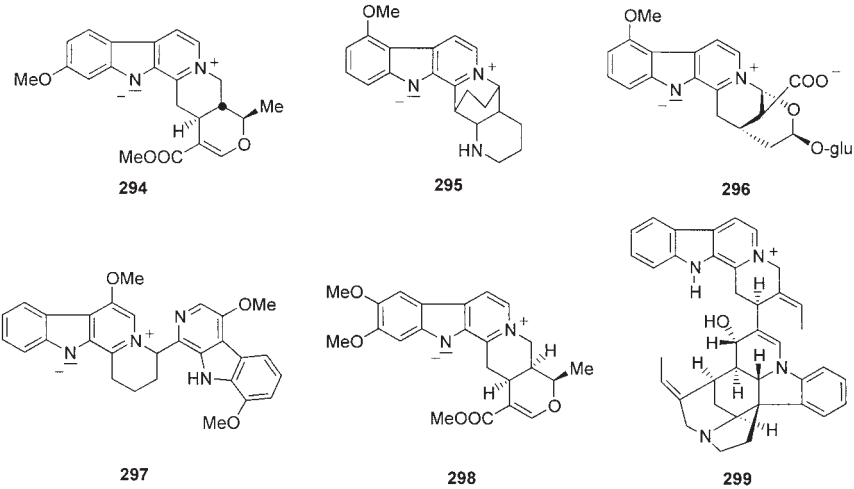
Scheme 92 proves that the β-carboline moiety is widespread in nature. Thus, 3,4,5,6-Tetradehydro-18,19-dihydrocorynantheol (**283**), 10-(Methoxy-3,4,5,6-tetradehydro-18,19-dihydrocorynantheol (**284**), the initially postulated structure 3,4,5,6-Tetradehydroochropposine (**285**) (cf. Scheme 96),



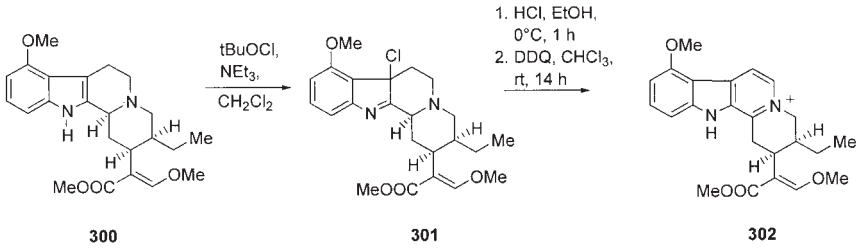
Scheme 92

10-Methoxy-3,4,5,6-tetradehydrocorynantheol (**286**), 3,4,5,6,18,19-Hexadehydroochropposinine (**287**), 3,4,5,6-Tetradehydrositsirikine (**288**), Alstonine (**289**), the no-name-alkaloid (**290**) (*Mitragyna* speciosa) (98T8433), 3,4,5,6-Tetradehydropalicoside (**291**) and its methylester which were isolated recently from *Strychnos mellodora* (99P1171), Serpentine (**292**), and Serpentinine (**293**) are known representatives of this class of alkaloids.

This ring system is also contained in Serpenticine (**294**), Schoberidine (**295**), and Ophiorine (**296**) (Scheme 93). Picrasidine F (**297**) was identified as a hydrochloride in *Picrasma quassioides* and its structure was elucidated by an X-ray structure analysis (86CPB3228). Bleekerine (**298**) is an additional example. 3′,4′,5′,6′-Tetradehydrolongicaudatine (**299**)was identified in 1998 in *Strychnos usambarensis* collected from the Ivory Coast. The roots are the main ingredients of African arrow poisons. The absorption maxima were found at $\lambda_{max} = 204$, 255, 308, and 367 nm in acidic as well as neutral solutions, thus suggesting a β-carbolinium chromophore. A bathochromic shift was observed on deprotonation, due to the formation of a zwitterionic species (98P1263).



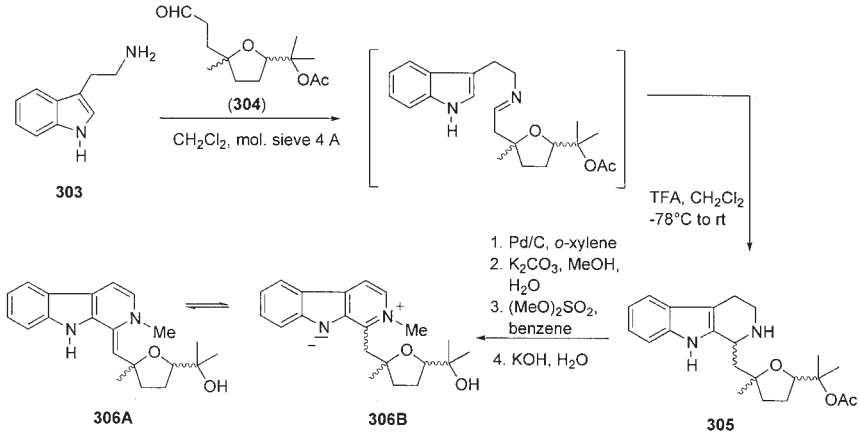
Scheme 93



Scheme 94

3,4,5,6-Tetrahydromitragynine (**302**) (Scheme 94) was extracted from the tropical plant *Mitragyna speciosa* (Rubiaceae), found in Thailand and the Malay Peninsula. The leaves are traditionally used as a stimulant, which is illegal now due to the narcotism of the plant. For structure and absolute stereochemistry elucidation the orange alkaloid was semisynthetically prepared from Mitragynine (**300**), which was treated with *t*-butylhypochlorite in the presence of triethylamine to give **301**. Ethanolic HCl and DDQ for aromatization converted **301** into the alkaloid **302** (98T8433).

The *β*-carboline alkaloid Chrysotricine (**306**) was identified in the Rubidea species *Hedyotis chrysotricha* and proved to inhibit the growth of HL-60 cells *in vitro* (97P1119). The form **306A** was established by an X-ray single crystal analysis and the $CDCl_3$ NMR spectra are consistent with this structure (Scheme 95). However, the spectra taken in CD_3OD display additional CH groups at $\delta = 86.4$ and 3.78 ppm, respectively, which are

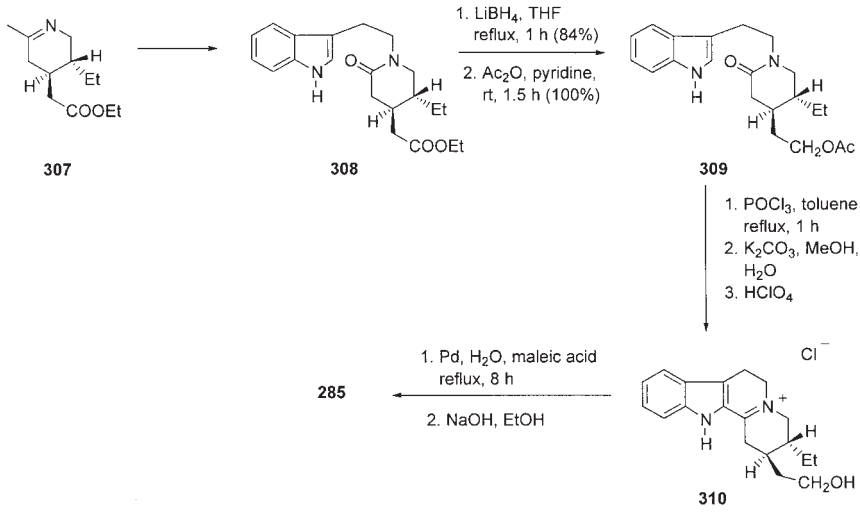


Scheme 95

in accord with the tautomeric structure **306B**. The racemate of this alkaloid and its diastereomer were prepared as outlined in Scheme 95 (00M383). Pictet–Spengler reaction of tryptamine (**303**) with **304** resulted in the formation of the tetrahydrocarboline **305** as mixture of four diastereoisomers. Dehydrogenation to the β-carboline, deacetylation with base, quaterization with dimethylsulfate and subsequent deprotonation with potassium hydroxide led to racemic Chrysotricine (**306**) and its diastereomer.

In 1983, a zwitterionic indolo[2,3-*a*]quinolizine alkaloid was detected in the trunk bark of *Aspidosperma marcgravianum* Woodson. The assigned structure of 3,4,5,6-Tetradehydro-17-hydroxycorynanium (**285**) was deduced on the basis of spectroscopic methods and a semisynthetic sample prepared from corynan-17-ol (83JNP694) (Scheme 96). In 1993 a total synthesis was attempted. Selective reduction of the lactam ester **308** prepared from **307** gave a lactam alcohol, which was acylated to give **309**. Bischler-Napieralski cyclization followed by hydrolysis yielded a tetracyclic alcohol **310**, which was isolated as a perchlorate salt. Aromatization was accomplished using palladium black and maleic acid in boiling water. The anhydronium base **285** was finally obtained after treatment with sodium hydroxide. The NMR spectra of the reaction product and the alkaloid isolated from the natural source as well as the signs of the specific rotation, however, were not identical.

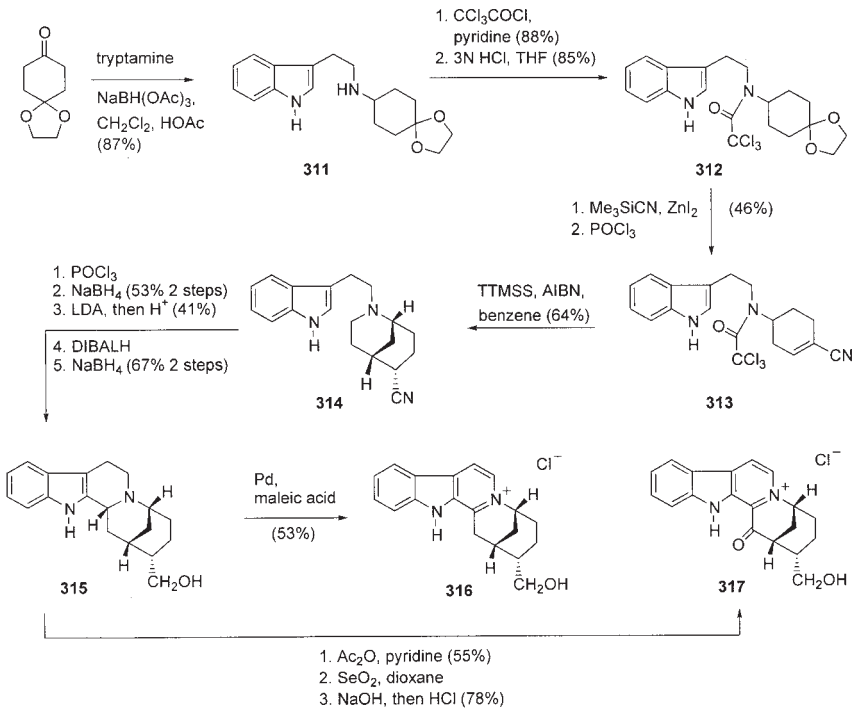
Total syntheses of racemic Melinonine E (**316**) and Strychnoxanthine (**317**) were performed using a radical cyclization process as the key step (98JOC968). Melinonine E was first isolated from the bark of *Strychnos melinoniana* in 1957 (57HCA1167), but structure elucidation was not carried



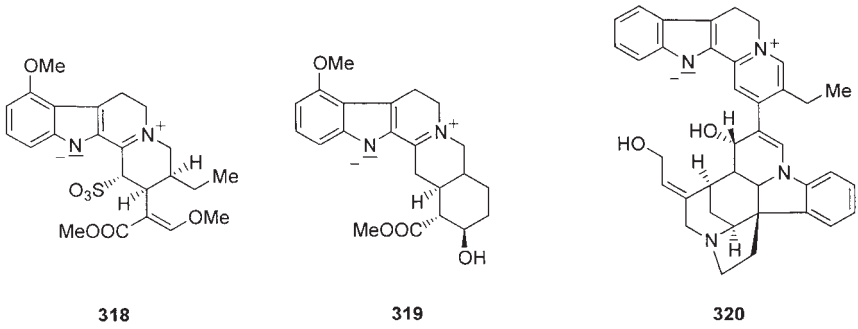
Scheme 96

out before 1984 (84HCA455). Strychnoxanthine was found in the bark of *Strychnos gossweileri* (84MI1). Reductive amination of the protected 1,4-cyclohexanedione with tryptamine yielded **311**, which was trichloroacetylated and hydrolyzed to give **312** (Scheme 97). For the purpose of the one carbon homologation the cyanhydrine was produced by treatment of **312** with trimethylsilyl cyanide and zinc iodide, followed by the hydrolysis of the intermediary O-silylcyanohydrine. Phosphorus oxychloride converted the cyanohydrine into the nitrile **313**. On treatment with tris(trimethylsilyl) silane (TTMSS) as the radical mediator cyclization to the 2-azabicyclo[3.3.1]nonane **314** took place. A sequence consisting of Bischler–Napieralski reaction and $NaBH_4$ reduction gave a 3-H β relative configuration and a trans C/D ring quinolizidine moiety. Epimerization of C-20 was partially accomplished by LDA and subsequent quenching with hydrochloric acid at $-78\,^{\circ}C$. Reduction of the nitrile to the imine, hydrolysis to the aldehyde and reduction gave the common precursor **315**. The target compounds were finally obtained as shown in Scheme 97.

Mitrasulgynine (**318**) (*Mitragyna speciosa*) (98T8433) and 3,4,5,6-Tetradehydro-β-yohimbine (**319**) possess the 2,3-dihydro β-carboline moiety. The asymmetric bisindole alkaloid Strychnocrysine (**320**) was isolated as an orange solid from *Strychnos nux-vomica* (98JNP139). The UV spectrum is not modified in alkali and no NH of the indole ring is detectable by NMR spectroscopy. The closely related structures 5′,6′-Dehydroguiaflavine and 5′,6′-Dehydroguiachrysine were recently identified in *Strychnos guianensis* (01P619) (Scheme 98).

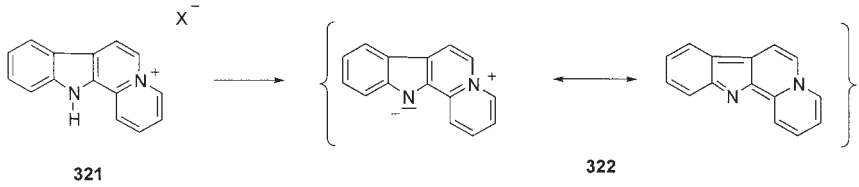


Scheme 97



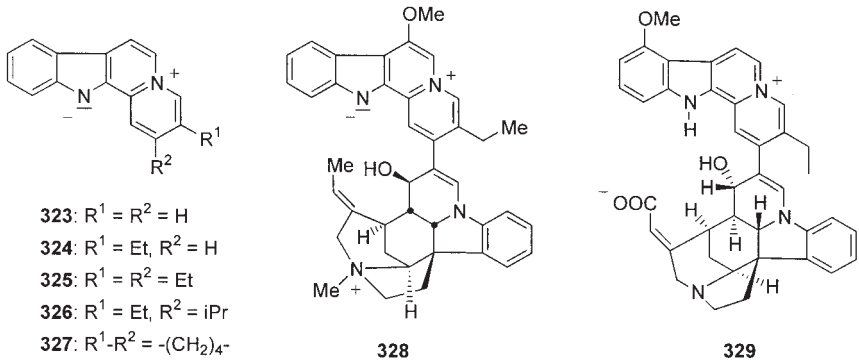
Scheme 98

The parent skeleton of the alkaloids containing the indolo[2,3-*a*] quinolizinium ring system **321** was examined spectroscopically (Scheme 99). On conversion to the deprotonated form **322** in CD_3OD, all resonance frequencies shift to higher field and this tendency is particularly



321 322

Scheme 99



323: $R^1 = R^2 = H$
324: $R^1 = Et$, $R^2 = H$
325: $R^1 = R^2 = Et$
326: $R^1 = Et$, $R^2 = iPr$
327: R^1-R^2 = -$(CH_2)_4$-

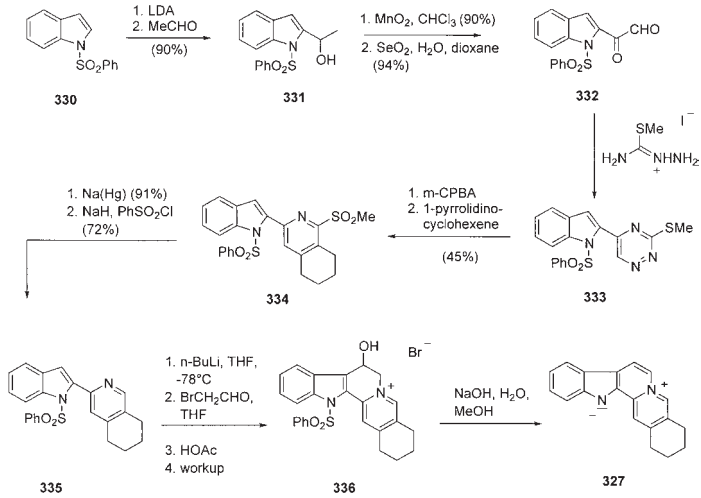
328 329

Scheme 100

remarkable for the C ring protons. An additional upfield shift is observed in $CD_3OD/NaOD$, whereas the reverse is the case for the solvent systems CD_3OD/D_2O and CD_3OD/DCl. The authors postulate an equilibrium between the uncharged and protonated forms in protic solvents (93T1879).

Indolopyridocoline (**323**), Flavopereirine (**324**) (Melinonine G), Flavocoryline (**325**), Flavocorynanthrine (**326**), and Sempervirine (**327**) are examples of this class of compounds (Scheme 100). Afrocurarine (**328**) was identified in *Strychnos usambarensis* (84MI2). Guianensine (**329**) (*Strychnos guianensis*) has a zwitterionic bis-indole structure with the negative and positive charges separated by interrupted conjugation. On treatment with alkali, a bathochromic shift of the UV absorption maxima is observable, suggesting an anhydronium moiety (95P1557).

The key step of an interesting synthesis of Sempervirine (**327**) is a triazine Diels–Alder annulation reaction with an enamine (88T3195). 1-(Phenylsulfonyl)indole **330** was converted to a ketone by a set of standard reactions followed by the selenium dioxide oxidation of the resulting acetyl goup to the ketoaldehyde **332** (Scheme 101). Methylthiosemicarbazide hydroiodide reacted with **332** to the triazine **333** in 83% yield. As Diels–Alder reactions with 1-pyrrolidinocyclohexene failed, **333** was first oxidized



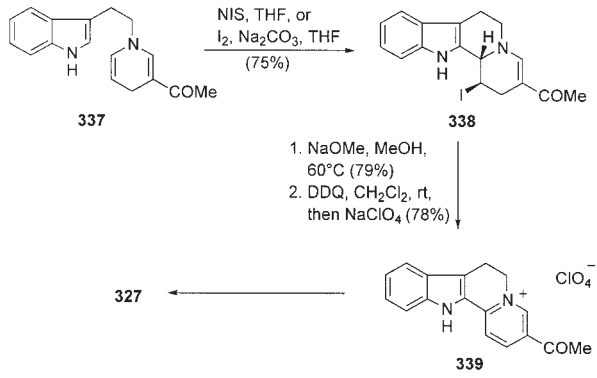
Scheme 101

to the corresponding sulfone triazine. Cycloaddition to the pyridine sulfone **334** was then accomplished in 45% yield for the two steps. Sodium amalgam under carefully controlled conditions caused a complete desulfonylation without reduction of the pyridine ring. Treatment of the sulfonylated species **335** with butyl lithium followed by quenching with bromoacetaldehyde provided the indoloquinolizinium bromide **336**, which on alkaline hydrolysis yielded the zwitterionic Sempervirine (**327**).

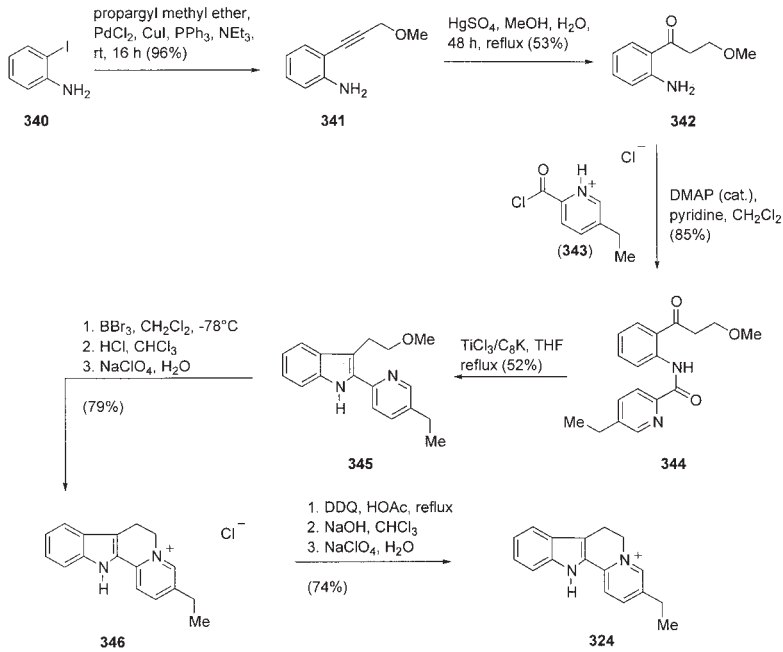
The iodocyclization of 1,4-dihydropyridines was used as the key step for the formal total synthesis of Sempervirine (**327**) as shown in Scheme 102 (99JOC2997).

Total syntheses of Flavopereirine (**324**) and 5,6-Dihydroflavopereirine (**346**) were performed as presented in Scheme 103 (96H1365). Palladium-catalyzed reaction of iodoaniline **340** with propargyl methyl ether gave alkyne **341**, which was subsequently hydrated to ketone **342** by slowly adding it to refluxing methanol containing catalytic amounts of mercuric sulfate. Acylation, low-valent titanium mediated indole formation with titanium graphite gave **345**. Bromination was accomplished by boron tribromide. Cyclization yielded 5,6-dihydroflavopereirine (**346**), which was finally aromatized with DDQ to give Flavopereirine (**324**). The perchlorate was finally converted into the free base (95T773).

An interesting observation has been described in Section II.C.3 (Scheme 70). 7,12-Dihydro-2-methyl-6*H*-indolo[2,3-*a*]quinolizinium chloride (**214**) can be deprotonated to give the orange–yellow zwitterion **215** or the vinylog amide **216** depending on the substitution pattern (Scheme 104).

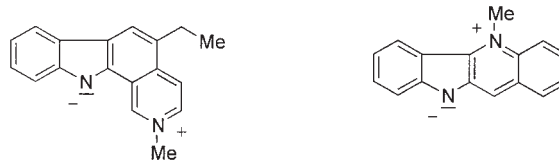


Scheme 102



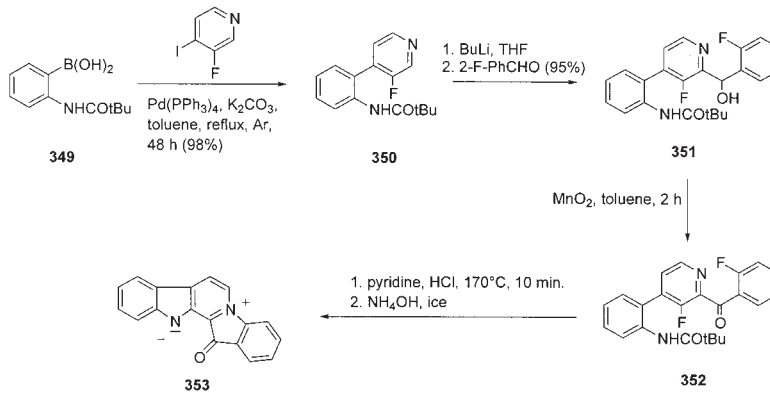
Scheme 103

Oxidation yields the cross-conjugated mesomeric betaine **217**, but no zwitterionic species, which would result by deprotonation of the indole NH group (88LA1111). The corresponding 5,6-unsaturated indole, however, gave the zwitterion. The same publication describes a total synthesis of Flavoserpentine.



347 348

Scheme 104

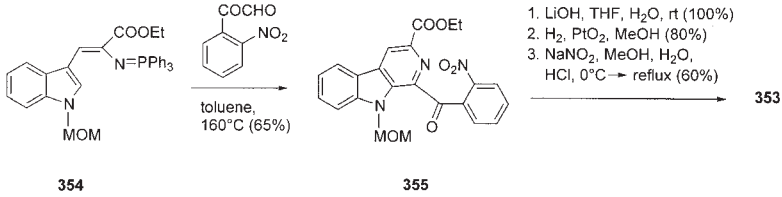


349 350 351 352 353

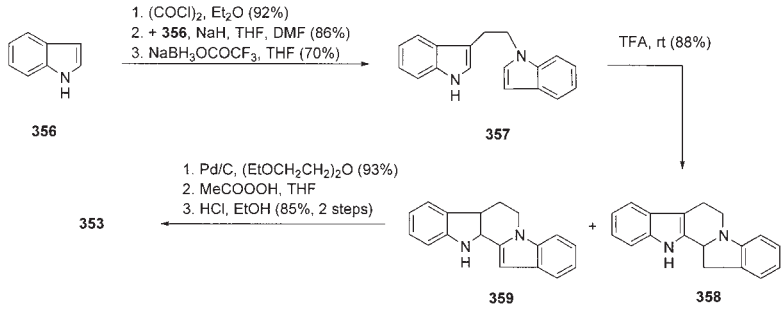
Scheme 105

The yellow colored, sparcely soluble 5-ethyl-2-methyl-11*H*-pyrido[3,4-*a*] carbazolium **347** isolated from *Aspidosperma gilbertii* exists as a hydroxide after filtration of the corresponding iodide over basic aluminum oxide. A short synthesis was described (80CB3245). The Pyrido[3,4-a]carbazole ring system is present in the alkaloid AG-1, whereas Cryptolepine (**348**) possesses the indolo[3,2-b]quinoline moiety (65MI1).

A heteroaromatic pentacycle is found in Fascaplysine (**353**) (Scheme 105). This bis-indole alkaloid is an antimicrobial and cytotoxic red pigment from the Fijian sponge *Fascaplysinopsis Bergquist* sp. It inhibits the growth of microbes and displays activity against mouse leukemia *in vitro*. A broad exchangeable resonance frequency at $\delta = 11.5$ ppm suggested the existence of an N–H functionality. In the X-ray single crystal analysis, the chloride is in close contact (210 pm) to the N–H group (88JOC3276). At least three total syntheses were performed. Suzuki's Palladium-catalyzed cross-coupling of **349** with 3-fluoro-4-iodopyridine followed by regioselective metalation of the resulting **350** and treatment of the lithio derivative with 2-fluorobenzaldehyde gave the trisubstituted pyridine **351**. Oxidation and subsequent cyclization with pyridinium chloride at



Scheme 106



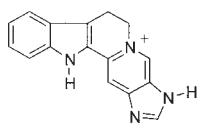
Scheme 107

170°C gave the dark red alkaloid **353** as chloride (93TL7917). The overall yield is 76%.

Another total synthesis used the rich chemistry of iminophosphoranes (95AHC159). The β-(3-indolyl)vinyl iminophosphorane **354** underwent an aza-Wittig/electrocyclic ring closure reaction to give the carboline **355** which was hydrolyzed with lithium hydroxide (Scheme 106). A selective reduction, deprotection, decarboxylation and diazotation followed by ring closure gave Fascaplysine (**353**) (94TL8851).

Another synthesis of Fascaplysin was reported by Gribble (90TL2381) and is presented in Scheme 107. The diindole **357** was available starting from indole **356**, which was first converted into 3-indolylglyoxylyl chloride. Reaction with 1-indolylsodium followed by a reduction of the resulting keto amide gave **357**. Trifluoroacetic acid at room temperature gave the cyclized products **358** and **359** in a 10:1 ratio, which were oxidized without separation to give the fully aromatic pentacycle. Final oxidation yielded Fascaplysine (**353**).

The indoloquinolizidine alkaloid Villagorgin B (**360**) was isolated from the Gorgonian *Villagorgia rubra* collected in New Caledonia (Scheme 108). The positive charge of the molecule was deduced from the chemical shifts of the C-6 and C-5 ethylene bridge. However, only one NH group was detectable in ^{1}H NMR in DMSO-d_6 (93TL7773). Additional heteroaromatic



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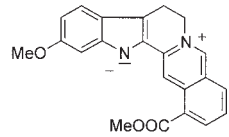
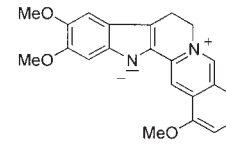
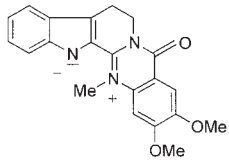


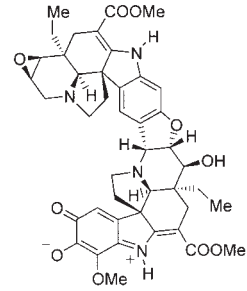
361



362



363



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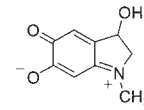
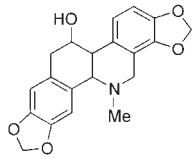


365

Scheme 108



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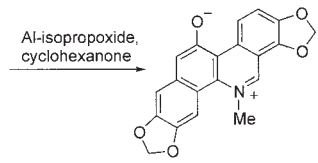

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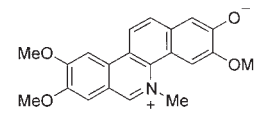


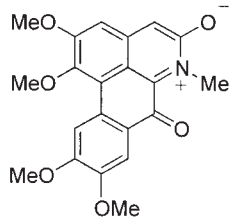
368

Scheme 109

pentacyclic systems are in 6,12-dihydroindolo[2,3-*a*]quinolizines present in Alstoniline (**361**) and Orouparine (**362**) from which Euxylophorine A (**363**) (68TL4865, 83MI5) has an additional keto group. The interesting molecule Polyervinine (**364**) was detected in *Ervatamia polyneura* (95P953). It possesses a quinoniminium chromophore (**365**), which was confirmed by a spectroscopic comparison with the dark red pigment adrenochrome.

F. Benzo[*c*]phenanthridinones

Hydroxysanguinarinebetaine (**367**) is formed on Oppenauer oxidation of Chelidonine (**366**) as a red compound (65MI2) (Scheme 109). Deprotonation of the benzo[*c*]phenanthridine alkaloid Fagaronine (93T10305), which is known to inhibit various reverse transcriptases (77MI1), resulted in the



369

Scheme 110

formation of a molecule **368** from which neutral as well as zwitterionic canonical formulae can be drawn. A total synthesis of Fagaronine has been described (02TL5323).

G. Dibenzo[*de*,*g*]quinoline-5,7-dione

Pontevedrine (**369**) is a red compound from Papaveraceae (71TL3093). The UV–VIS absorption maxima λ_{max} in ethanol were found at 245 (4.59), 312 (4.28), 325 (4.39), and 470 (4.01) nm. On addition of acid or alkali no changes were observable. A zwitterionic structure was proposed on the basis of the NMR data (Scheme 110).

IV. Conclusions

This review, which cannot be comprehensive because the reports describing these interesting classes of natural products are scattered throughout the literature, demonstrates that conjugated heterocyclic mesomeric betaines (CMB) including their subdivision of N-ylides form by far the largest group of mesomeric betaines in nature. Most of the betainic alkaloids and nucleobases described here are isoconjugate with odd alternant hydrocarbon anions and are therefore members of the classes 1 (CMB), 5 (N-ylides), 9 (CCMB), and 13 (PCCMB), respectively. The classes 4, 7, and 16 are also relatively populated whereas representatives of some classes seemingly have not yet been isolated from natural materials. It is interesting to note that mesomeric betaines of class 1 and 4 (which include mesoions such as sydnones and münchnones) are well-known in heterocyclic chemistry and numerous compounds have been synthesized to date. The same is true for the class of N-ylides. Cross-conjugated mesomeric betaines, which belong to the classes 9 and 12, are extremly rare in synthetic

heterocyclic chemistry. It is astonishing, therefore, that the former mentioned class obviously occurs relatively often in nature. Little information about pseudo-cross-conjugated heterocyclic mesomeric betaines has been collected to date. In comparison to their synthetic analogs, they were relatively frequently isolated from natural materials. No representatives of PCCMB belonging to class 16 were known when the classification of heterocyclic mesomeric betaines was published in 1985 (85T2239). This review presents six alkaloids (**234**, **237**, **244**, **251**, **252**, **253**), which belong to that class.

Acknowledgments

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Recent Development in the Chemistry of Pyrido-oxazines, Pyrido-thiazines, Pyrido-diazines and Their Benzologs. Part 2

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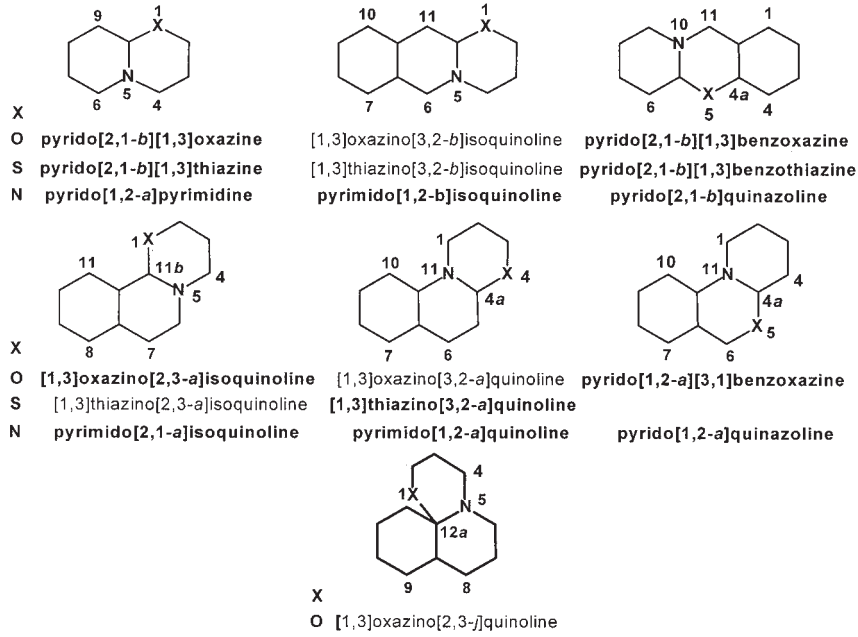
I. Introduction

This review is the second part of a survey on the recent developments in the chemistry of pyrido-oxazines, pyrido-thiazines, pyrido-diazines and their benzologs. The first part was published recently (03AHC(84)219), and the second part covers the ring systems depicted in Scheme 1. The chemistry of the bicyclic 6–6 system containing one ring junction nitrogen and one extra heteroatom and their benzologs was reviewed in 1996 (96CHC-II(8)563). The early articles on pyrido[1,2-*a*]pyrimidines (61HC(15-2)1141), pyrido[2,1-*b*]quinazolines (61HC(15-2)1153) and pyrimido[1,2-*a*]quinoline (61HC(15-2)1160) were covered by Mosby's book in 1961.

A review in 1986 dealt with pyrido[2,1-*b*]quinazolines among others (86AHC(39)281). The chemistry of pyrido[2,1-*b*][1,3]oxazines, pyrido[2,1-*b*][1,3]thiazines and their benzologs (Scheme 1) was summarized in 1999 (99AHC(72)225), and that of pyrido[1,2-*a*]pyrimidines in 1995 (95AHC(63)103), in 1994 (94KGS579), and in 1983 (83AHC(33)241, 85MI1). The chemistry of the benzologs of pyrido[1,2-*a*]pyrimidines was surveyed in 1999 (99AHC(73)178).

This chapter covers the primary chemical literature of bicyclic 6–6 systems containing one ring junction nitrogen and one extra heteroatom and their benzologs contained in *Chemical Abstract* Chemical Substance Indexes up to Volume 135 from Volume 127 for pyrido[2,1-*b*][1,3]oxazines, pyrido[2,1-*b*][1,3]thiazines and their benzologs; from Volume 120 for pyrido[1,2-*a*]pyrimidines, and from Volume 127 for its benzologs. In Scheme 1 the names of ring systems are in bold; they were treated in papers and patents during the above indicated period.

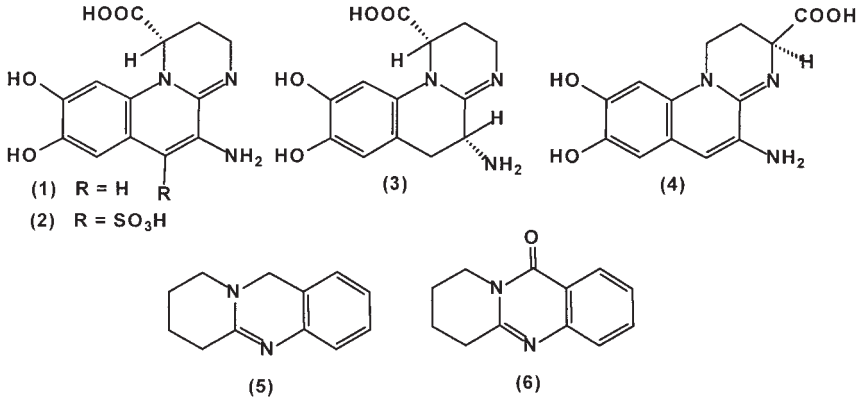
The perhydropyrido[2,1-*b*][1,3]oxazine skeleton is a constituent part of macrocyclic xestospongine/araguspongine and aragupetrosine alkaloids



Scheme 1

isolated from different marine sponges. Many microorganisms growing under iron deficient conditions produce Fe^{3+} complexing agents, so-called siderophores (among them pseudobactins, pyoverdins, isopyoverdins, and azoverdins), which consist of three distinct substructural parts: a heterocyclic unit, which may be (1*S*)-8,9-dihydroxy-5-amino-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-1-carboxylic acid (**1**), its 7-sulfonic acid **2**, 5, 6-dihydro derivatives **3**, and (3*S*)-8,9-dihydroxy-5-amino-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-3-carboxylic acid (**4**) chromophore; a peptide chain (containing both L- and D-amino acids) bound to the carboxylic group of pyrimido[1,2-*a*]quinoline moiety; and a dicarboxylic acid (amide) connected to a 5-amino group of a pyrimido[1,2-*a*]quinoline part (Scheme 2). 6,7,8,9-Tetrahydro-11*H*-pyrido[2,1-*a*]quinazoline (**5**) and its 11-oxo derivative **6** were isolated from *Mackinlaya subulata* and *M. macrosciadia*.

More then a dozen representatives of the pyrido[1,2-*a*]pyrimidine ring system were introduced into human therapy. Pemirolast (**7**) is applied as an orally active antiallergic-asthmatic agent, and its derivative, AS-35 (**8**) is under development for treating allergic disorders. Pirenperone (**9**) is a selective serotonin-2 (5-HT_2) and D-LSD antagonist, metrenperone (**10**) is also a selective 5-HT_2 antagonist, applied in the veterinary field. Risperidone



Scheme 2

(**11**) became a block-buster as an atypical antipsychotic drug in recent years. Its active metabolite, paliperidone (**12**) is under preclinical investigations. Ocaperidone (**13**) exhibits both D_2-dopaminergic and 5-HT_2 serotonergic antagonist activities, lusaperidone (**14**) is in a development phase as an antidepressant, seganserin (**15**) is a specific $5HT_2$ antagonist, and ramastine (**16**) is an antihistaminic compound (Scheme 3).

The pharmacological activities of other derivatives of these ring systems are examined intensively. Whereas other representatives of the above ring systems are patented as photographic sensitizers, catalysts for curing polyisocyanates, or dyes for acrylic nylon, polyester filters, and photographic material.

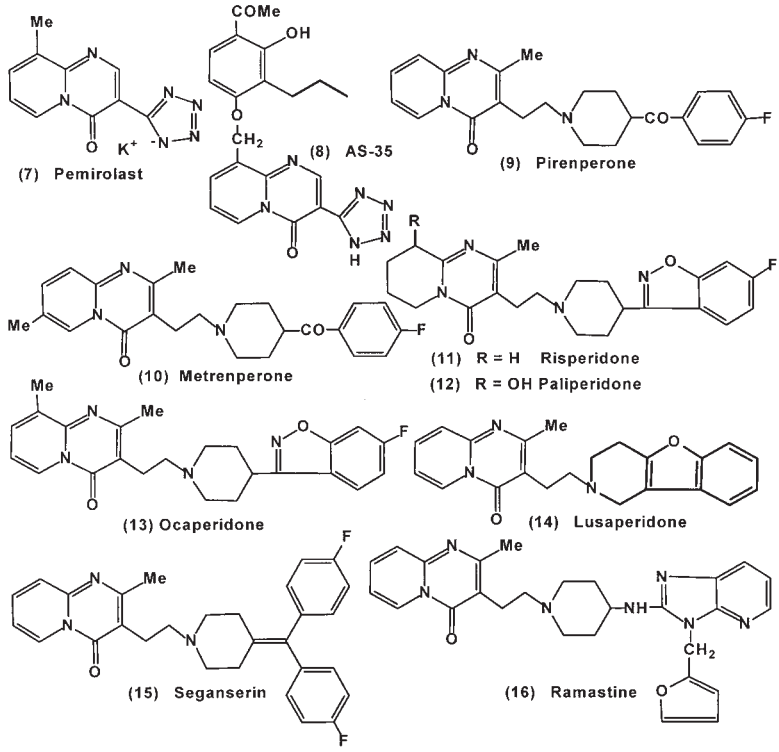
In the following sections structure, thermodynamic aspects, theoretical calculations, spectroscopic properties, reactions, syntheses, and more briefly, utilization of the representatives of these ring systems are discussed.

II. Pyrido[2,1-*b*][1,3]oxazines and Their Benzologs

A. Structure

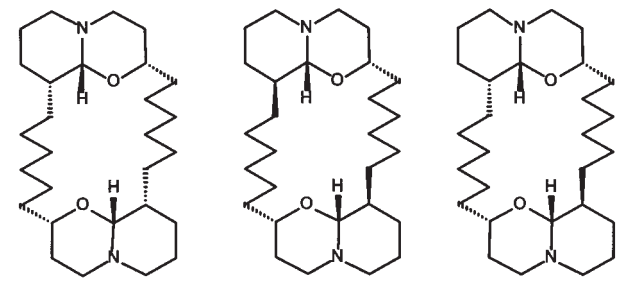
1. *Theoretical Calculations*

Molecular mechanics calculations with the molecular mechanics force field program were performed to compare thermodynamic stability among araguspongine B (**17**) (containing two *cis*-fused perhydropyrido[2,1-*b*][1,3]oxazine bicycles), araguspongine D (**18**) (containing two *trans*-fused perhydropyrido[2,1-*b*][1,3]oxazine bicycles), and araguspongine E (**19**)



Scheme 3

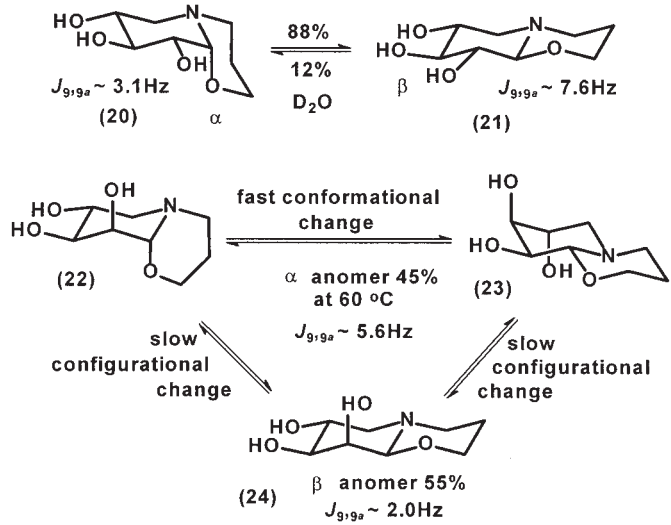
(containing one *cis*-, and one *trans*-fused perhydropyrido[2,1-*b*][1,3]oxazine bicycles). The total energies of araguspongines B (**17**) and *E* (**19**) indicate 1.37 and 0.60 kcal/mol of unstability compared to that of araguspongine D (**18**), respectively (98H(47)195).



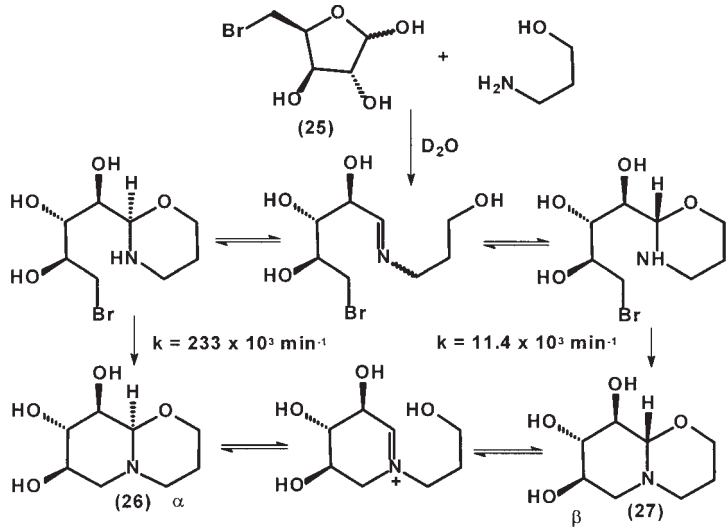
Theoretical calculations (B3LYP/6-31G*) were reported for geometries (bond lengths and bond angles) and ^{13}C chemical shifts of 3-methyl- and 3-phenyl-4-hydroxy-2-oxo-2*H*-pyrido[2,1-*b*][1,3]oxazinium inner salts (00JCS(P2)2096).

2. *NMR Spectroscopy*

^{1}H and ^{13}C NMR data for araguspongines B (**17**), D (**18**), and E (**19**) were assigned from a detailed analysis by 2D NMR (COSY, C–H COSY HMBC, and COLOC experiments). Araguspongine B (**17**) and D (**18**) have C_2 symmetry as only 14 carbon signals appear in their ^{13}C NMR spectra. NOE correlation and coupling constant showed that the 2,9-disubstituted perhydropyrido[2,1-*b*][1,3]oxazine moiety of araguspongine B (**17**) has a *cis*-decaline-like conformation, while that of araguspongine D (**18**) has a *trans*-decaline-like conformation (98H(47)195). On the basis of these results the C(9) stereochemistry of araguspongines B (**17**) and E (**19**) was revised.

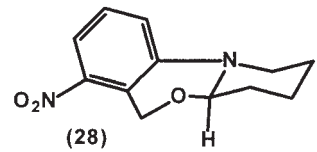


In D_2O (7*R*)-7α,8β,9α-trihydroxy- (**20**) (99T6759) and (7*R*)-7α,8β,9β-trihydroxyperhydropyrido[2,1-*b*][1,3]oxazines (**22**) (99T14251) exist as an 88:12 and a 45:55 mixture of α and β anomers, respectively. α-Anomer **20** adopts a *cis*-fused ring junction containing the anomeric oxygen atom axial to the piperidine ring due to a strong *endo*-anomeric effect. The coupling constants of the averaged conformations **22** and **23** could be determined at 60 °C. α and β-Anomers **20**, **22**, **23** and **21**, **24**, respectively were characterized by ^{1}H and ^{13}C NMR data.



Scheme 4

Reaction of 3-amino-1-propanol and 5-bromo-5-deoxy-D-furanoxylose (**25**) in D_2O was monitored by ^1H NMR (Scheme 4). The α-anomer of trihydroxypyrido[2,1-*b*]-[1,3]oxazine **26** formed 20 times faster, but the β-anomer **27** was more stable ($K_{\alpha/\beta} \approx 7.3$). The faster formation of the α-anomer is a consequence of a kinetic anomeric effect that destabilizes the transition state for equatorial *N*-alkylation and formation of the β-anomer **27** (00JOC889).



On the basis of coupling constants for 4*a*-H (9.3 and 13.6 Hz) and a $\Delta_{ax,eq}$ value for the $C(1)H_2$ methylene group (1.1 ppm), *trans* ring junction was assigned in 8-nitro-1,2,3,4,4*a*,6-hexahydropyrido[1,2-*a*][3,1]benzoxazine (**28**) (98ZN(B)37).

3. *X-ray Investigations*

The solid state structure of 3-methyl- and 3-phenyl-4-hydroxy-2-oxo-2*H*-pyrido[2,1-*b*]-[1,3]oxazinium inner salts were established by X-ray diffraction analysis (00JCS(P2)2096). The ''amide type'' N(5)–C(4)O bonds are

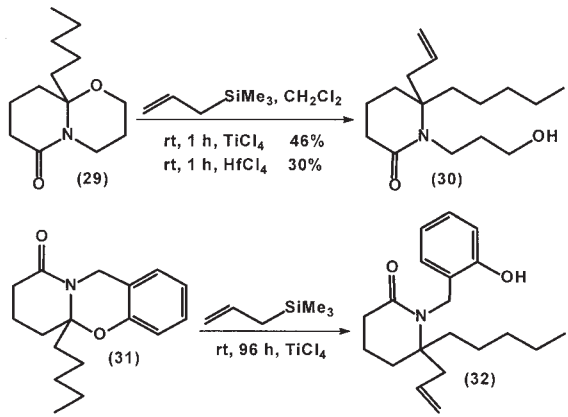
unusually long (148.7 pm); they are long N–C single bonds showing no sign of an amide type conjugation. The C(4)=O group tilted towards the ring N(5) atom with an O–C(4)–N(5) angle of 114°–116° (instead of 120°), and the C(2)=O group tilted just as much towards O(1) [O–C(2)–N(1) 112°–114°]. The presence of a rather unusual hydrogen bond C(6)–H(6)···O(4) with a distance of ~30 pm was identified.

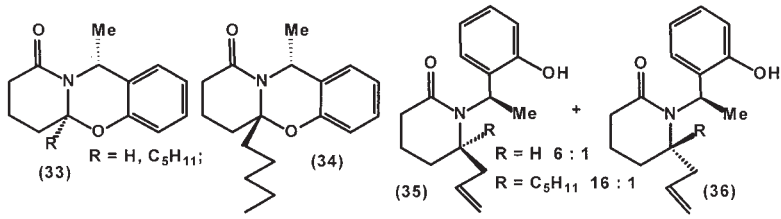
The stereostructure of (−)-aragusponginе B (**17**) was determined by X-ray crystallographic analysis. This confirmed the results of NMR investigations. The X-ray analysis elucidated that (−)-aragusponginе B (**17**) contains 9*R*,9′*R* configurations. On the basis of the structural correlation among aragusponginеs B, D and E it was clarified that (−)-aragusponginе E (**19**) has 9*R*,9′*S* configurations (98H(47)195).

B. Reactivity

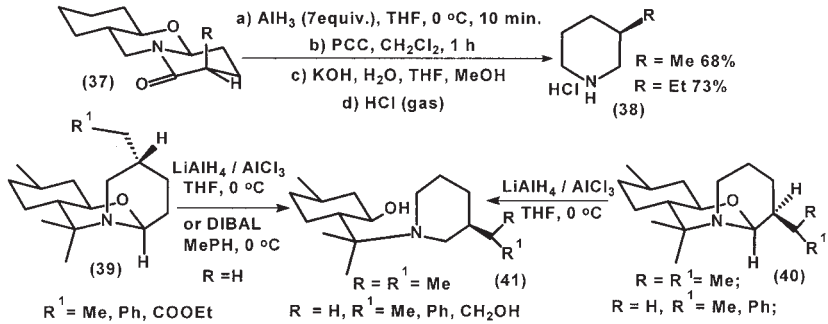
1. *Ring Opening*

Treatment of 9*a*-pentylperhydropyrido[2,1-*b*][1,3]oxazin-6-one (**29**) and 5*a*-pentyl-5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-9-one (**31**) with allyltrimethylsilane (3 equiv) in the presence of a Lewis acid ($TiCl_4$ and $HfCl_4$) gave ring-opened allylated products **30** and **32**, respectively (99SL37). In the case of tricyclic derivative **31** $HfCl_4$ and $ZnCl_2$ did not work. The $TiCl_4$-induced allylation reactions of diastereomeric 11-methyl-5*a*-pentyl-5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-9-ones **33** (R = H, pentyl) and **34** in CH_2Cl_2 at 50 °C in a sealed tube afforded a 16:1 mixture of ring-opened allylated piperidones **35** and **36** (99TL739, 01OL193).

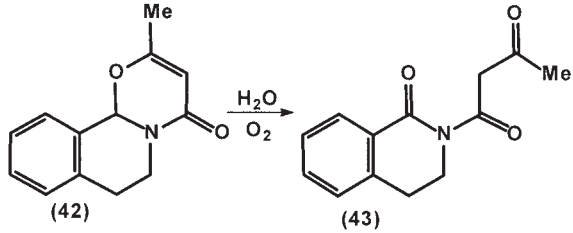




Enantiopure (*R*)-3-alkylpiperidines (**38**, R = Me, Et) were obtained when perhydropyrido[2,1-*b*][1,3]benzoxazin-9-ones (**37**, R = H, Me) were treated first with an excess of AlH_3, then with PCC, followed by a 2.5 N solution of KOH (99TL2421). Treatment of optically active perhydropyrido[2,1-*b*][1,3]benzoxazines **39** and **40** with LAH in the presence of $AlCl_3$ and DIBALH (if R = COOEt) yielded 3-substituted piperidines **41** (00TA2809).



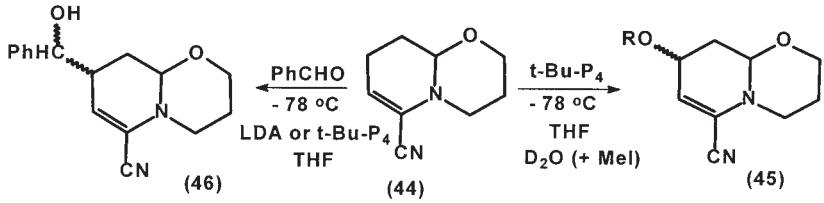
Hydrolysis and subsequent oxidation of 2-methyl-4,6,7,11*b*-tetrahydro[1,3]oxazino[2,3-*a*]isoquinoline-4-one (**42**) afforded ring opened product **43** (99TL8269).



2. *Reactivity of Ring Carbon Atoms*

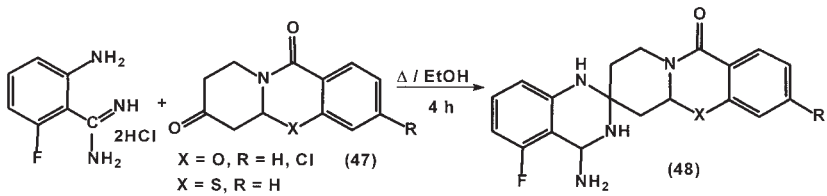
Neither deuterium incorporation nor double bond migration occurred when 6-cyano-2,3,4,8,9,9*a*-hexahydropyrido[2,1-*b*][1,3]oxazine (**44**) was

treated with an alkyllithium base (BuLi, *sec*BuLi, MeLi) or LDA in THF or Et_2O at −78 °C to −20 °C followed by quenching with D_2O (99TL7211). However, diastereomeric mixtures of 8-hydroxy or 8-methoxy derivatives **45** (R = H, Me) were obtained when *t*-BuP_4 phosphazene base was used, followed by treatment with D_2O, or with D_2O and MeI, respectively. Diastereomeric 2:1:1:2 and 1:3:3:1 mixtures of 8-(α-hydroxybenzyl) derivatives **46** were prepared from **44** with PhCHO in the presence of LDA and *t*-BuP_4, respectively.



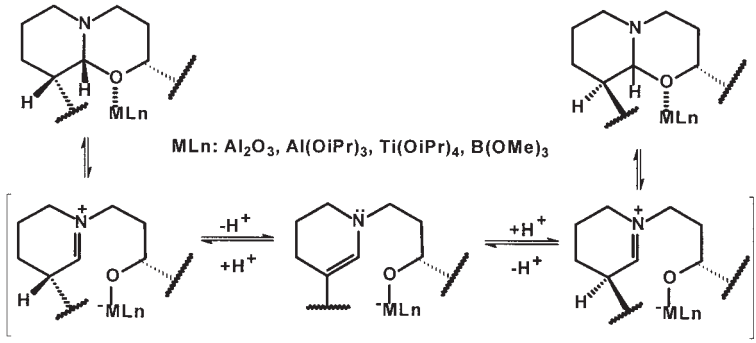
3. *Reactivity of Substituents Attached to a Ring Carbon Atom*

Reaction of 5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazine-7,11-diones **47** (X = O, R = H, Cl) and 2-amino-6-fluorobenzamidine dihydrochloride afforded a diastereomeric mixture of spiroderivatives **48** (X = O, R = H, Cl), which were separated by flash column chromatography (00MIP1).



4. *Miscellaneous*

Isomerization of araguspongine E (**19**) in boiling $Cl(CH_2)_2Cl$ over dry Al_2O_3 for 24 h gave a 58:36:6 mixture of araguspongines B (**17**), D (**18**) and E (**19**). Similar reaction mixtures were obtained from araguspongines B (**17**) and D (**18**) under the same conditions. Starting from araguspongine E (**19**) a mixture of deuterium labeled araguspongines B, D and E in positions 9 and 9′ was obtained in 35:10:55 ratio under reflux for 5 h, when the reaction mixture contained D_2O (98H(47)195). The isomerization was studied in the presence of other catalysts (Scheme 5). No isomerization occured in the



Scheme 5

cases of $AlCl_3$, $ZnCl_2$, BBr_3 and $CuCl_2$ treatment, but proceeded in the presence of $(MeO)_3B$, $(i\text{-}PrO)_3Al$, and $(i\text{-}Pr)_4Ti$. On the basis of these results it was concluded that the isomer distribution of **17**–**19** is in accordance with the thermodynamic stability of the individual isomers. Because the substituents at positions 2 and 9 are in equatorial positions both in **17** and **18**, araguspongine D (**18**) having *trans*-decaline-like conformation, and in araguspongine B (**17**) having a *cis*-decaline-like conformation, it was presumed that the isomerization of the C-9 position was accompanied by inversion of the nitrogen lone-pair.

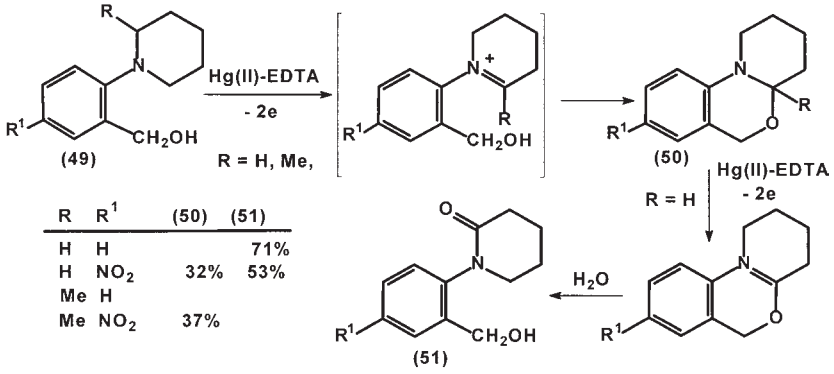
C. Synthesis

1. *By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0 (β)]*

Intramolecular electrochemical alkoxylation of racemic 1-(3-hydroxybutyryl)piperidine afforded a diastereomeric mixture of 2-methylperhydropyrido[2,1-*b*][1,3]oxazin-4-ones (00MI11).

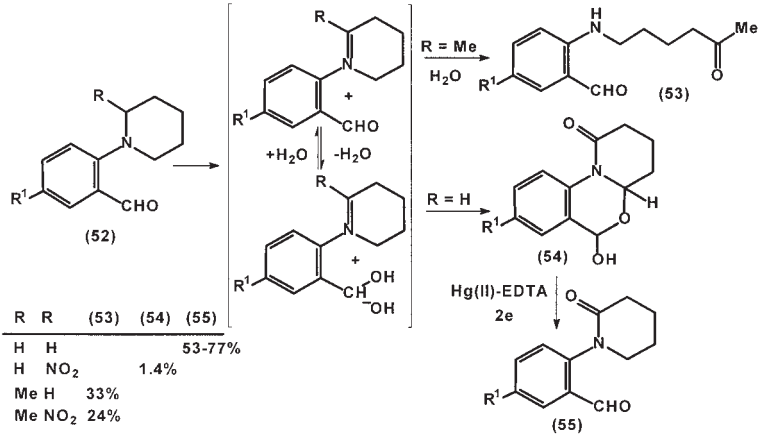
Depending upon the structure of the substrates **49**, **52**, and **56** hexahydropyrido[1,2-*a*]-[3,1]benzoxazines **50**, **54**, 2-aminobenzaldehyde **53**, 1-substituted piperidones **51**, **55**, **57**, 3,4,5,6-tetrahydropyridinium salt **58**, or their mixture was obtained during the oxidation of 1-(2-hydroxymethyl-, 2-formyl- and 2-acetylphenyl)piperazines (**49**, **52**, **56**) with Hg(II)–EDTA complex (Schemes 6–8) (79AP219, 98ZN(B)37, 98ZN(B)1369).

Iodocyclization of 1,4-dihydropyridine **59** with I_2 gave a 2 : 3 mixture of 2,3,4,8,9,9*a*-hexahydropyrido[2,1-*b*][1,3]oxazine-7-carboxylates **60** and **61** (98TL5089, 99EJOC2997). When the reaction was carried out in the



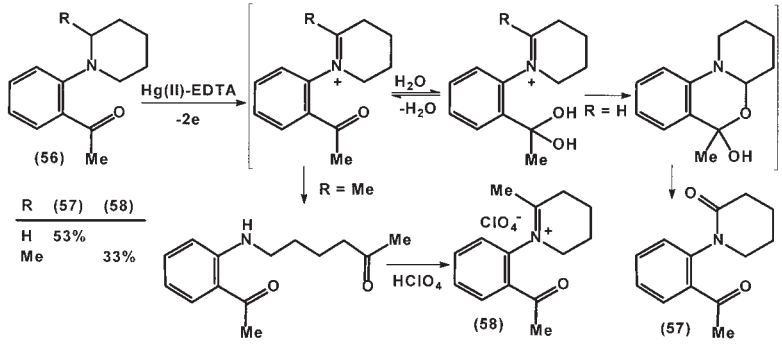
R	R^1	(50)	(51)
H	H		71%
H	NO_2	32%	53%
Me	H		
Me	NO_2	37%	

Scheme 6



R	R	(53)	(54)	(55)
H	H			53-77%
H	NO_2		1.4%	
Me	H	33%		
Me	NO_2	24%		

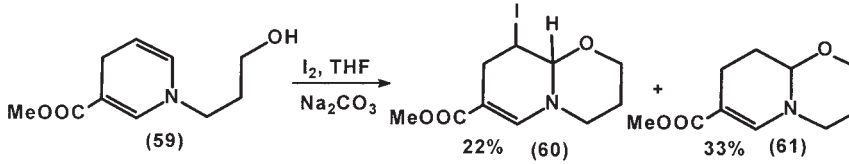
Scheme 7



R	(57)	(58)
H	53%	
Me		33%

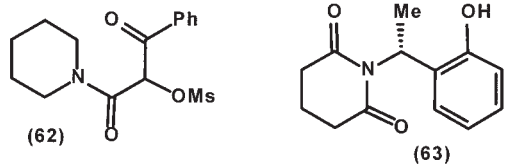
Scheme 8

presence of $NaHCO_3$ only 9-iodohexahydro derivative **60** formed in 67% yield.



Treatment of 1-(2-acetoxybenzoyl)- and 1-(4-chloro-2-acetoxybenzoyl)-1,2,3,4-tetrahydropyridin-4-ones with aqueous LiOH in THF at room temperature gave 5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazine-7,11-diones **47** (X = O, R = H, Cl) (00MIP1).

Irradiation of piperidine **62** in CH_2Cl_2 at concentration of 3 mg/ml in the presence of 1-methylimidazole using a high-pressure mercury lamp (150 w) yielded 2-phenyl-4,6,7,8,9,9*a*-hexahydropyrido[2,1-*b*][1,3]oxazin-4-one (01S1258).



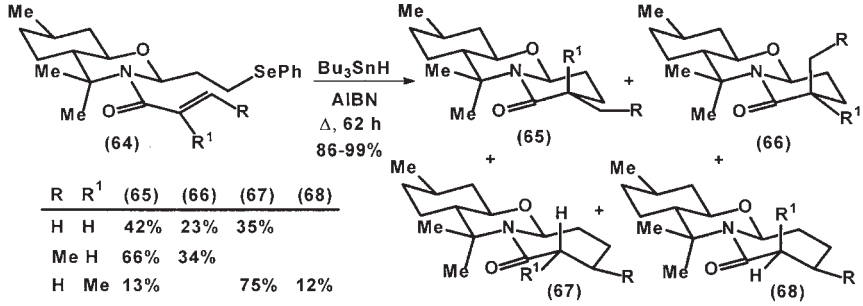
The rhodium(II) acetate catalyzed reaction of 2-(3-oxo-2-diazobutyryl)-1,2,3,4-tetrahydroisoquinoline in boiling toluene yielded 2-methyl-4,6,7,11*b*-tetra-hydro[1,3]oxazino[2,3-*a*]-isoquinoline-4-one in 72% yield (99TL8269).

By partial reduction of glutarimide **63** with Vitride® in toluene at −78 °C followed by acid treatment (HCl) afforded pyrido[2,1-*b*][1,3]benzoxaine **33** (R = H) (01OL193).

2. *By Formation of One Bond γ to the Bridgehead Nitrogen Atom [6+0 (γ)]*

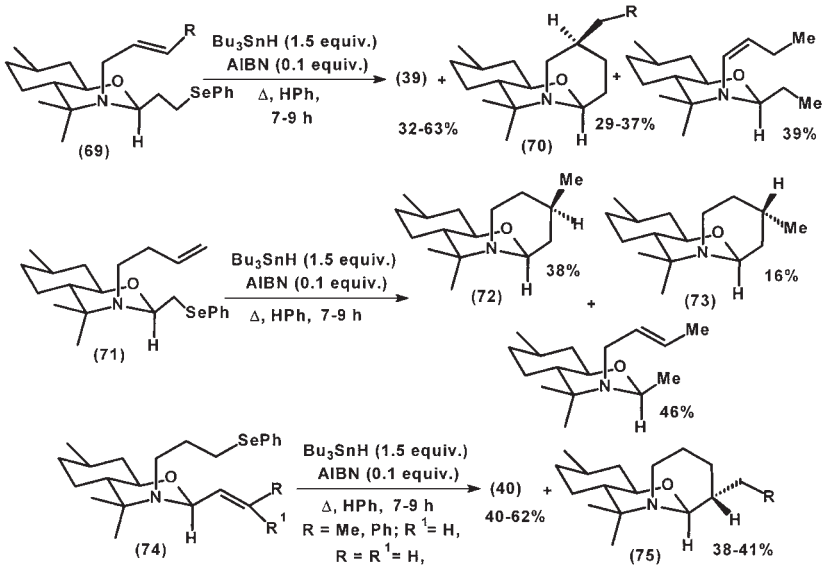
Radical cyclization of perhydro-1,3-benzoxazines **64**, promoted by Bu_4SnH in the presence of AIBN gave a mixture of perhydropyrido[2,1-*b*][1,3]benzoxazin-9-ones **65** and **66** and seven membered tricyclic derivatives **67** and **68**, formed in a 6-exo and 7-endo cyclization process, respectively (99TL2421). Cyclization of parent acrylamide **64** ($R = R^1 = H$) occured with moderate regioselectivity (6-exo/7-endo ratio: 65 : 35) and poor stereoselectivity (**65**/**66** ratio: 42 : 43). The presence of a *β*-methyl group in

crotylamide **64** (R = Me, R^1 = H) disfavored the 7-endo cyclization process, but did not influence the stereoselectivity of the cyclization (**65**/**66** ratio: 66 : 34). The presence of an α-methyl group in methylacrylamide **64** (R = H, R^1 = Me) caused a retardation of the 6-exo attack, in favor of 7-endo cyclization in a higher stereoselectivity (**67**/**68** ratio: 75 : 12).



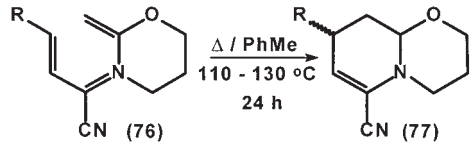
R	R^1	(65)	(66)	(67)	(68)
H	H	42%	23%	35%	
Me	H	66%	34%		
H	Me	13%		75%	12%

Diastereoselective 6-exo-trig radical cyclization of (−)-perhydro-1,3-benzoxazines **69**, **71**, **74** with Bu_3SnH and AIBN gave a diastereomeric mixture of perhydropyrido[2,1-*b*][1,3]-benzoxazines **39**, **70**, and **72**, **73**, and **40**, **75**, respectively (00TA2809).



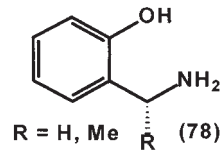
Intramolecular Diels–Alder reactions of azadienes **76** afforded 6-cyano-2,3,4,8,9,9*a*-hexahydropyrido[2,1-*b*][1,3]oxazines **77** (99TL7211, 99TL7215). Cyclization was carried out smoothly at or below room temperature in

the presence of different Lewis acids [$Cu(OTf)_2$, BCl_3, $TiCl_4$, $AgSbF_6$, $Cu(oxaz)_2(OTf)_2$] (99TL7215).



3. *By Formation of Two Bonds from [5+1] Atom Fragments*

Cyclocondensation of 3-aminopropanol and 2-hydroxybenzylamines **78** with 5-oxodecanoic acid in boiling benzene gave 9*a*-pentylperhydropyrido[2,1-*b*][1,3]oxazine-6-one (**29**) and 5*a*-pentyl-5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-9-ones **31**, **33** ($R = C_5H_{11}$), **34** in good yields (99SL37, 99TL739). 2-Hydroxy-α-methylbenzylamine (**78**, R = Me) afforded a 46:1 diastereomeric mixture of 11-methylhexahydropyrido[2,1-*b*][1,3]benzoxazin-9-ones **33** ($R = C_5H_{11}$) and **34** (99TL739).



4. *By formation of Two Bonds from [4+2] and [3+3] Atom Fragments*

Cycloaddition of 2-styryl-4*H*-3,1-benzoxazines and malononitrile gave 1-amino-3-aryl-2-cyano-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazin-4-ones (99ZN(B)923). These tricyclic derivatives were also prepared in the reaction of 2-methyl-4*H*-3,1-benzoxazin-4-one and arylidenemalononitrile in AcOH in the presence of NaOAc.

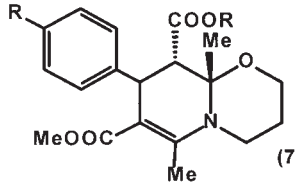
3-Methyl- and 3-phenyl-4-hydroxy-2-oxo-2*H*-pyrido[2,1-*b*]oxazinium inner salts were prepared in the reaction of 2-pyridone and 2-substituted malonyl chloride, prepared *in situ* from 2-substituted malonic acid with PCl_5 in CH_2Cl_2 (00JCS(P2)2096).

5. *Miscellaneous*

Reaction of 3-aminopropanol with an α and β mixture of 5-bromo-5-deoxy-2-xylofuranose (**25**) and 5-*O*-tosyl-D-lyxofuranose in MeCN afforded anomeric mixtures of trihydroxypyrido[2,1-*b*]1,3]oxazines **20**, **21** and **22**–**24**, respectively (99T6759, 99T14251).

D. Applications and Important Compounds

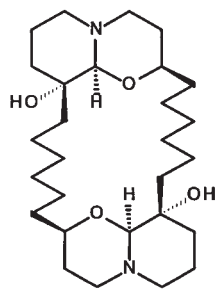
Chiral 3-alkylpiperidines were prepared through perhydropyrido[2,1-*b*][1,3]benzoxazines (99TL2421, 00TA2809). 5*a*-Pentyl-5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-9-ones **31**, **33** (R = C_5H_{11}) and **34** were used in the total synthesis of racemic and natural (−)-(*R*) forms of adalinine alkaloid (99SL37, 99TL739).



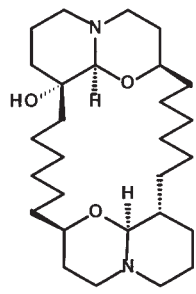
R = Cl, R^1 = Me;
R = NO_2, R^1 = Me, Et;

(79)

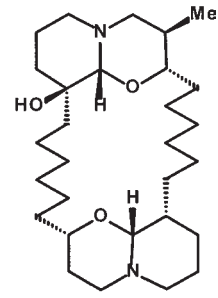
The antihypertensive activity of 8-aryl-6,9*a*-dimethyl-2,3,4,8,9,9*a*-hexahydropyrido[2,1-*b*][1,3]oxazine-7,9-dicarboxylates **79** was evaluated in conscious spontaneously hypertensive rats. They resulted in potent and long-lasting antihypertensive action (97MI14).



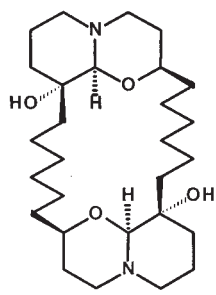
Araguspongine C
(80)



Araguspongine A
(81)



(82)



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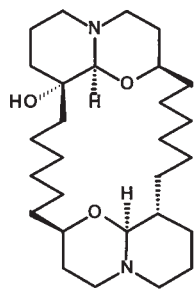

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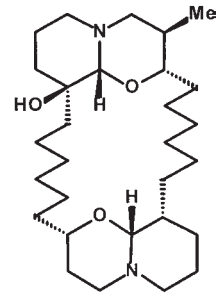

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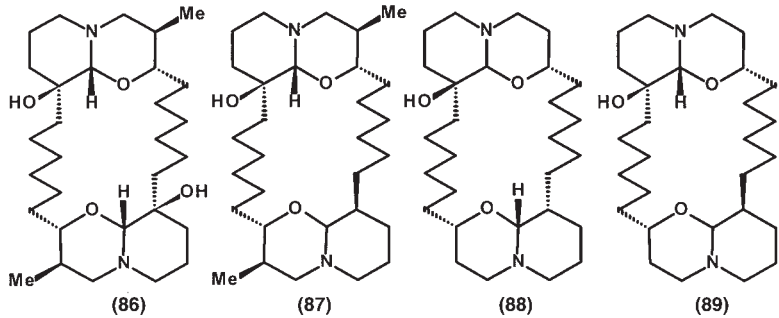


Araguspongines B, D, C, A and other six bis-pyrido[2,1-*b*][1,3]oxazine alkaloids **17**, **18**, **80**–**87** were isolated from an unidentified marine sponge and they were patented as antitumor agents (97MIP1). Araguspongine C (**80**) was isolated from the marine sponge Haliclona exigus (96MI6). 3β,3β'-Dimethylxestospongine was isolated from the Palaun-Sponge *Xestospongia* sp. (97MI3). Araguspongine/Xestospongine derivatives **17**–**19**, **88**, **89** are shown to be potent blockers of the inositol 1,4,5-trisphosphate receptor-mediated Ca^{2+} release from endoplasmic reticulum vesicles of rabbit cerebellum (97MI19).

III. Pyrido[2,1-*b*][1,3]thiazines and Their Benzo Derivatives

A. Structure

1. *Theoretical Calculations*

A molecular mechanics prediction of the conformation of *trans*-8,9*a*-H-8-phenyl-perhydropyrido[2,1-*b*][1,3]thiazin-6-one gave similar data as NMR experiments (00BAP19).

2. *^{1}H NMR Spectroscopy*

Some coupling constants of *trans*-8,9*a*-H-8-phenyl-, -8-(2-methoxyphenyl)-, and -8-(4-methylphenyl)phenylperhydropyrido[2,1-*b*][1,3]thiazin-6-ones in $CDCl_3$ were measured by ^{1}H NMR spestroscopy (00BAP19).

B. Reactivity

1. *Ring Opening*

Treatment of *trans*-8,9*a*-H-8-(2-methoxyphenyl)perhydropyrido[2,1-*b*][1,3]thiazin-6-one with 2.5 equiv of $HSnBu_3$ in the presence of AIBN in boiling benzene for 1.5 h yielded 4-(2-methoxyphenyl)-1-[3-(tributylstannylthio)propyl]piperidin-2-one (01S135).

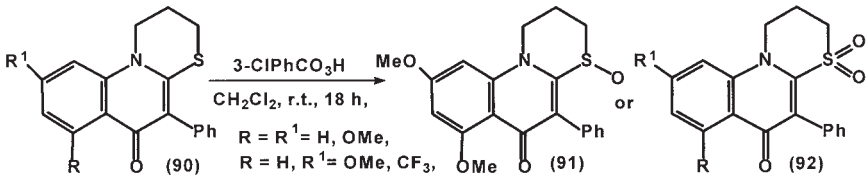
2. *Hydrogenation, Reduction*

Diethyl *cis*-3*H*,4*H*-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate was obtained from the 3-methyl-6-oxo-4*H*,6*H* derivative by catalytic hydrogenation over 5% Rh on alumina in EtOH for 5 days. Catalytic reduction in a D_2 atmosphere in EtOAc overnight yielded a 2,3-dideutero-4*H*,6*H* derivative. *cis*-3*H*,4*H*-3-Methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate was also prepared from the 3-methyl-6-oxo-2*H*,6*H* isomer by reduction with an aqueous solution of $NaBH_4$ in THF at room temperature for 3 h (00JCS(P1)4373). Treatment of 4-alkoxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]-thiazine-9-carboxylic acid first with ClCOOEt in the presence of NEt_3 in THF at 0 °C for 1 h, then with an aqueous solution of $NaBH_4$ at 0 °C for 1 h, then at room temperature for 3 h afforded a 9-hydroxymethyl-6-oxo-2*H*,6*H* derivative. In another experiment starting from the ethyl ester at −15 °C, ethyl 3,4-*cis*-H-9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate was obtained in 57% yield. The latter product was prepared in a similar yield from 4-ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido-[2,1-*b*][1,3]thiazine-9-carboxylic acid using ClCOOEt and NEt_3 at −15 °C in THF, and then aqueous $NaBH_4$. Hydrogenation of ethyl 9-hydroxymethyl-3-methyl-6-oxo-4*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate over Rh–Al_2O_3 in acidified MeOH at room temperature for 15 h gave a 2:1 mixture of 9-methoxymethyl-3,4-dihydro-2*H*,6*H*- and 9-hydroxymethyl-3,4-dihydro-2*H*,6*H* derivatives (00JCS(P1)4373).

3. *Oxidation*

Oxidation of diethyl 3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate and its 7,8-dihydro derivative with CF_3CO_3H in CH_2Cl_2 at room temperature gave the respective sulfone in 73% and 38% yields, respectively (99JCS(P1)3569). Sulfoxide **91** or sulfone **92** of

5-phenyl-1,2,3,6-tetrahydro[1,3]thiazino[3,2-*a*]quinolin-6-ones **90** were prepared depending on the molar ratio of oxidizing agent and substrate (97JAP(K)97/278780).



4. *Reactivity of Substituents Attached to Ring Carbon Atoms*

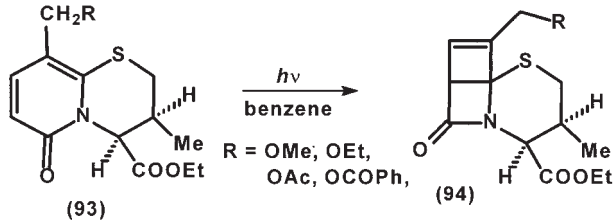
[4*R*-(4α,9β,9aβ)]-9-(Benzyloxycarbonylamino)-6-oxoperhydropyrido[2,1-*b*][1,3]thiazine-4-carboxylic acid was obtained from the methyl ester by treatment with 2 N LiOH in MeOH at 0 °C for 4.5 h. The carboxyl group was coupled with amino esters. The 9-(benzyloxycarbonylamino) group was deprotected by treatment with a 1:1 mixture of TFA and CH_2Cl_2 at room temperature and the amino group was acylated with an amino acid (97MIP4, 98USP5710129).

Treatment of alkyl 9-benzyloxycarbonyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylates with BBr_3 in CH_2Cl_2 at −70 °C for 0.5–1 h and at room temperature for 3 h yielded 9-carboxyl derivatives. The decarboxylation of these acids was unsuccessful. Hydrolysis of diethyl *cis*-3,4-H-3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate in aqueous EtOH with KOH at room temperature for 3 days yielded 4-ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido-[2,1-*b*][1,3]thiazine-9-carboxylic acid (00JCS(P1)4373). Alkyl 9-hydroxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylates were *O*-acylated with Ac_2O and $(PhCO)_2O$ in pyridine at room temperature for 12–48 h.

Reaction of 5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzothiazine-7,11-dione (**47**, X = S, R = H) and 2-amino-6-fluorobenzamidine dihydrochloride in boiling EtOH yielded a diastereomeric mixture of spiro derivatives **48** (X = S, R = H), which were separated by flash column chromatography (00MIP1).

5. *Ring Transformation*

Irradiation of 9-substituted 6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[1,2-*b*]-[1,3]thiazine-4-carboxylate **93** in benzene afforded tricyclic derivatives **94**, sometimes as a diastereomeric mixture (00JCS(P1)4373).



6. *Miscellaneous*

Ethyl 9-ethoxycarbonyl- and 9-hydroxymethyl-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylates were isomerized into 4*H*,6*H*-pyrido[2,1-b][1,3]thiazine-4-carboxylates by treatment with KOH overnight at room temperature and by treatment with NaOEt at 0 °C for 1 h and room temperature for 3 h in EtOH, respectively. In another experiment, when the 9-hydroxymethyl derivative was treated with NaOEt in EtOH at −10 °C for 3 h, a 2.5:1 mixture of ethyl 3,4-*cis*-H-9-ethoxymethyl-3-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4-carboxylate and the aforementioned 4*H*,6*H*-isomer were obtained (00JCS(P1)4373).

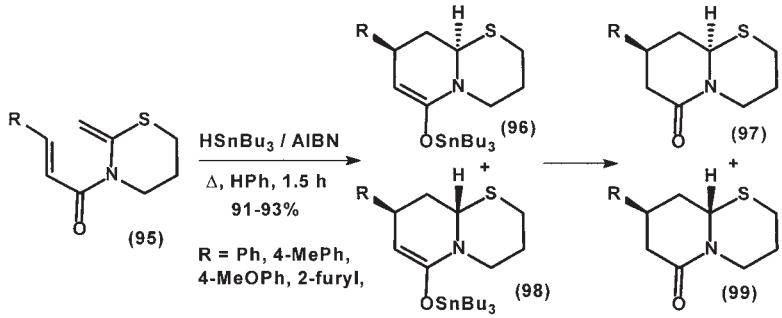
C. Synthesis

1. *By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0 (β)]*

Treatment of 1-(2-thioacetoxybenzoyl)-1,2,3,4-tetrahydropyridin-4-one with aqueous NaOH in MeOH yielded 5*a*,6,7,8,9,11-hexahydropyrido[2,1-b][1,3]benzothiazine-7,11-dione (**47**, X = S, R = H) in 44% yield (00MIP1).

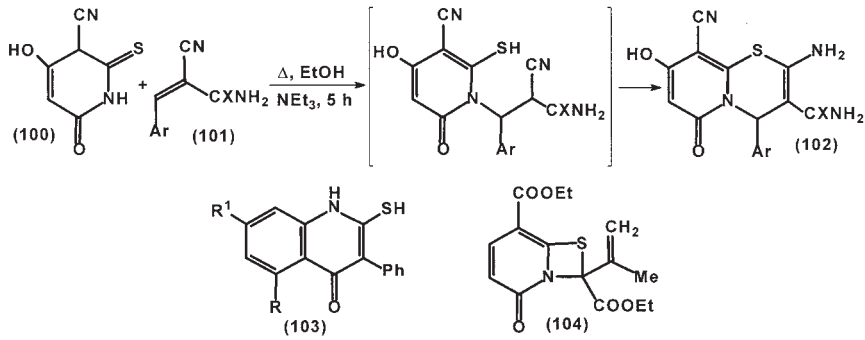
2. *By Formation of One Bond γ to the Bridgehead Nitrogen Atom [6+0 (γ)]*

Radical cyclization of 2-methylene-3-[3-(het)arylacroyl]perhydrothiazines **95** on the action of $HSnBu_3$ in the presence of AIBN in boiling benzene gave a mixture of *cis*-8,9*a*-H- and *trans*-8,9*a*-H-8-(het)aryl-6-(tributylstannyloxy)-3,4,8,9-tetrahydro-2*H*,9*aH*-pyrido[2,1-*b*][1,3]thiazines **96** and **97**, which were hydrolyzed to a 1:3 mixture of *cis*-8,9*a*-H- and *trans*-8,9*a*-H-8-(het)arylperhydropyrido[2,1-*b*][1,3]thiazin-6-ones **98** and **99** (01S135).



3. *By Formation of Two Bonds from [3+3] Atom Fragments*

Cyclocondensation of pyridine-2-thione **100** with cinnamonitriles **101** in the presence of a catalytic amount of NEt_3 afforded 4,6-dihydropyrido[2,1-*b*][1,3]thiazine-6-ones **102** (98MI10, 99MI26).



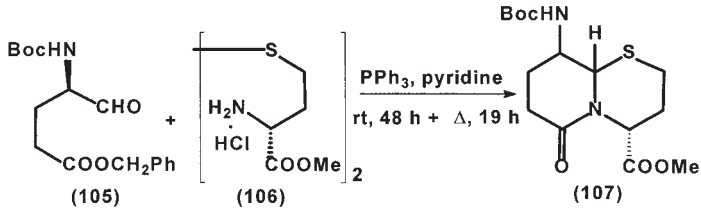
5-Phenyl-1,2,3,6-tetrahydro[1,3]thiazino[3,2-*a*]quinolin-6-ones **90** were prepared in the reactions of 2-mercapto-5-phenyl-1,4-dihydroquinolin-4-ones **103** and 1,3-dihalopropane in 55–79% yields (97JAP(K)97/278780).

4. *Rearrangement*

Oxidation of 8-(1-methylethenyl)-2-oxo-7-thia-1-azabicyclo[4.3.0]octa-3,5-diene-5,8-dicarboxylate (**104**) and its 3,4-dihydro derivative in $CHCl_3$ with peracids (*m*-chloroperbenzoic acid and CF_3CO_3H) at room temperature gave diethyl 3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate and its 7,8-dihydro derivative in 66% and 56% yield, respectively (99JCS(P1)3569).

5. *Miscellaneous*

Cyclocondensation of D-homocystine methyl ester hydrochloride (**106**) and aldehyde **105** in the presence of Ph_3P yielded 9-(benzyloxycarbonylamino)-6-oxoperhydropyrido[2,1-*b*][1,3]thiazine-4-carboxylate (**107**) and its diastereomer (97MIP4, 98USP5710129).



IV. Pyrido[1,2-*a*]pyrimidine

A. Structure

1. *Thermodynamic Aspects*

Gas-phase basity and proton affinity values for 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine were determined and they were compared to other super bases, including its lower and higher piperidine ring homologs (94JPO725, 01JPO25).

Stability constants of metal complexes of 9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one [Ni(II), Co(II), Zn(II), and Cd(II)] were determined by potentiometric and polarographic investigations (93JCC283). The distribution coefficient of risperidone (**11**) in H_2O-*n*-octanol at pH 7.4 ($\log D = 2.04$) was determined by an RP-HPLC method (01JMC2490).

The chromatographic retentions (TLC, R_f values) of alkyl derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 6,7,8,9-tetrahydro derivatives were calculated with high accuracy by a quantitative structure–retention relationship study using quantum chemical, topological, electrical indices and physicochemical properties of molecular fragments (92MI3). Good correlations were found between H_2O–*n*-octanol partition coefficients of 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one and its 6 alkyl derivatived by the shake-flask technique, and TLC R_M and HPLC $\log k'$ values (99MI10). The lipophilic character of pirenperone (**9**) was characterized by R_M values using a reversed-phase TLC system, and a reversed-phase high-performance TLC.

The chromatographic parameters were compared with calculated H_2O–*n*-octanol log *P* value (2.23) (by CLOGP program) (96JC(A)135).

Sensitive HPLC methods were also developed for the determination of **11** and its active 9-hydroxy metabolite, paliperidone (**12**), in biological media (97JC(B)209, 97MI11, 99MI2, 99MI3, 99MI6, 99MI11, 00JC(B)173, 00MI13, 01MI1) and in formulations (00MI16, 00MI37). The plasma levels of **11** and **12** were monitored by a HPLC (97MI12, 00MI29). Effects of amine additives on the resolution of **11** on a cyanoalkyl HPLC column were investigated (98MI13). Risperidone was also used to evaluate the performance of new HPLC conditions (00MI28, 00MI35). Risperidone and **12** were determined in biological media by LC–MS–MS methods (00JC(B)141, 00MI20). Nortriptyline was determined in human serum in the presence of **11** by HPLC (00JC(B)233). A capillary zone electrophoresis method was developed to determine **11** and other drugs from whole blood (95MI3), and in pharmaceutical formulations (00MI1). In tablets **11** was determined by a first order derivative of its UV spectrum (01MI11). Plasma protein binding of **11** and **12** was investigated by equilibrium dialysis (94MI10).

An algorithm for an assesment of chromatographic peak purity was proposed. In this study ethyl 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate was also used (97MI13). Ethyl 7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, among other compounds, was applied to show practical mathematical tools for the creation of several figures of merit of *n*th order instrumentation, namely selectivity, net analyte signal and sensitivity (96ANC1572).

2. *Theoretical Calculations*

Bond orders and charge densities of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its protonated form were calculated by the semiempirical AM1 method with full optimization of geometry (97MI22).

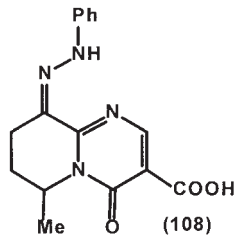
Theoretical calculations (B3LYP/6-31G*) were reported for geometries (bond lengths and bond angles), IR, ^{1}H and ^{13}C chemical shifts of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide and its 1-methyl-, 3-methyl- and 3-phenyl derivatives and 2-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 3-methyl derivative (00JCS(P2)2096). The optimized geometry of *anhydro*-(2-hydroxy-3-benzyl-1-phenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide in the gase phase was calculated on a semiempirical AM1 level by HyperChem Release 4 (00MI26).

Among others, **11** was included in a series of drugs to study quantitative structure–activity relationships (96KFZ(6)29, 98MI7, 99BMC2437). A statistically significant CoMFA model was developed for describing the

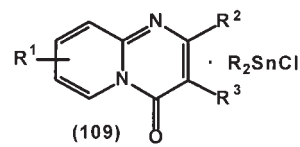
variation of the antiplatelet activity of 2-(substituted amino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their congeners in terms of molecular steric and electrostatic potential changes (00BMC751). A QSAR model was set up for prediction of drug human oral bioavaibility (00JMC2575). Risperidone (**10**) was included in the test compounds.

Conformations of 4-oxo-1,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and -3-carboxamides were studied by semiempirical quantum chemical calculations at the AM1 level (97H(45)2175). While 1-methyl-9*a*-unsubstituted derivatives adopt a *cis*-fused conformation, 9*a*-ethoxy-1-methyl derivatives adopt a *trans*-fused one to avoid a serious non-bonding interaction between 9*a*-ethoxy and 1-methyl groups, which would be present in an alternative *cis*-fused conformation.

Chinoin-1045 (**108**) was including a series of structurally divers compounds designing sedative/hypnotic derivatives from novel substructural graph–theoretical approach (98MI11).



(108)



(109)

R = Me, Ph;
R^1 = H, 8-Me; R^2 = H, CH_2Br; R^3 = H;
R^1 = 9-Me; R^2 = R^3 = H;

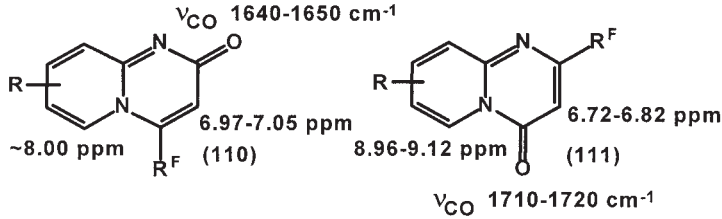
3. *UV Spectroscopy*

Diorganotin(IV) complexes with 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **109** (96MI4), complexes of 2-methyl- and 2-methyl-8-nitro-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with Ag(I), Cu(II), Ni(II), Co(II), and Mn(II) ions (00MI23), 2,4-dimethyl-9-hydroxypyrido[1,2-*a*]pyrimidinium perchlorate and its complexes with prasedynium, neodymium, samarium and europium (00MI24) were characterized by UV spectroscopy.

4. *IR Spectroscopy*

Diorganotin(IV) complexes **109**, and complexes of 2-methyl- and 2-methyl-8-nitro-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with Ag(I), Cu(II), Ni(II), Co(II), and Mn(II) ions (00MI23), 2,4-dimethyl-9-hydroxypyrido[1,2-*a*]pyrimidinium perchlorate and its complexes with prasedynium, neodymium, samarium and europium (00MI24) were characterized

by IR spectroscopy (96MI4). In the IR spectra of 4-fluoroalkyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **110** the CO stretching band is shifted by 60–70 cm^{-1} to lower wavenumbers as compared with that of 2-fluoroalkyl-4-oxo-4*H* isomers **111** (97JCS(P1)981).

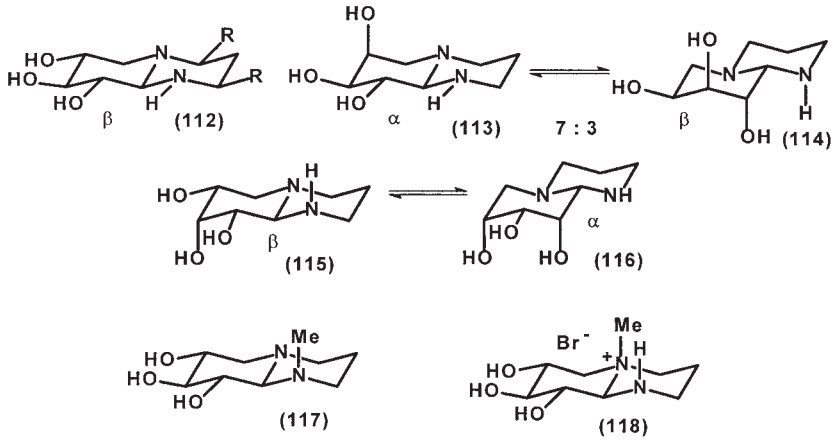


IR spectra in conjunction with theoretical calculations (B3LYP/6-31G*) indicate that the *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)-hydroxide form exists in solution and in the crystal, but the 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one tautomer dominates in the gas phase (00JCS(P2)2096).

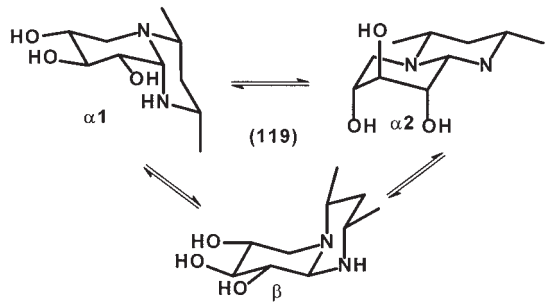
Polymorphic forms of I and II of 3-{2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was characterized by IR spectroscopy (99MIP1).

5. *NMR Spectroscopy*

Diorganotin(IV) complexes **109** were characterized by ^{1}H NMR spectroscopy (96MI4). The downfield chemical shift of 6-H in 2-fluoroalkyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **111** is attributed to the anisotropic effect of the 4-carbonyl group (97JCS(P1)981).



^{1}H and ^{13}C NMR investigations using D_2O showed that bicyclic diazasugar analogs of D-xylose, L-arabinose, and D-ribose exist as pure β anomer **112** (R = H) (98JOC391, 99T6759), a 7 : 3 mixture of α and β anomers **113** and **114**, and mainly as β anomer **115** (98T5097), respectively. In the latter case the minor compound was believed to be the α anomer **116**. ^{1}H NMR investigations of *N*(1)-methyl **117** and *N*(5)-methyl **118** derivatives of **112** (R = H) revealed that they adopted a similar conformation as the parent **112** (R = H) (99T6759). Both *N*-methyl derivatives contain the methyl group in an axial position. All of them have a *trans*-ring junction. Whereas, *cis*-2*H*,4*H*,9*aH*-dimethyl derivative **112** (R = Me) exists in a single conformation, its *cis*-2*H*,4*H*-*trans*-9*aH* diastereomer **119** is conformationally complex, consisting of α1, α2, and β anomers in equilbrium in D_2O (00JOC889).



Theoretical calculations (B3LYP/6-31G*) indicated that in their ^{13}C NMR spectra C(2) and C(9) carbons of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide mesoionic forms appeared at significantly higher field (ca. 159–160 ppm and 115–116 ppm, respectively), than in the 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one tautomers (ca. 169–173 ppm and 130 ppm, respectively) (00JCS(P2)2096). C(8) carbon of mesoions (pyridine-γ type carbon) appeared at lower field (144–146 ppm) than 6-C (140 ppm, pyridine-α type carbon), as is typical of pyridinium compounds.

A 9 : 1 mixture of 2,4-difluoro-4-pentafluoroethyl-3-trifluoromethyl-2*H*-, and 2,4-difluoro-2-pentafluoroethyl-3-trifluoromethyl-4*H*-, as well as 2-pentafluoroethyl-3-trifluoromethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine were characterized by ^{1}H, ^{13}C, and ^{19}F NMR (00JFC105). 2-Trifluoromethyl-3-cyano-4-imino- and -4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines were characterized by ^{1}H and ^{19}F NMR (00MI27).

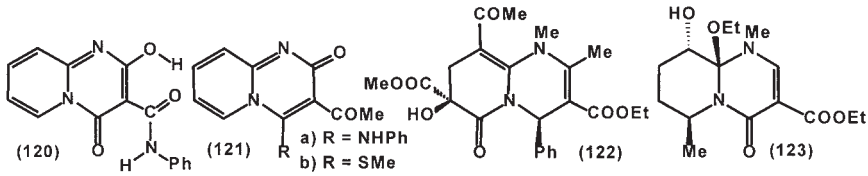
Polymorphic forms I and II of 3-{2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one were characterized by solid state ^{13}C NMR (99MIP1).

6. *Mass Spectrometry*

The mass spectrometric behavior of the isomeric 2-oxo-2*H*- and 4-oxo-4*H*-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidines was studied under electron-impact induced polarization (97RCM664). The molecular ion of the 2-oxo-2*H* isomer appeared to be much more stable than that of the 4-oxo-4*H* isomer. The fragmentation of the molecular ion (M+) of the 4-oxo-4*H* isomer is related mostly to the saturated piperidine ring, whereas that of the 2-oxo-2*H* isomer is much more selective, the only significant process is the primary loss of a CO molecule from the pyrimidinone ring via contraction of the ring. Electrospray ionization quadrupole ion-trap mass spectrometric characterization of risperidon (**11**) was presented and a possible mechanism for the observed MS^n fragmentation pattern was proposed (00JC(B)141).

7. *X-ray Investigations*

The structure of 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**120**) was confirmed by X-ray investigations. The crystal unit cell contains one mol of $CHCl_3$ and two crystallographically independent pyrido[1,2-*a*]pyrimidines with substantially identical geometries (93JHC33). The structures of 2,4-dimethyl-9-hydroxypyrido[1,2-*a*]-pyrimidinium perchlorate (00MI24), 3-acetyl-4-phenylamino- and 3-acetyl-4-methylthio-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **121** (95MI2, 96MI22), *anhydro*-(2-hydroxy-3-benzyl-1-phenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium) hydroxide (00MI26), 2-pentafluoroethyl-3-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (00JFC105), 3-cyano-7-methyl-2-trifluoromethyl-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine (00MI27) and 2-methyl-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (00MI23) were established by X-ray diffraction analysis.



The solid state structures of *anhydro*-(3-methyl- and 3-phenyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyridinium)hydroxides, 2-methoxy-3-methyl-4*H*- and 2-(2-pyridylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were established by X-ray diffraction analysis. The "amide type" N(5)–C(4)–O bonds are unusually long (144–149 pm) showing no sign of an amide type conjugation.

The C(4)=O group tilted towards the ring N(5) atom [O–C(4)–N(5) angle: 115°–118° instead of 120°], and C(2)=O groups just tilted as much towards O(1) [O–C(2)–N(1) angle: 116°–118°). The presence of a rather unusual hydrogen bond C(6)–H(6)···O(4) with a distance of 22–23 pm was detected (00JCS(P2)2096).

The relative stereostructure of 9-acetyl-7-hydroxy-1,2-dimethyl-7-methoxycarbonyl-4-phenyl-6-oxo-1,4,7,8-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **122** was justified by an X-ray diffraction analysis (97JOC3109). The stereochemistry and solid state structure of racemic *trans*-6,9-*H*-1,6-dimethyl-9*a*-ethoxy-9-hydroxy-4-oxo-1,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**123**), adopting a *cis*-fused conformation, were determined by X-ray investigations (97H(45)2175).

Solid state structure of pirenperone (**9**) was determined by X-ray investigations (95AX(C)533). The pyrido[1,2-*a*]pyrimidine ring system deviates significantly from planarity with maximum deviations for C(3) and C(8) atoms [46(7) and 58(7) pm, respectively]. An analysis was carried out on the available crystal structures of 5-HT_1, 5-HT_2 (including **9** and **11**) and 5-HT_3 selective drugs to identify their similarities with the endogenous ligand serotonin (5-HT) and the stereochemical differences, which determine selectivity for the various receptor subtypes (96AX(B)509).

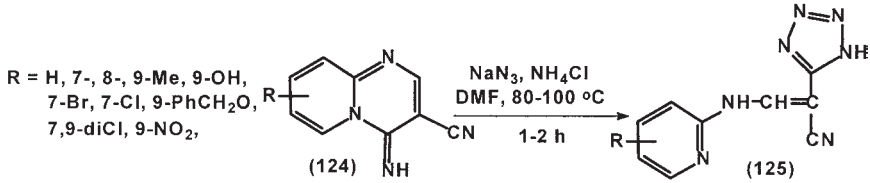
X-ray diffraction investigations of *cis*-8,9*a*-H-*trans*-7,9-H-7,8,9-trihydroxyperhydropyrido[1,2-*a*]pyrimidine (**112**, R = H), obtained in the reaction of D-xylose and 1,3-diaminopropane, revealed that it was the *β*-anomer with a *trans*-fused conformation containing all the hydroxy groups in equatorial positions (98JOC391, 98T5097). X-ray crystallography established that the bicyclic diazasugar analog of L-arabinose exists in the solid state as a single configuration and conformation of **114**, containing an axial NH bond (98T5097). Both the bicyclic diazasugar analog of D-ribose and its HCl salt have similar conformation **115**. Protonation occured on N(1), and in the base the NH bond occupied an axial orientation (98T5097). X-ray diffraction studies justified that in the solid state both 1-methyl **117** and 5-methyl **118** derivatives of perhydropyrido[1,2-*a*]pyrimidine **112** (R = H) contain the methyl group in axial position (99T6759). 5-Methyl derivative **118** contains an axial N(1)H bond, and a much shorter N(1)–C(9*a*) bond (139.7 pm) than that of the N(5)–C(9*a*) bond (157.4 pm), suggesting the presence a very strong *exo*-anomeric effect in the molecule.

Polymorphic forms I and II of 3-{2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one were characterized by the powder X-ray diffraction model (99MIP1).

B. Reactivity

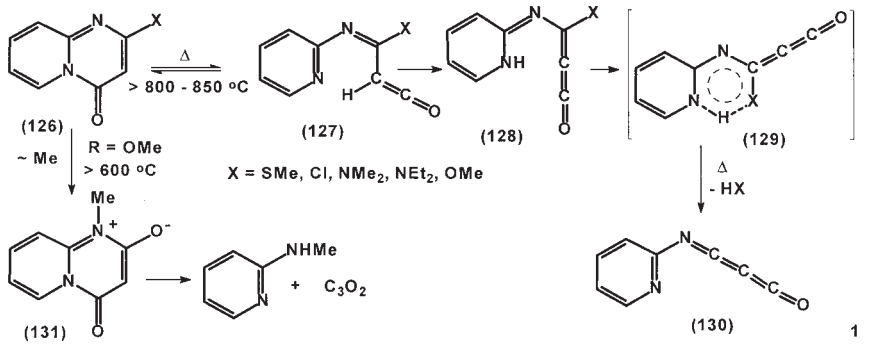
1. *Ring Opening*

Reaction of 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles **124** with NaN_3 in the presence of NH_4Cl gave 3-(2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylonitriles **125** (93MIP3).



Flash vacuum thermolysis (FVT) of 2-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **126** above 800 °C afforded (2-pyridyl)iminopropadienone (**130**) (99JCS(P2)1087). These reactions were interpreted in terms of reversible ring opening of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones to imidoylketenes **127**. A 1,5-H shift in **127** generated the N(1)H-tautomeric methylene ketene **128**, in which facile elimination of HX took place via a six-membered cyclic transition state **129** to yield **130**. In the case of 2-methoxy derivative **126** (X = OMe) another competing pathway was also identified at lower temperature, which resulted in the formation C_3O_2 and 2-methylaminopyridine via mesoionic isomer **131** (Scheme 9). The products were identified by IR spectroscopy.

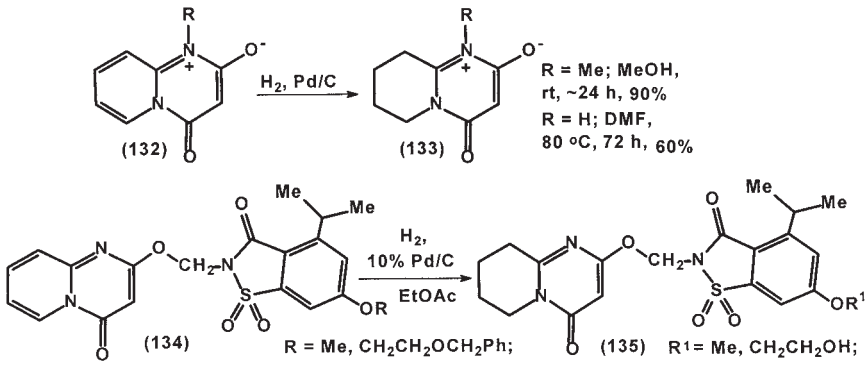
For some further example see Section IV.B.8.



Scheme 9

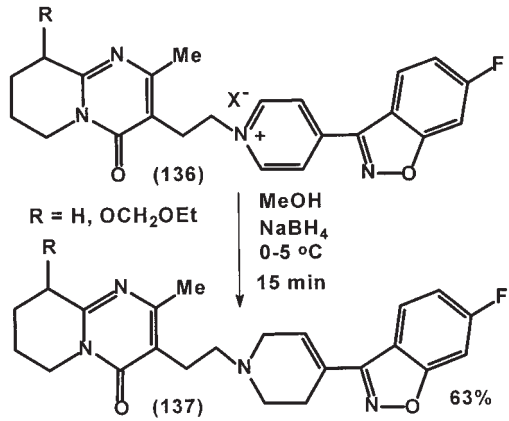
2. *Hydrogenation, Reduction*

Hydrogenation of mesoionic pyrido[1,2-*a*]pyrimidin-4-ones **132** over Pd/C catalyst yielded 6,7,8,9-tetrahydro derivatives **133** (95H(40)681, 96JHC663). Catalytical hydrogenation of 2-(4-methyl-1-piperazinyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one over Raney Ni in EtOH under hydrogen pressure (45 psi) (93FES1225), and that of 2-(1-piperazinyl)- (00BMC751), 3-(2-hydroxyethyl)- (94MIP8), 3-(2-chloroethyl)- (01MIP11), 9-hydroxy-3-(2-bromoethyl)- (96MIP2), 9-methoxy-3-(2-hydroxyethyl)- (95MIP4, 96MIP2), 3-(acetamido)- and 3-(benzamido)- (98MI8, 00JHC783), and 9-dodecyloxy-3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (95MIP4) over Pd/C catalyst afforded the appropriate 6,7,8,9-tetrahydro derivative. Catalytic hydrogenation of 3-(benzyloxycarbonylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones over Pd/C gave 3-amino-6,7,8,9-tetrahydro derivatives, whereas hydrogenation over 10% Pt/C yielded 3-(benzyloxycarbonylamino)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (00JHC783). 3-Amino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was also obtained by the catalytic hydrogenation of 3-[(2-acetyl-2-ethoxycarbonyl-1-ethenyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one over Pd/C in EtOH (00JHC783). Catalytic hydrogenation of 3-[2-(bisbenzylamino)ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-4-one over 10% Pd/C catalyst in EtOH gave 3-(2-aminoethyl) derivative (94MIP8).



Hydrogenation of 2-{(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxymethyl}-4-isopropyl-6-alkoxysaccharins **134** over 10% Pd/C catalyst at 50 psi in a Parr hydrogenator yielded 6,7,8,9-tetrahydro derivatives **135** (94EUP626378, 95JMC4687, 95USP5378720). When 6-[2-(benzyloxy) ethoxy] derivative **134** ($R = CH_2CH_2OCH_2Ph$) was hydrogenated

6-(2-hydroxyethoxy) derivative **135** ($R^1 = CH_2CH_2OH$) was the product (94EUP626378, 95USP5378720).



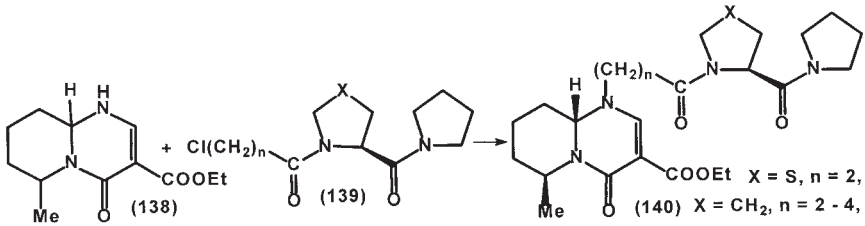
3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1,2,3,6-tetrahydro-1-pyridyl]-ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidon-4-ones **137** were obtained by reduction of pyridinium salts **136** with $NaBH_4$ (95MIP5, 99MIP1, 00MIP10). Reduction of 9-formyl-7-methyl-2-morpholino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with $NaBH_4$ in MeOH at room temperature gave a 9-hydroxymethyl derivative (01MIP9).

Reduction of pehydropyrido[1,2-*a*]pyrimidine with DIBAL-H in toluene led to the formation of 1,5-diazacyclodecane in 60% yield (99JCS(CC)1279).

For further examples see Section IV.B.7.

3. *Oxidation*

Oxidation of 9-(4-pyridylvinyl)-7-methyl-2-morpholino-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one with cetyltrimethylammonium permanganate in CH_2Cl_2 at room temperature for 5 h yielded a 9-formyl derivative (01MIP9).



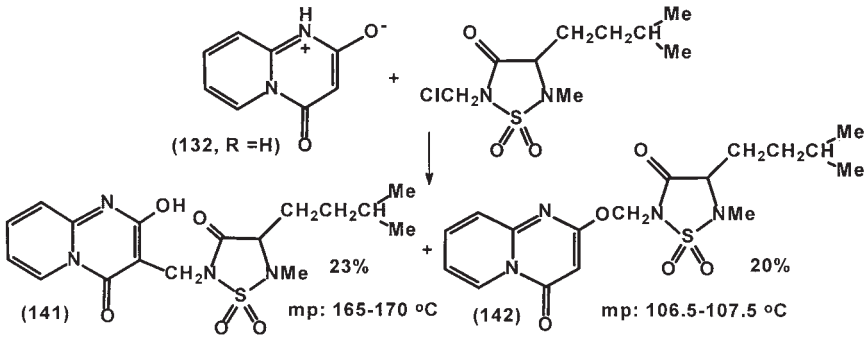
4. *Reactivity of Ring Nitrogen Atoms*

Perhydropyrido[1,2-*a*]pyrimidin-2-one was *N*-alkylated with 1,4-dibromobutane to yield a 1-(4-bromobutyl) derivative (94MIP6). 6-Methyl-4-oxo-4*H*-1,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **138** was alkylated with alkyl chlorides **139** to give 1-substituted derivatives **140** (97MIP2).

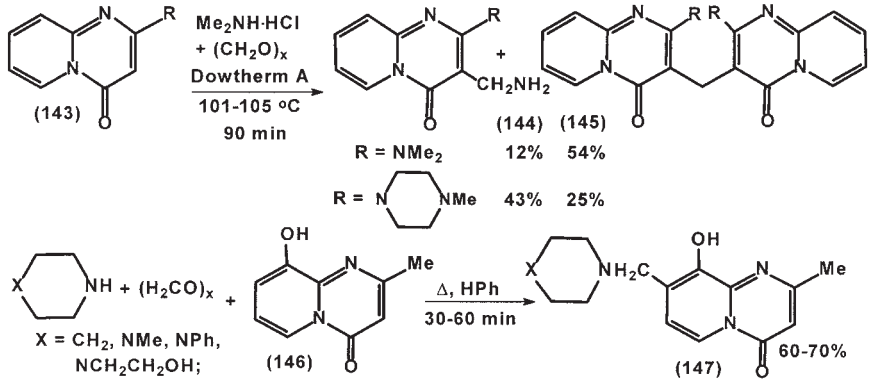
5. *Reactivity of Ring Carbon Atoms*

Nitration of 2-(1-piperazinyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with 99% HNO_3 in 96% H_2SO_4 at 0 °C (00BMC751) and that of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 6-, 7-, 8-, and 9-methyl derivatives with a mixture of HNO_3 and 96% H_2SO_4 in the presence of Ac_2O at 0 °C (93IJC(B)978) gave the appropriate 3-nitro derivative. Nitration of 2-chloromethyl-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in conc. H_2SO_4 with fuming HNO_3 at 0 °C yielded the 3-nitro derivative (01H(55)535).

Chlorination of 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with NCS in a mixture of AcOH and TFA at room temperature for 72 h yielded a 3-chloro-2-hydroxy derivative (95JMC4687). Bromination of 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidone with Br_2 in a mixture of CH_2Cl_2 and pyridine at room temperature for 15 min gave a 3-bromo derivative (00BMC751).

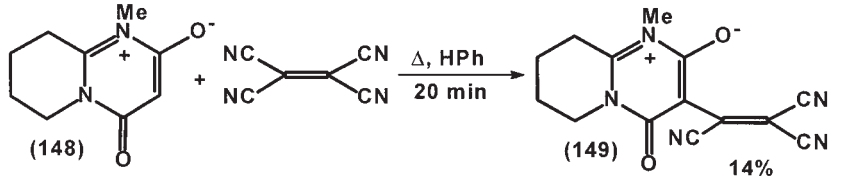


Alkylation of mesoionic **132** (R = H) with 2-chloromethyl-4-(3-methylbutyl)-5-methyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide gave a mixture of C-3 and 2-*O*-alkylated products **141** and **142** (96USP5512576).

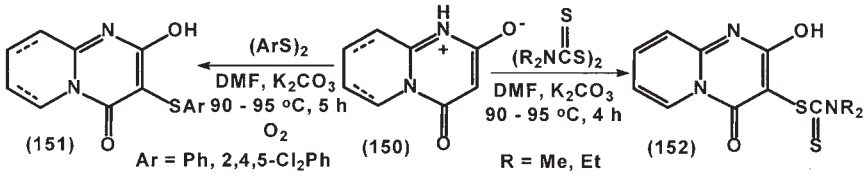


Reaction of 2-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **143** with $HNMe_2 \cdot HCl$ and paraformaldehyde in Dowtherm A afforded a mixture of 3-(*N*,*N*-dimethylamino)methyl derivatives **144** and bis-compounds **145** (93FES1225). Mannich reaction of 9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**146**) yielded 8-aminomethyl derivatives **147** (94KFZ(10)23).

Vilsmeier-Haack formylation of 2-(4-methyl-1-piperazinyl)-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one with a mixture of $POCl_3$ and DMF at 95 °C gave a 3-formyl derivative (93FES1225) while ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-acetate at 50 °C yielded a 9-dimethylaminomethylene-3-formyl derivative (01MI4). 3-Formyl-2-hydroxy-8-[2-(4-isopropyl-1,3-thiazol-2-yl)-1-ethenyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained from the 3-unsubstituted derivative with oxalyl chloride–DMF reagent in CH_2Cl_2 at room temperature for 3 h (01MIP1).

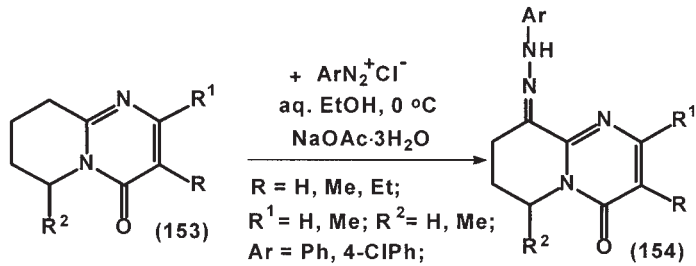


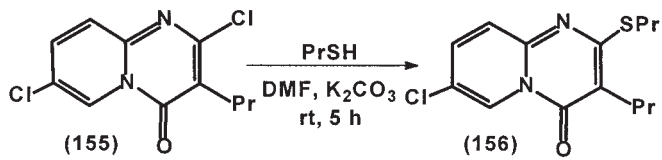
Reaction of 1-methyl–4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium-2-olate (**148**) with tetracyanoethylene afforded 3-substituted derivative **149** (95H(40)681).



3-Arylsulfenyl derivatives **151** were obtained from mesoionic **150** with diaryl disulfides in the presence of K_2CO_3 when air was bubbled through the reaction mixture (99M1147). *anhydro*-(2-Hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide (R = H) afforded 3-dialkylaminothiocarbonylthio derivatives **152** in the reaction of tetraalkylthiuram disulfides under similar conditions.

9-Arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **154** were obtained from 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **153** with aryldiazonium chlorides in the presence of $NaOAc \cdot 3H_2O$ at 0 °C overnight (96JHC799, 99MI12, 00MI22).





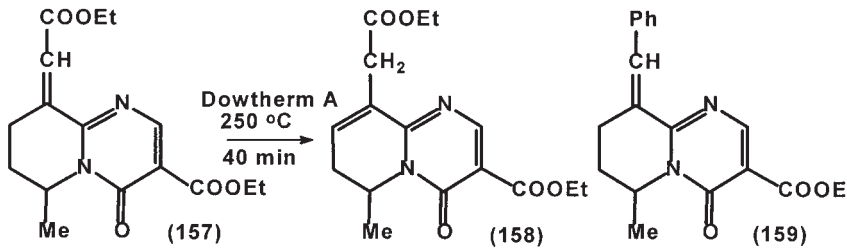
2,7-Dichloro-3-propyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**155**) was obtained from *anhydro*-(2-hydroxy-7-chloro-3-propyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide in boiling $POCl_3$ for 88 h in 27% yield, and then the 2-chloro atom was changed for a 2-propylthio group with PrSH to give **156** (93MIP4). Treatment of 9-benzyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with excess $POCl_3$ under reflux yielded a 2-chloro derivative (01MIP9). 2-Ethylamino and 2-(disubstituted amino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles were obtained in the reaction of 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile with an excess of $EtNH_2$ and secondary amines in boiling MeCN for 48–52 h (95MI9).

In the series of reactions the chloro atom of 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was substituted by different primary and cyclic amines (93FES1225, 95EJM27, 00BMC751, 01MIP9), and by ethylenediamine and 1-aminopiperazine (00BMC751) in boiling EtOH; by an excess of Me_2NH in a mixture of CH_2Cl_2 and Et_2O at room temperature for 16 h and by Et_2NH in boiling $CHCl_3$ for 24 h (99JCS(P2)1087), by *i*-Bu_2NH and cyclohexylamine in $HOCH_2CH_2OH$ at 160 °C for 2 h, and by 2-aminopyridine and its 4- and 5-methyl derivatives in a melt at 200 °C for 4 h (93FES1225, 01JCS(P2)602). The chloro atom of 2-chloro-3-formyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one was also substituted by different secondary amines (96T13081).

Reaction of 9-bromo-2-morpholino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with 4-vinylpyridine in DMF at 80 °C for 16 h in the presence of Cs_2CO_3 and $PdCl_2$(dppf), and with amines and phenols in boiling THF for 20 h in the presence of KO*t*-Bu and $PdCl_2$(dppf) yielded 9-[2-(4-pyridyl)vinyl), 9-(substituted amino), and 9-aryloxy derivatives, respectively (01MIP9). 4-Hydroxyaniline gave a 9-(4-hydroxyphenyl)amino derivative.

2-Methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with NaOMe in MeOH for 16 h, and from *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyridinium)hydroxide with Me_2SO_4 in the presence of NaOMe in MeOH for 3 h at room temperature in 93% and 41% yields, respectively (99JCS(P2)1087). 2-(2-Hydroxyethoxy)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from the 2-chloro derivative with $HOCH_2CH_2OH$ in the presence of K_2CO_3 at 160 °C for 1 h (00BMC751).

2-Chloro-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione was obtained by the treatment of the 4-oxo derivative with Lawesson's reagent in boiling anhydrous toluene, and then the 2-chloro atom was changed for a piperazino group with piperazine in boiling EtOH (00BMC751). Treatment of 7-chloro-3-propyl-2-propoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with $(P_2S_5)_2$ (93MIP4), and that of 1,3,3-trimethyl-9-phenyl-1,2,3,6,7,8-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione with Lawesson's reagent (96H(42)117) afforded 4-thione and 2,4-dithione derivatives, respectively.

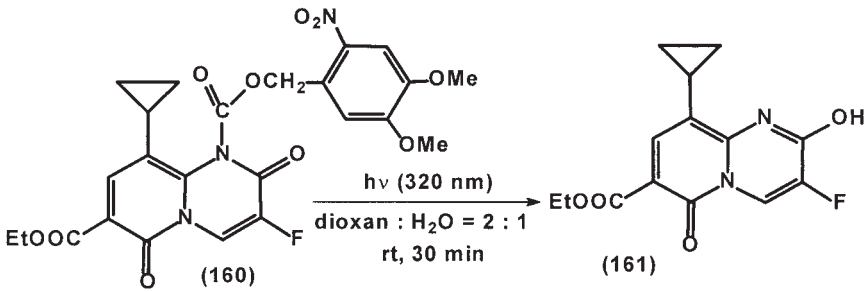


Heating 9-ethoxycarbonylmethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylate (**157**) at 250 °C yielded 6,7-dihydro derivative **158** (99T10221). Under similar conditions 9-benzylidene-6,7,8,9-tetrahydro derivatives **159** did not gave the respective 9-benzyl-6,7-dihydro isomer.

For further example see Section IV.B.7.

6. *Reactivity of the Substituents Attached to a Ring Nitrogen Atom*

Photolytic cleavage of the substituent in position 1 of 1,2-dihydro-6*H*-pyrido[1,2-*a*]pyrimidine-2,6-dione **160** with 320 nm light gave 6*H*-pyrido[1,2-*a*]pyrimidin-6-one **161** (95MIP1, 96MIP4, 96USP5580872).



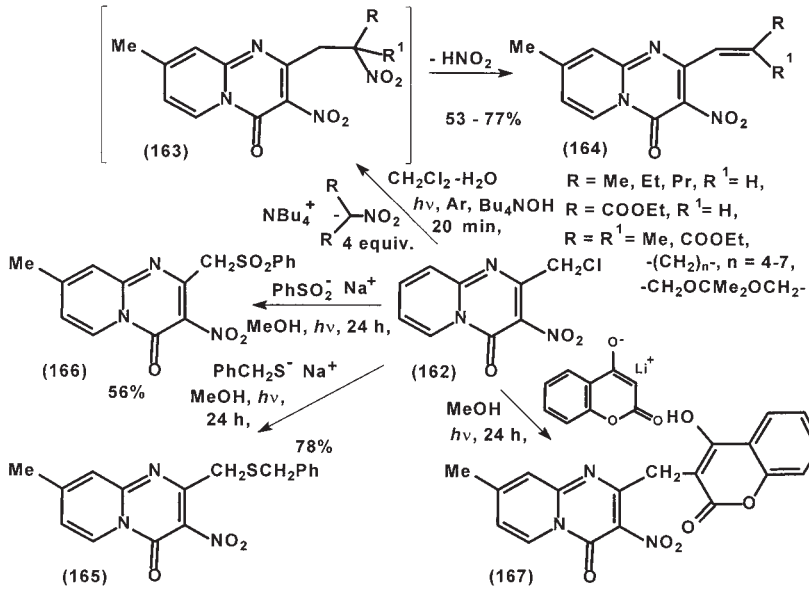
7. *Reactivity of the Substituent Attached to a Ring Carbon Atom*

The hydroxy group of 3-(2-hydroxyethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was replaced by a chloro atom on treatment with $SOCl_2$ in CH_2Cl_2 at ambient temperature (94MIP8), or with boiling $POCl_3$ (95MIP4) and by a bromo atom with conc. HBr in MeOH (96MIP2). The hydroxy group of 3-(2-hydroxyethyl)-9-methoxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 6,7,8,9-tetrahydro derivative was acylated with $MeSO_2Cl$ in CH_2Cl_2 in the presence of NEt_3 (95MIP4).

The side chain chloro atom of 2-chloromethyl-4*H*- **162** (95FES69, 00BMC751), and that of 3-(2-chloroethyl)-, and 3-(3-chloropropyl)-2-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their 6,7,8,9-tetrahydro derivatives was replaced by cyclic amines (93GEP4243287, 93MIP2, 94MIP1, 94MIP4, 94MIP5, 94MIP8, 95JAP(K)95/33744, 95JAP(K)95/188215, 95MIP4, 95USP5468763, 97MIP8, 97MIP9, 98MIP5, 99MIP2, 00BMCL71, 00MIP3, 00MIP4, 00MIP7, 01MIP10, 01MIP11). Sometimes instead of 3-(2-chloroethyl) derivatives 3-(2-bromoethyl) (96MIP2) and 3-[2-(methylsulfonyloxo)ethyl] (95MIP4, 96MIP2, 98MIP5) derivatives were

also used as starting materials. The bromo atom of 1-(4-bromobutyl)perhydropyrido[1,2-*a*]pyrimidin-2-one was replaced by 3-(4-piperidyl)-1,2-benzisothiazole (94MIP6). Pyridinium salts **136** were obtained in the reaction of 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-fluoro-3-(4-pyridinyl)-1,2-benzisoxazole in boiling MeCN (95MIP5, 00MIP10).

^{18}F-Labeled pirenperone (**9**) was prepared with high radiochemical yield (72%) and high purity (99%) for PET studies from pirenperone using a [^{18}F] fluoride–cryptand–oxalate system (95CL835).



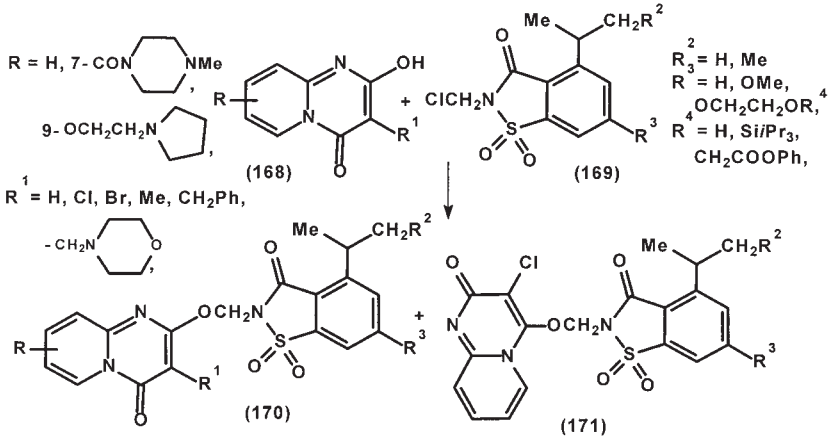
Reaction of 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-one **162** with various nitronate anions (4 equiv) under phase-transfer conditions with Bu_4NOH in H_2O and CH_2Cl_2 under photo-stimulation gave 2-ethylenic derivatives **164** (01H(55)535). These alkenes **164** were formed by single electron transfer C-alkylation and base-promoted HNO_2 elimination from **163**. When the ethylenic derivative **164** ($R = R^1$) was unsymmetrical, only the *E* isomer was isolated. Compound **162** was treated with *S*-nucleophiles (sodium salt of benzyl mercaptan and benzenesulfinic acid) and the lithium salt of 4-hydroxycoumarin to give compounds **165**–**167**, respectively.

2-(Piperazinomethyl)-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained by hydrolysis of the 2-(4-formylpiperazino)methyl derivative in boiling 10% HCl. The hydrolysis of the 2-(4-ethoxycarbonylpiperazino) derivative in NaOH solution was unsuccessful (95EJM27).

Treatment of 9-benzyloxy-2-morpholino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with $(CF_3SO_2)_2O$ in CH_2Cl_2 overnight at room temperature gave a 9-hydroxy derivative (01MIP9). The 9-hydroxy group was derivatized by a copper promoted arylation using $Cu(Ac)_2$ and arylboronic acids [e.g., $PhB(OH)_2$] in CH_2Cl_2 in the presence of NEt_3 at room temperature, or by base catalyzed alkylation using (het)arylmethyl halides [e.g., (2-ClPh) CH_2Br] in MeCN at 80 °C in the presence of K_2CO_3 overnight to yield 9-aryloxy or 9-[(het)aryl)methoxy] derivatives (01MIP9). The hydroxy group of 9-hydroxymethyl-7-methyl-2-morpholino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was acylated with $MeSO_3Cl$ in the presence of NEt_3 in CH_2Cl_2 at 0 °C, then the 9-(mesyloxymethyl) group was allowed to react with different anilines under reflux to give 9-(arylamino)methyl derivatives.

The hydroxy group of ethyl 9-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate was *O*-alkylated with 2-chloromethyl-4-isopropyl-1, 3-thiazole in DMF at 115 °C in the presence of K_2CO_3 and KI (01MIP1).

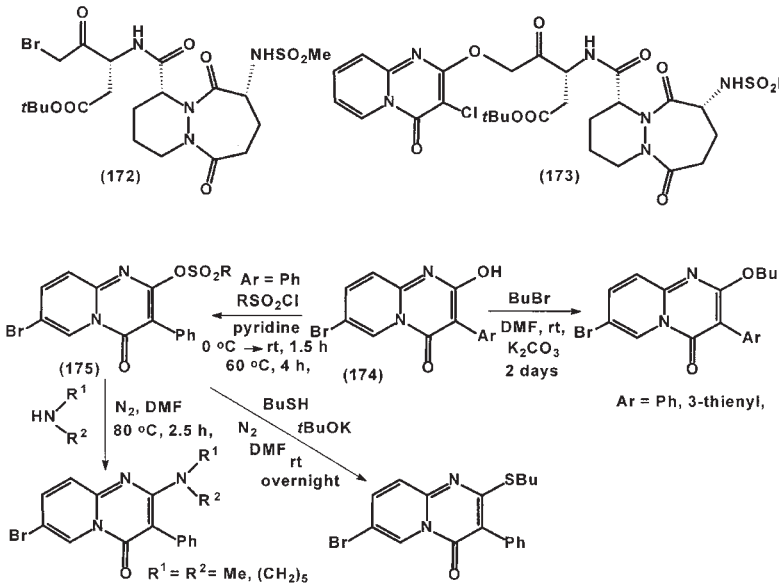
The hydroxy group of 2-hydroxy-3-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was *O*-alkylated with alkyl bromides in boiling MeCOMe (94BMCL183), with alkyl iodides and allyl bromide in DMF at room temperature in the presence of K_2CO_3 (93MIP4), and with 2-bromomethyl-4-isopropyl-6-alkoxy-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides in DMF in the presence of NEt_3 (01MIP8). 2-Hydroxy-3-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one, its 6- and 7-methyl, and their 6,7,8,9-tetrahydro derivatives were *O*-alkylated with 4-substituted benzyl bromides (96EUP733633).



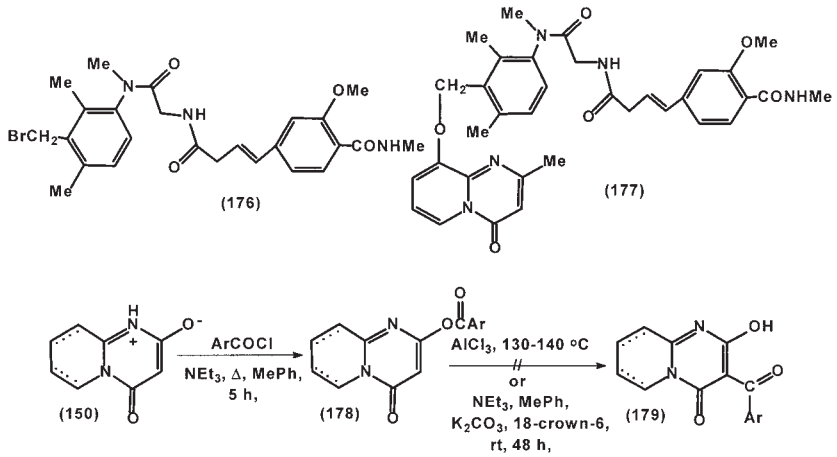
Reaction of 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **168** and 2-chloromethylsaccharins **169** in the presence of a base gave 2-*O*-alkylated products **170** (94EUP626378, 95JMC4687, 95USP5378720). From the reaction mixture of 3-chloro derivative **168** ($R = H$, $R^1 = Cl$) and

2-chloromethyl-4-*sec*-butylsaccharin (**172**, $R^2 = Me$, $R^3 = H$) in DMF in the presence of methyltriazabicyclodecene in addition to the 4-oxo-4*H* derivative **170** ($R^1 = Cl$, $R = R^3 = H$, $R^2 = Me$) (~47%), the isomeric 2-oxo-2*H* compound **171** (~4%) was also isolated. Treatment of triisopropylsilyloxy derivative **170** ($R^1 = Cl$, $R = R^2 = H$, $R^3 = OCH_2CH_2OSiiPr_3$) with 2 N HCl in a mixture of MeOH and THF at ambient temperature yielded 6-(2-hydroxyethoxy) derivative **170** ($R^1 = Cl$, $R = R^2 = H$, $R^3 = -OCH_2CH_2OH$), and the hydroxy group then was acylated with 2-(dimethylamino)acetic acid in CH_2Cl_2 in the presence of 1,3-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine at room temperature (94EUP626378, 95USP5378720).

2-Hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **168** ($R = H$, $R^1 = Cl$) was *O*-alkylated with compound **172** in DMF in the presence of KF at room temperature (97MIP3). The *tert*-butoxycarbonyl group of compound **173** was converted to a carboxyl group by treatment with TFA. The hydroxy group of 3-aryl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **174** was *O*-alkylated and *O*-acylated with BuBr and with arylsulfonyl chlorides and $MeSO_3Cl$, respectively (97BRP2307177). The phenylsulfonyloxy group of **175** was changed for secondary amino groups with secondary amines and for a butylthio group with BuSH (Scheme 10).



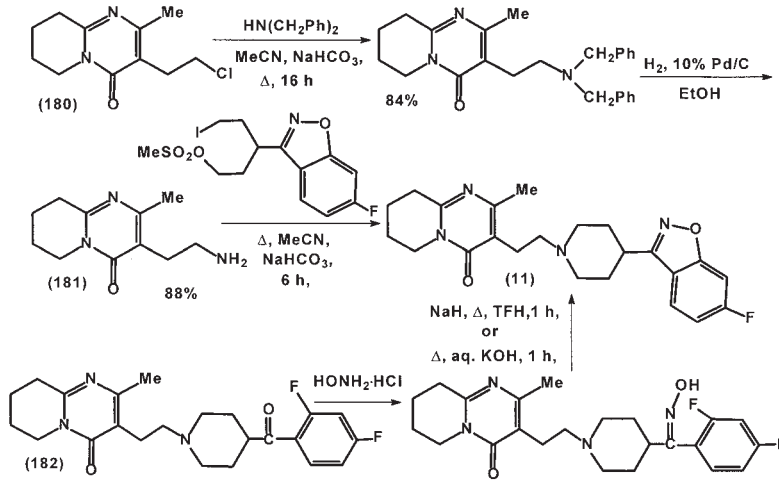
Scheme 10



The 9-hydroxy group of 9-hydroxy-2-methyl-3-(2-hydroxyethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was alkylated with Me_2SO_4 in aqueous NaOH at room temperature for 15 min followed by heating at 95–100 °C (95MIP4, 96MIP2), and with $MeOCH_2CH_2I$ in DMF in the presence of K_2CO_3 at 60–70 °C for 1 h (95MIP4) to give 9-methoxy (42%) and 9-(2-methoxyethoxy) (66%) derivatives, respectively. 9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was *O*-alkylated with benzyl bromide **176** in DMF to give compound **177** (96MIP1). 9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was *O*-alkylated with other benzyl halogenide derivatives (98FRP2765222).

The side chain hydroxy group of 3-(2-hydroxyethyl)-2-methyl-9-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, and that of its 6,7,8,9-tetrahydro derivative was acylated with $MeSO_2Cl$ in the presence of NEt_3 in CH_2Cl_2 at room temperature (95MIP4, 96MIP2). The hydroxy group of 2-[4-(4-hydroxybenzoyl)benzyloxy]-3-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one, its 6-methyl derivative and 2-[4-(4-hydroxybenzoyl)benzylthio]-3-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was alkylated with 4-(2-chloroethyl)morpholine hydrochloride and 4-picolyl chloride hydrochloride (96EUP733633).

Acylation of mesoionic pyrido[1,2-*a*]pyrimidin-4-ones **150** with aroyl chlorides in the presence of NEt_3 yielded 2-aroyloxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **178** (96JHC663). None of the esters **178** could be rearranged to the 2-hydroxy-3-aroyl derivatives **179**. The hydroxy group of 9-hydroxy-2-methyl-3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl}-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was acylated with hexadecanoic acid in CH_2Cl_2 in the presence of dicyclohexylcarbodiimide and 4-pyrrolidinopyridine at room temperature for 3 days in 80% yield (97MIP7).

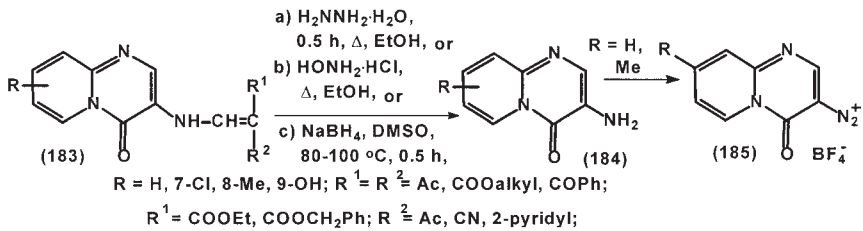


Scheme 11

Treatment of 9-(ethoxymethoxy)-3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl] and -1-piperidyl]ethyl}-2-methyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones with conc. HCl afforded 9-hydroxy derivatives (95MIP4, 00MIP10).

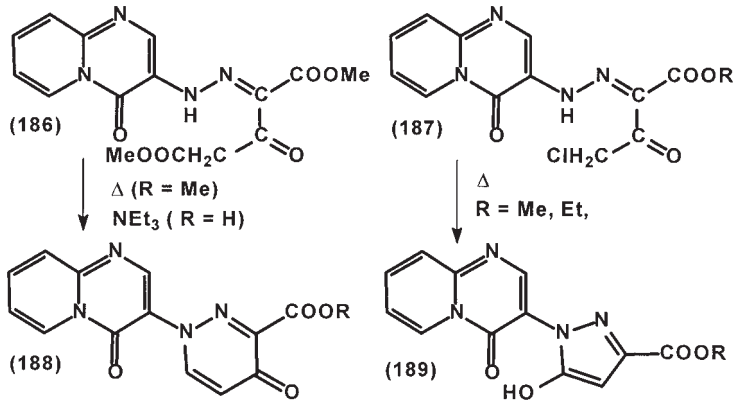
2-Mercapto-3-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 6,7,8,9-tetrahydro derivative were *S*-alkylated with 4-substituted benzylbromides (96EUP733633).

Risperidone (**11**) was prepared starting from 3-(2-chloroethyl) **180**, via 3-(2-aminoethyl) **181**, and 3-{2-[4-(2,4-difluorobenzoyl)piperidino]ethyl} **182** derivatives of 4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones as depicted in Scheme 11 (94MIP8, 95MIP7).



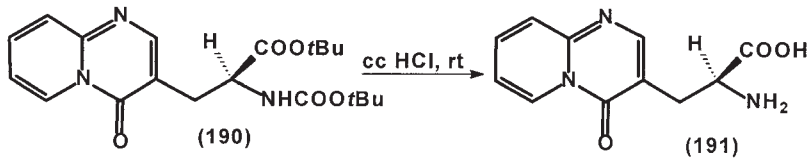
3-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **184** were obtained from 3-(2,2-disubstituted ethenylamino) derivatives **183** with $H_2NNH_2 \cdot H_2O$ or $HONH_2 \cdot HCl$ in good yields, and from **183** ($R^1 = COOCH_2Ph$, $R^2 =$ acetyl) by treatment with $NaBH_4$ in moderate yields (97H(45)2349,

97HCA2418, 97JHC1511, 98ACH613, 98H(47)1017, 98H(49)133, 98JHC1275, 01JHC869). 3-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were also prepared from 3-(benzyloxycarbonylamino) derivatives by catalytic transfer hydrogenation over 10% Pd/C catalyst with cyclohexene in boiling EtOH (99CCC177), or by treatment with HBr in AcOH (00MI33). 3-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **184** (R = H, 8-Me) were transformed into the stable 3-diazonium tetrafluoroborates **185** by treatment with $NaNO_2$ in 1:1 HCl below 0 °C, then with 50% HBF_4 or with *t*-$BuNO_2$ and $BF_3 \cdot EtO_2$ in CH_2Cl_2 at −15 °C (00H(53)1793, 00MI33).

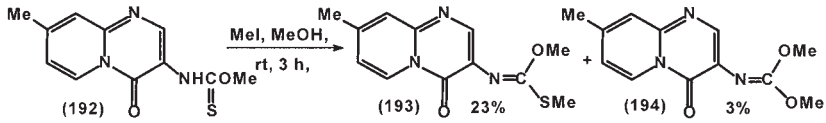


3-Diazonium salt **185** (R = H) when coupled with different CH active compounds yielded 3-hydrazono derivatives (e.g. **186** and **187**). Hydrazono derivatives **186** and **187** were cyclized into 3-(1,4-dihydropyridazin-1-yl) **188** and 3-(pyrrolin-1-yl) derivatives **189**, respectively (00MI33).

The 3-formyl group of 8-substituted 3-formyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was reacted with (cyanomethyl)- and (*tert*-butoxycarbonylmethylene)triphenylphosphorane in THF, and with 5-aminotetrazole in boiling MeOH for 9 h to yield (*E*)-3-propenenitrile, *tert*-butyl (*E*)-3-propenoate and 3-[(2*H*-tetrazol-5-yl)imino]methyl derivatives, respectively (01MIP1).



Deprotection of 2-(*tert*-butoxycarbonylamino)-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)propionate **190** with conc. HCl afforded the amino acid **191** in quantitative yield (95TL7503, 97JCS(P1)1297).



Reaction of 3-methoxythiocarbonylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **192** with MeI gave a mixture of 3-(1-methylthio-1-methoxymethylene)amino **193** and 3-(dimethoxymethylene)amino derivatives **194** after a chromatographic work-up (94JHC125).

Acidic hydrolysis of 4-imino-3-cyano-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]pyrimidines in boiling EtOH with aqueous hydrochloric acid afforded 4-oxo derivatives (00MI27).

The chloro atom of 2-[4-(6-chloronicotinoyl)benzyloxy]-3-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, its 6-methyl derivative and 2-[4-(6-chloronicotinoyl)benzylthio]-3-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was replaced by a 4-piperidinopiperidino and 4-phenylpiperazino group with 4-piperidinopiperidine and 4-phenylpiperazine (96EUP733633). The carboxyl group of 2-[4-(4-carboxybenzoyl)benzyloxy]-3-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, prepared by hydrolysis of methyl ester in DMF with 1 N NaOH, was reacted first with diethyl pyrocarbonate in DMF at room temperature and then with 4-phenylpiperazine and 4-piperidinopiperidine to give the appropriate amide derivatives (96EUP733633).

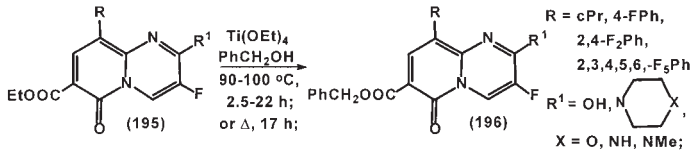
The *N*-substituted derivatives of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides and -3-acetamides and 1,6-dimethyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide were prepared by treatment of the appropriate 3-carboxylic acids and acetic acid, first with an alkyl chloroformate in the presence of NEt_3 in $CHCl_3$ below $-10\,^{\circ}C$, then with an amine (98ACH515). *N*-Phenethyl and *N*-[2-(3,4-dimethoxyphenyl)ethyl] derivatives of 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetamide were obtained in the reaction of 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetic acid and phenethylamines in boiling xylene under a H_2O separator. Hydrazides of 4-oxo-4*H*- and 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetic acid were prepared from the appropriate ester with $H_2NNH_2 \cdot H_2O$ in EtOH. Heating 4-oxo-4*H*- and 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetic hydrazides in EtOH in the presence of excess Raney Ni afforded the appropriate 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetamide. In the case of the 4-oxo-4*H* derivative, in addition to N–N bond

cleavage, saturation of the pyridine moiety of 4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide also occurred. *N*-Substituted 2-hydroxy-4-oxo-4*H*-pyrido [1,2-*a*]pyrimidine-3-carboxamides were prepared from alkyl 2-hydroxy-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylates with (het)arylamines in boiling bromobenzene for 2–30 h (99JHC237).

An ester group in the side chain at position 9 of 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one was hydrolysed and the carboxyl group was converted into an *N*-{3-[(4-cyanophenyl)carbonylamino]propyl derivative of carboxamide group with *N*-(3-aminopropyl)-4-cyanobenzamide in the presence of [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, 1-hydroxy-7-azabenzotriazole and *N*-methylmorpholine in CH_2Cl_2 at ambient temperature. Treatment of a cyano group in the side-chain at position 9 of 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one with $HONH_2 \cdot HCl$ in the presence of NEt_3 in DMSO afforded an *N*-hydroxycarboxamidine derivative. Its hydroxy group was acylated with Ac_2O, and catalytic reduction of *N*-acetoxycarboxamidine over 5% Pd Lindlar catalyst in MeOH yielded a carboxamidine derivative (98FRP2765222).

2-Methylthio-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared by FVT of 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid at 650 °C at 8×10^{-5} mbar for 4 h (99JCS(P2)1087).

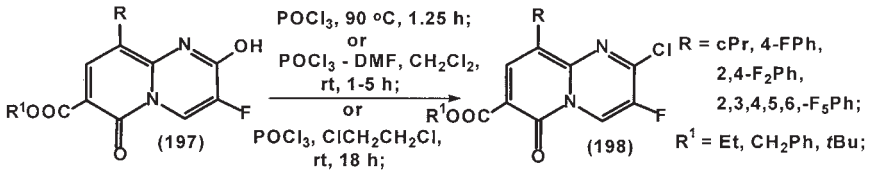
Acidic and basic hydrolysis of ethyl 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxylates gave 3-carboxylic acid derivatives (01MIP1). Stirring *tert*-butyl (*E*)-3-(2-hydroxy-8-[2-(4-isopropyl-1,3-thiazol-2-yl)-1-ethenyl]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-2-propenoate in CF_3CO_2H at room temperature yielded (*E*)-3-substituted 2-propenoic acid.



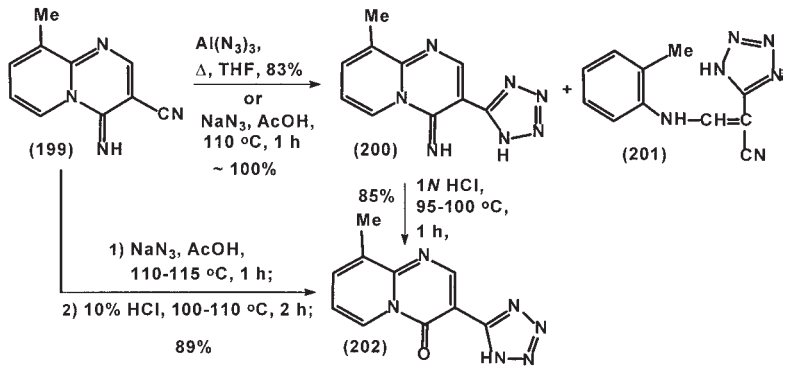
2,9-Disubstituted 3-fluoro-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylates **195** on treatment with $Ti(OEt)_4$ in dry benzyl alcohol yielded benzyl esters **196**. The 7-benzyl esters **196** were converted to 7-carboxylic acids by catalytic hydrogenation over 10% Pd/C catalyst at room temperature under 1–4 atm of hydrogen, or by treatment with 98% HCOOH in the presence of 10% Pd/C catalyst at ambient temperature for 20–110 min (95MIP1, 96JMC3070, 96MIP4, 96USP5580872). When the substituent in position 2 contained a benzyloxycarbonylamino group, then 7-carboxylic acid derivatives, containing a free amino group in the side-chain at position 2 were obtained. 2,9-Disubstituted 3-fluoro-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylic acids were also prepared from 7-*tert*-butyl esters on

the action of 4 N HCl in dioxane (95MIP1, 96JMC3070, 96MIP4, 96USP5580872). When the substituent in position 2 contained a *tert*-butoxycarbonylamino group, then a 7-carboxylic acid containing a free amino group was obtained (96JMC3070).

9-(4-Fluorophenyl)-3-fluoro-2-hydroxy-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylic acid (**197**, R = 4-FPh, R^1 = H) was obtained from the 2-(4-methyl-1-piperazinyl)-7-ester derivative by the treatment with 1 N NaOH in an 1:1 mixture of H_2O and THF at room temperature for 6 h (95MIP1, 96JMC3070, 96MIP4, 96USP5580872).



2-Chloro derivatives **198** were prepared from 2-hydroxy derivatives **197** with $POCl_3$ (96JMC3070, 96MIP4,96USP5580872). The chloro atom of compounds **198** was changed for a cyclic amino group by treatment with a cyclic amine in CH_2Cl_2, sometimes in the presence of NEt_3, at room temperature overnight (95MIP1, 96JMC3070, 96MIP4, 96USP5580872). The amino group of benzyl 2-(3-amino-1-pyrrolidinyl)-3-fluoro-9-(2,4-difluorophenyl)-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate was *N*-acylated with different protected dipeptide derivatives in DMF in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl and 1-hydroxybenzotriazole hydrate at 0 °C for 30 min, then at room temperature for 2 h (95MIP1, 96JMC3070, 96MIP4, 96USP5580872).

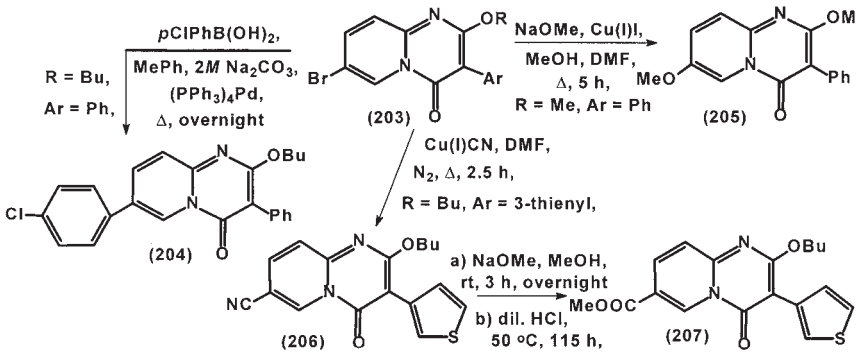


Reaction of **199** with NaN_3 or NH_4N_3 in DMF at 90–95 °C afforded a 1:4–5 mixture of **200** and ring opened **201** products. When the reactions

were carried out with $Al(N_3)_3$, prepared *in situ* from $AlCl_3$ and NaN_3 in boiling THF or in AcOH, 3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidine **200** resulted. Acidic hydrolysis of **200** gave 3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **202** with high purity. Treatment of 4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (**199**) first with NaN_3, then with 10% HCl gave 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**202**) (95CPB683).

The cyano group of 2-alkoxy-3-{4-[(2-cyanophenyl)phenyl]methyl}-4*H*-pyrido[1,2-*a*]pyrimidine-4-ones was converted to a 5-tetrazoyl group by treatment with NaN_3 in the presence of Bu_3SnCl in boiling xylene (94BMCL183). From the 7-iodo-2-alkoxy-3-{4-[(2-cyanophenyl)-phenyl]-methyl}-4*H*-pyrido[1,2-*a*]pyrimidin-4-one 7-methoxycarbonyl-, 7-vinyl-, and 7-(1-ethoxyvinyl) derivatives were prepared on the treatment with CO in the presence of $(Ph_3P)_2Pd(II)Cl_2$ and NEt_3 in boiling MeOH, with vinyltributyltin in the presence of $(Ph_3P)_4Pd$ in toluene at 80 °C, and with (2-ethoxyvinyl)tributyltin in the presence of $(Ph_3P)_2Pd(II)Cl_2$ in toluene at 80 °C, respectively. The 7-(1-ethoxyvinyl) group was hydrolyzed into an acetyl group in a mixture of 5 N HCl and THF at ambient temperature and then the acetyl group was reduced with $NaBH_4$ in the presence of $CeCl_3$ in EtOH to a 1-hydroxyethyl group.

Reaction of 8-substituted 3-[2-(4-methoxybenzyl)-2*H*-tetrazol-5-yl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with CF_3COOH for 2 days at room temperature gave 3-(2*H*-tetrazol-5-yl) derivatives (01MIP1). The cyano group of a 3-(8-substituted 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-2-propenenitrile was converted into a 5-tetrazolyl group by treatment with NaN_3 in the presence of $AlCl_3$ in DMF at 100 °C for 2 days.

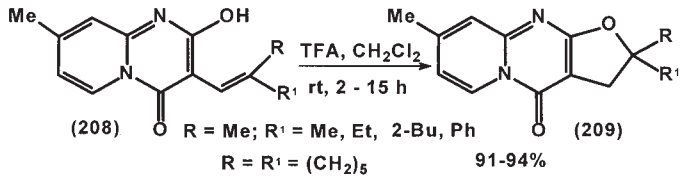


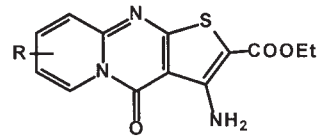
Reaction of 7-bromo-2-butoxy-3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**203**, R = Bu, Ar = Ph) and (4-ClPh)BH_2 in the presence of a 2 M solution of Na_2CO_3 and $(Ph_3P)_4Pd$ afforded 7-(4-chlorophenyl) derivative

204 (97BRP2307177). The bromine atom of **203** was also replaced by a methoxy and a cyano groups with NaOMe in the presence of Cu(I)I; and with Cu(I)CN to give compounds **205** and **206**, respectively. The nitrile group of **206** was converted into a methoxycarbonyl group to give compound **207**.

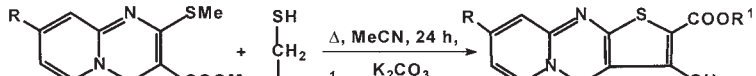
8. *Reactions Leading to Polycondensed Ring System*

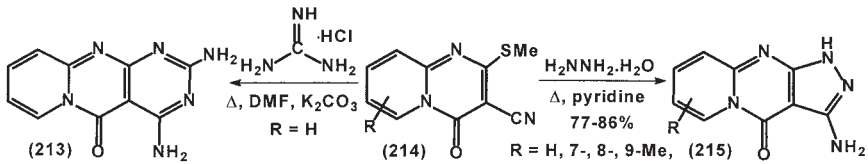
Treatment of 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **208** with TFA furnished tricyclic derivatives **209** (99ACS901, 99MI29).



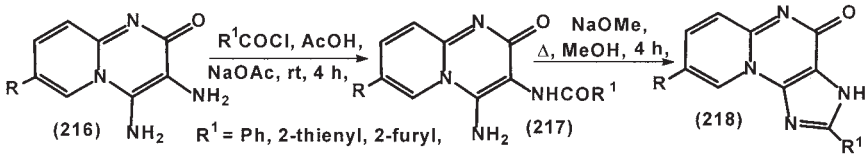


Cyclocondensation of 3-cyano-2-methylthio-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and ethyl mercaptoacetate in boiling EtOH in the presence of NaOEt afforded 4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidin-4-ones **210** (00HC571). 2-Methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **211** and mercaptoacetates afforded tricyclic derivatives **212** (93MIP1). Cyclocondensation of 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carbonitriles **213** with $H_2NNH_2 \cdot H_2O$ and with guanidine HCl afforded tricyclic derivatives **214** and **215**, respectively (96FES781).

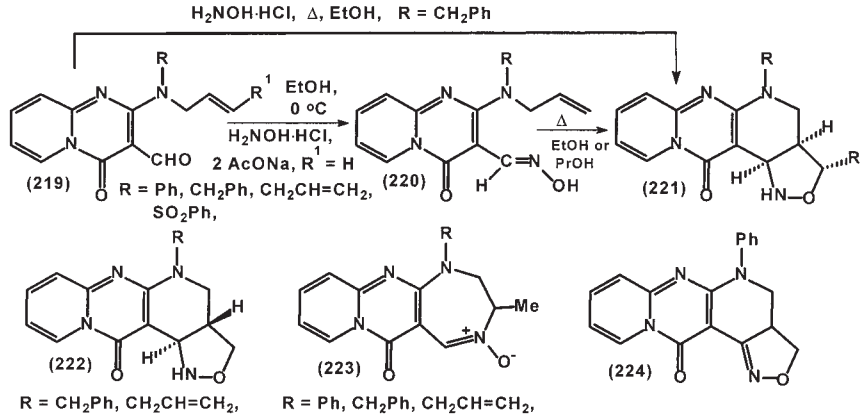




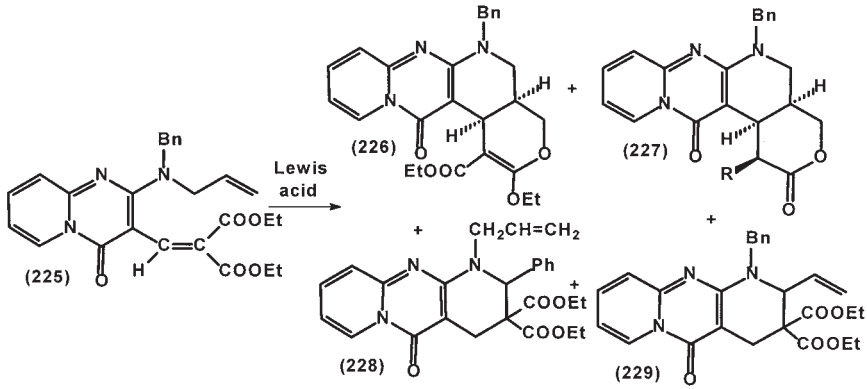
Treatment of ethyl 9-dimethylaminomethylene-3-formyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-acetate with saturated NH_3 ethanolic solution in a closed ampule at 100 °C for 24 h, then with 5% HCl for 1 h at room temperature gave 6-formyl-2,3,6,7,8,9-hexahydro-11*H*-dipyrido[1,2-*a*;5,6-*c*]pyrimidine-2,11-dione (01MI4).



The 3-amino group of 3,4-diamino-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **216**, obtained from 3-nitroso derivatives by reduction with $Na_2S_2O_4$ in 30% NH_4OH at 70–80 °C, was acylated with acyl chlorides, and the acylated products **217** were cyclized to pyrido[2,1-*b*]purin-10-ones **218** by treatment with NaOMe (95JHC1725).

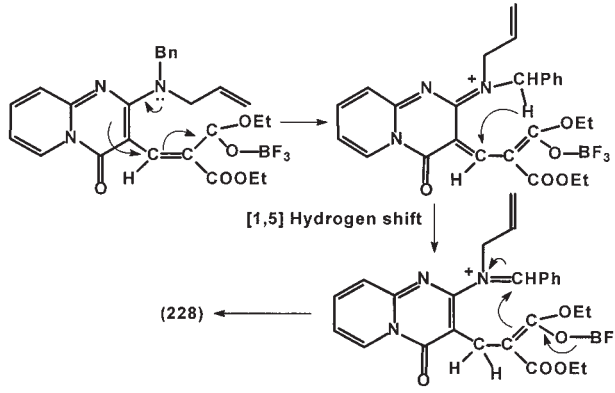


Reaction of 2-(*N*-allylamino)-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **219** in EtOH with $HONH_2 \cdot HCl$ yielded (*E*)-oximes **220** at 0 °C and **221** ($R = PhCH_2$) under reflux. Heating **220** ($R^1 = H$) in a boiling solvent afforded *cis*-fused tetracyclic cycloadducts **221** ($R^1 = H$). In an aprotic solvent (e.g., benzene or MeCN) the main *cis*-fused cycloadducts **221** ($R^1 = H$) were accompanied by a mixture of *trans*-fused cycloadducts **222**, *N*-oxides **223** and tetracyclic isoxazoline **224** (96T887). The basicity of the 2-allylamino moiety of compounds **219** affected the rate of the conversion. Cycloadditions were also investigated in dioxane and BuOH.

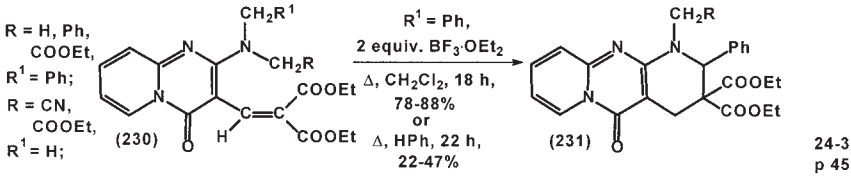


Treatment of the 2-(*N*-allylamino) derivative of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **225** with a Lewis acid afforded a mixture of hetero-Diels–Alder adduct **226**, tetracyclic pyrane **227**, and tricyclic derivatives **228** and **229**. Whereas $TiCl_4$ (in CH_2Cl_2) and $EtAlCl_2$ (in HPh) gave a mixture of **226** and **227**, Et_2AlCl (in HPh) yielded a mixture of tricyclic derivatives **228** and **229**, $BF_3 \cdot OEt_2$ (in CH_2Cl_2) afforded **228** with a trace of **229**. A mixture of **226** or **227** accompanied with **228** and **229** was obtained in the presence of $ZnCl_2$ and $ZnBr_2$, respectively. The formation of compound **228** was explained as depicted on Scheme 12 (98JCS(P1)3327).

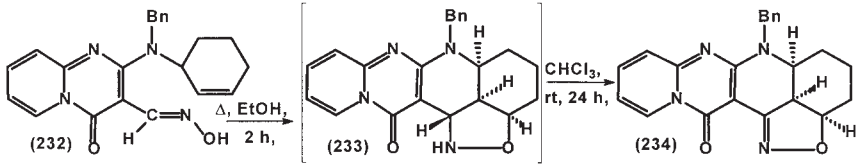
A similar reaction of 2-(*N*-benzylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **230** ($R = R^1 = Ph$) gave tricyclic derivative **231** ($R = Ph$) on the action of $BF_3 \cdot OEt_2$. 2-(*N*-Ethoxycarbonylmethyl-*N*-methyl), and *N*-cyanomethyl-*N*-methyl) derivatives **230** ($R = COOEt$, CN; $R^1 = H$) did not yield any tricyclic product (98JCS(P1)3327).



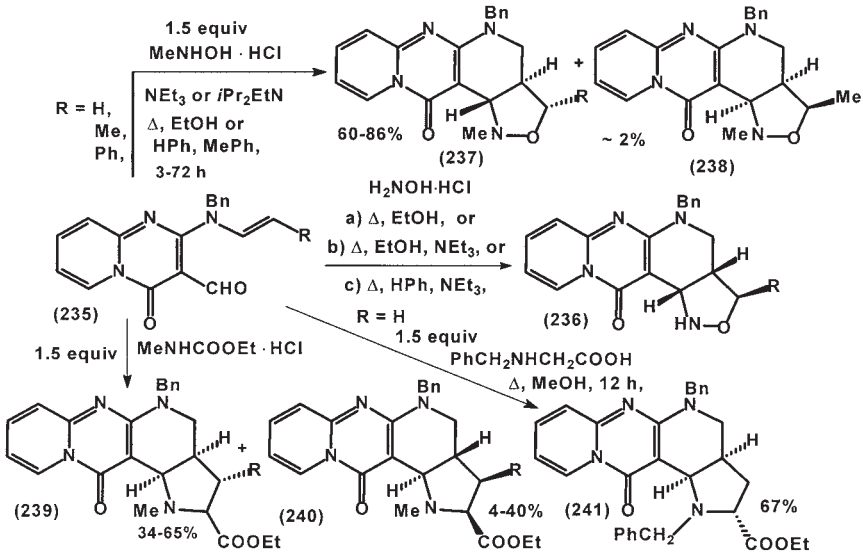
Scheme 12



Heating oxime **232**, prepared from the corresponding 3-formyl derivative, gave an unstable cycloadduct **233** in an *exo*-approaching manner (the *endo* one is unfavorable owing to steric crowding), which converted spontaneously into a dehydrogenated pentacyclic derivative **234** (96T887).

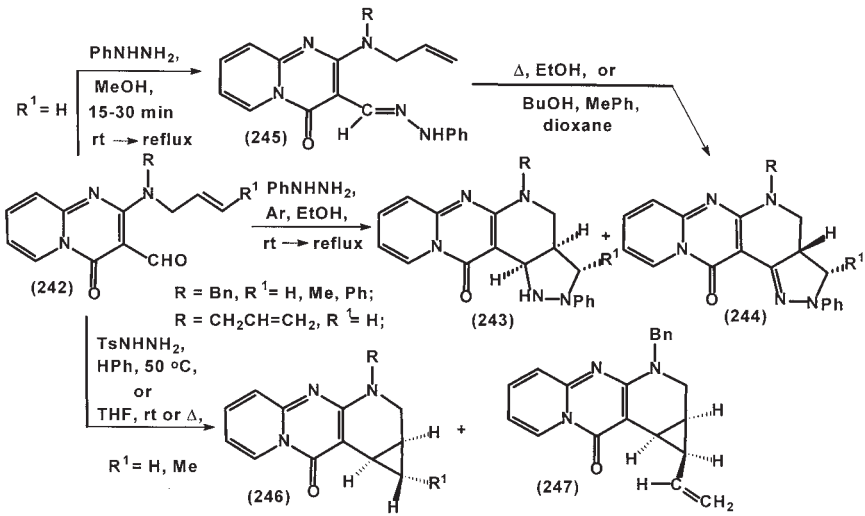


Reaction of 2-[*N*-(2-alkenyl)amino]-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **235** with $HONH_2 \cdot HCl$ under both acidic and basic conditions (in the absence or in the presence of NEt_3) gave tetracyclic derivatives **236** in good yields. Higher yields were achieved in the presence of NEt_3 (96T887).



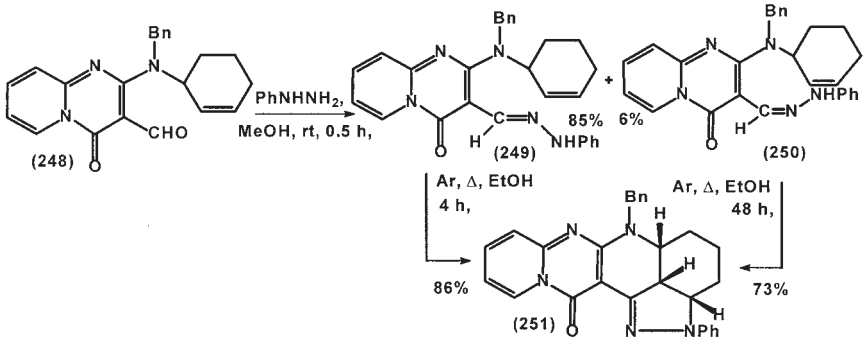
Intramolecular cycloadditions of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **235** (R = H, Me Ph) and MeNHOH · HCl gave tetracyclic isoxazolo derivatives **237**. In the case of **235** (R = Me) a minor epimer **238** was also isolated (00JCR(S)414). Similar reaction of **235** (R = H, Me, Ph) and sarcosine ethyl ester HCl afforded an isomeric mixture of epimeric tetracyclic pyrrolo derivatives **239** and **240**. In the reaction of **235** (R = H) and $PhCH_2NHCH_2COOEt$ only one product **241** was obtained.

The phenylhydrazones of 2-[(2-alkenyl)amino]-3-formyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones **242** underwent a thermally induced intramolecular 1,3-dipolar cycloaddition leading to a mixture of tetracyclic compounds **243** and **244** at room temperature or to **244** under reflux (96T901). Derivatives **243** were not stable and converted to compounds **244** gradually on standing or on heating their ethanolic solutions in air. The (*E*)-hydrazones **245** could be isolated only in the case of 2-(*N*-allyl-*N*-phenyl-, -*N*-benzenesulfonyl-, and -*N*-ethoxycarbonylamino)-3-formyl derivatives **242** (R = Ph, $PhSO_2$, COOEt, R^1 = H). The hydrazones **245** (R = Ph, $PhSO_2$, R^1 = H) could be converted into a mixture of tetracyclic derivatives **243** and **244** or into pure **244** in a boiling solvent. No reaction occurred in the case of ethoxycarbonylamino derivative (**245**, R = COOEt) in EtOH, while decomposition happened in BuOH.

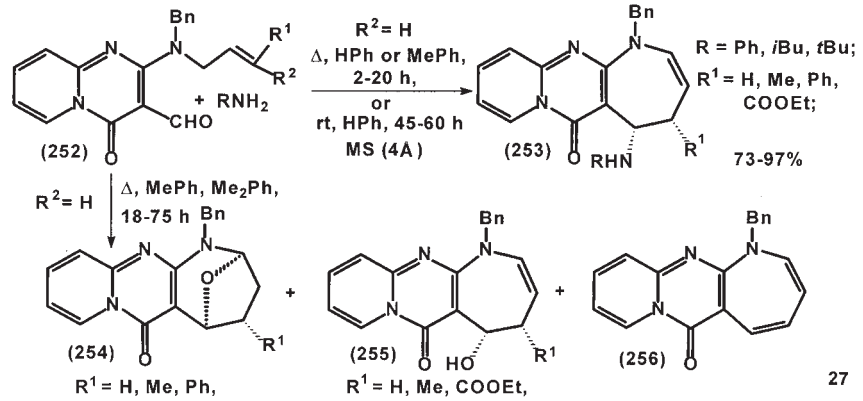


Reaction of 3-formyl-2-[*N*-(2-alkenyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **242** with $TsNHNH_2$ gave tetracyclic cyclopropanes **246** in good

yields (97S53). The yields were lower (46–47%) in EtOH or MeCN at 50 °C. *N*-Allyl- and *N*-(2-butenyl) derivatives **242** ($R^1 = H$, Me) gave intractable mixtures of unidentified products. 2-[*N*-(*E*,*E*)-(hexa-2,4-dienyl)-*N*-benzylamino] derivative **242** (R = Bn, R^1 = *trans*-CH=CH–Me) afforded two cyclopropane derivatives **246** (R = Bn, R^1 = *trans*-CH=CH–Me) and **247** in a 5:1 ratio.

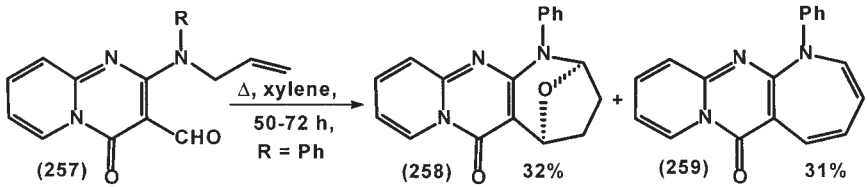


A 14:1 mixture of (*E*)- and (*Z*)-phenylhydrazones **249** and **250** was obtained from 2-[*N*-(cyclohex-2-en-1-yl)]-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **248** with $PhNHNH_2$. Pentacyclic compound **251** was obtained from both (*E*)- and (*Z*)-phenylhydrazones **249** and **250** by heating in boiling EtOH (96T901).



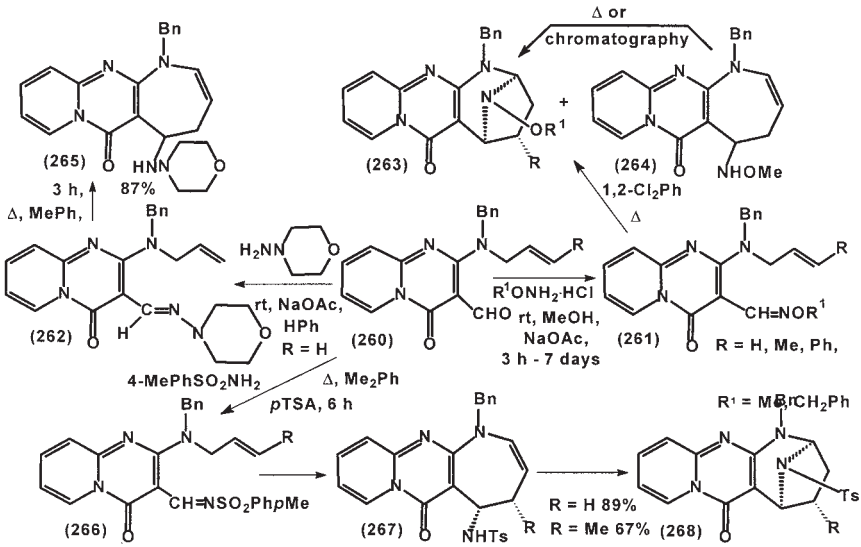
Reaction of 3-formyl-2-[*N*-(2-alkenyl)-*N*-benzylamino]-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones **252** and primary amines in the presence of MS (4 Å) afforded pyrido[1′,2′:1,2]pyrimido[4,5-*b*]azepin-6-ones **253** (96T13081).

No reaction occured when dimethyl derivative **252** ($R^1 = R^2 = Me$) was the starting material. The reaction of **252** ($R^1 = COOEt$, $R^2 = H$) and $PhNH_2$ gave **253** (R = Ph, $R^1 = COOEt$); **254** ($R^1 = COOEt$) was also isolated from the reaction mixture. When pyrido[1,2-*a*]pyrimidin-4-ones **252** ($R^2 = H$) were heated in boiling toluene or xylene a mixture of tricyclic derivatives **254**–**256** was obtained. Heating **252** ($R^1 = R^2 = Me$) in toluene and xylene did not provide any changes.

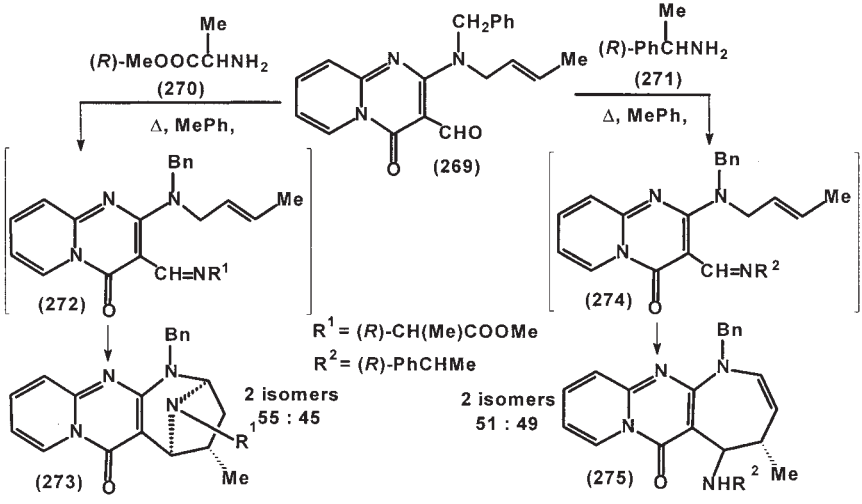


Whereas heating 3-formyl-2-(*N*-allyl-*N*-phenylamino)-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one **257** (R = Ph) in boiling deoxygenated xylene yielded a mixture of **258** and **259**, 2-(*N*-allyl-*N*-ethoxycarbonylamino) and 2-(*N*-allyl-*N*-benzenesulfonylamino) derivatives **257** (R = COOEt, SO_2Ph) gave only **257** (R = H) (96T13081). MO calculations by the PM3 method suggested that the electron-withdrawing substituent on the amino group could be unfavorable to the 1,7-electrocyclic ring-closure process to the azepine ring.

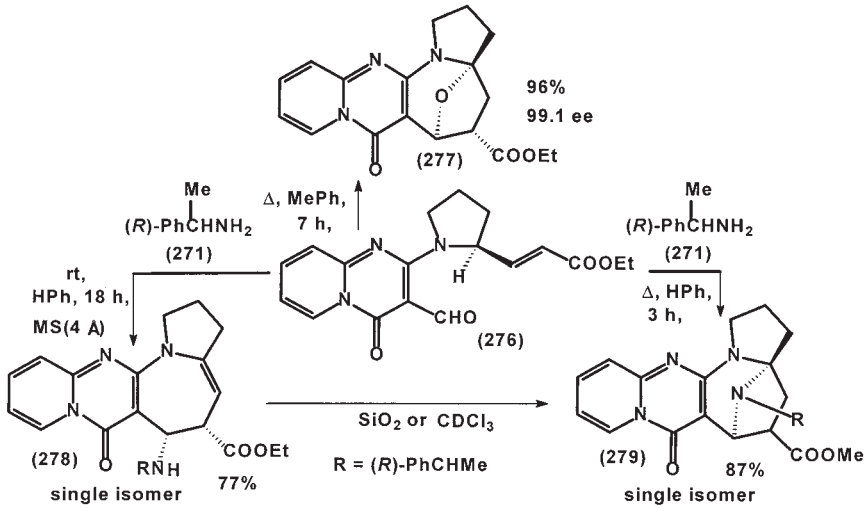
Reactions of 3-formyl-2-[*N*-(2-alkenyl)-*N*-benzylamino]-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones **260** with $MeONH_2 \cdot HCl$ and $BnONH_2 \cdot HCl$ or with 4-aminomorpholine gave oximes **261** (mainly as the *E* isomer) and Schiff bases **262** (as the pure *E*-isomer), respectively (96T13097). Reaction of 3-formyl derivative **260** (R = H) with $MeONH_2 \cdot HCl$ in MeCN and benzene for 20 h yielded a 85 : 15 and 66 : 34 mixture of *E* and *Z* isomers of oximes **261** (R = H, $R^1 = Me$). Heating *E*-isomers of **261** in deoxygenated *o*-dichlorobenzene for 2–24 h gave tetracyclic derivatives **263**. When the *E* isomer of compound **261** (R = H, $R^1 = Me$) was heated only 1 h, a 69 : 31 mixture of **263** (R = H, $R^1 = Me$) and **264** was obtained. On further heating or during chromatography compound **264** converted gradually to compound **263** (R = H, $R^1 = Me$). Progress of these reactions in 2-methoxyethyl ether was monitored by HPLC and revealed that only the *E* isomer of oximes **261** underwent cyclization and the *Z* isomers were unchanged. No interconversion between *E*- and *Z*-isomers of the oximes was observed. Heating hydrazone **262** in toulene afforded tricyclic derivative **265** (96T13097).



Reaction of 2-(*N*-alkyl-*N*-benzylamino)- and 2-[*N*-(*trans*-crotyl)-*N*-benzylamino]-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**260**, R = H, Me) with tosylamine gave compounds **268** via compounds **266** and **267** (96T13097). The results of kinetic studies and MP3 calculations on the 3-formyl derivatives **252**, **260** and the imines **262**, **263** suggested a concerted nature for azepine-ring formation.

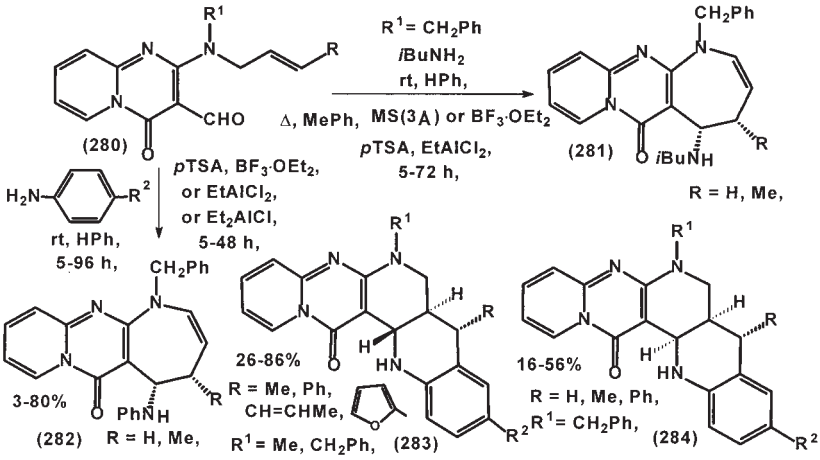


Reaction of 2-[*N*-(*trans*-crotyl)-*N*-benzylamino]-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**269**) with chiral primary amines **270** and **271** gave mixtures of diastereoisomers of tetracyclic compounds **273** and tricyclic **275** (96T13111). The chiral centers in **272** and **274** did not provide any stereocontrol for the formation of diastereomers **273** and **275**, respectively.



Heating optically active 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **276**, prepared from 2-chloro-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and (2′*S*,3*E*)-ethyl 4-(2-pyrrolidinyl)-but-3-enoate in THF in the presence of NEt_3 gave single isomer **277**. Reaction of **276** with (*R*)-1-phenylethylamine (**271**) in the presence of MS (4 Å) gave also a single isomer **278**, which converted to compound **279** on silica gel, or in a solution of $CDCl_3$. Reaction of 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one **276** and **271** in boiling benzene yielded also **279** (96T13111).

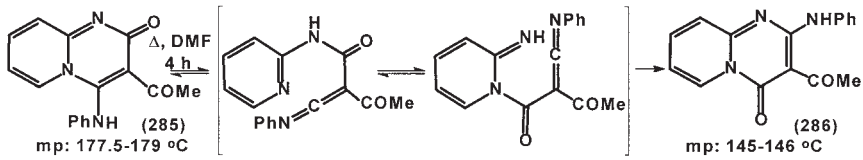
Heating 2-(2-alkenylamino)-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **280** (R = H, Me, Ph) in boiling toluene in the presence of $BF_3 \cdot OEt_2$, *p*TSA, $MgCl_2 \cdot OEt_2$, $EtAlCl_2$, or Et_2AlCl, did not gave any identifiable products, only starting materials **280** could be recovered (97BCJ2201). Reaction of **280** ($R^1 = CH_2Ph$, R = H, Me) with *i*-$BuNH_2$ in the presence of the above additives or MS (3 Å) resulted in the formation of tricyclic derivatives **281** (R = H, Me). It was suggested that additives catalyzed only the formation of a Schiff-base from aldehyde **280** and *i*-$BuNH_2$, and did not influence azepine-ring formation. Reaction of **280** ($R^1 = PhCH_2$, R = Me) with $PhNH_2$ in the presence of MS (3 Å) gave tricyclic product **282** (R = Me). When the reaction was carried out in the presence of a Brönsted



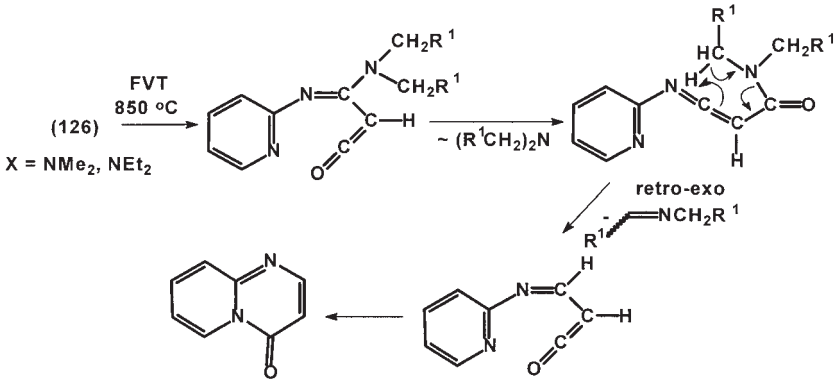
or a Lewis acid ($BF_3 \cdot OEt_2$, *p*TSA, $EtAlCl_2$, Et_2AlCl) either **283** (R = CH=CHMe, 2-furyl; R^1 = Me, CH_2Ph) or a mixture of **283** and **284** were obtained, sometimes together with tricyclic derivatives **282**. While the isolated **284** was stable under the reaction conditions, **283** partially decomposed under similar conditions. The tetraazapentaphene **283** and **284** was formed by an intramolecular [4+2] cycloaddition between the *N*-arylimine and ene moieties.

9. *Ring Transformations*

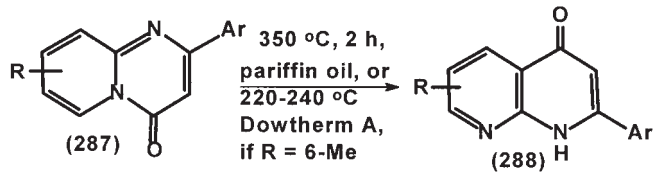
3-Acetyl-4-phenylamino-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**285**) isomerized into 4-oxo isomer **286** by heating in DMF at 100 °C (95MI2).



Flash vacuum thermolysis of 2-dialkylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **126** (X = NMe_2, NEt_2) at 850 °C led to the formation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Scheme 13). The product was identified by ^1H NMR and GC-MS (99JCS(P2)1087).



Scheme 13

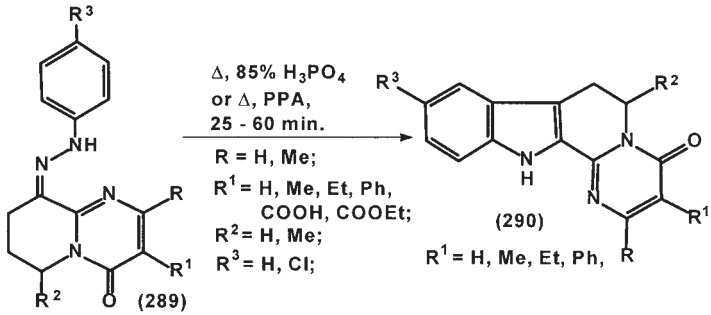


2-(Het)aryl-1,4-dihydro-1,8-naphthyridin-4-ones **288** were obtained by heating 2-(het)aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **287** at 350 °C (97JMC2266, 99JMC4081) and in Dowtherm A at 220–240 °C (00JMC2814). Not only the 6-methyl derivatives **287** (R = 6-Me) but also 6-unsubstituted derivatives could be rearranged into 1,8-naphthyridines (97JMC2266, 97JMC3049, 98MIP3, 99JMC4081). The 6-methyl derivatives of **287** (R = 6-Me) provided 1,8-naphthyridines **288** (R = 6-Me) at lower temperature (~240 °C) in excellent yield (>95%) within 2 h in a concentration 0.5–1% (w/v) (98MIP3, 00JMC2814). In the case of 6-unsubstituted derivatives of **287** tar formation was also observed, and therefore shorter reaction period was applied, and 7-unsubstituted derivatives were isolated by column chromatography in 25–45% yields (99PC1). Earlier it was reported that only 6-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones could be thermally transformed into 1,8-naphthyridine derivatives (75TL1019, 77JCS(P1)789, 79JHC457). In the case of 6-unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones only tar formation was observed. Probably in the case of 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones the C(4)–N(5) bond is the weakest one and therefore tar formation is suppressed.

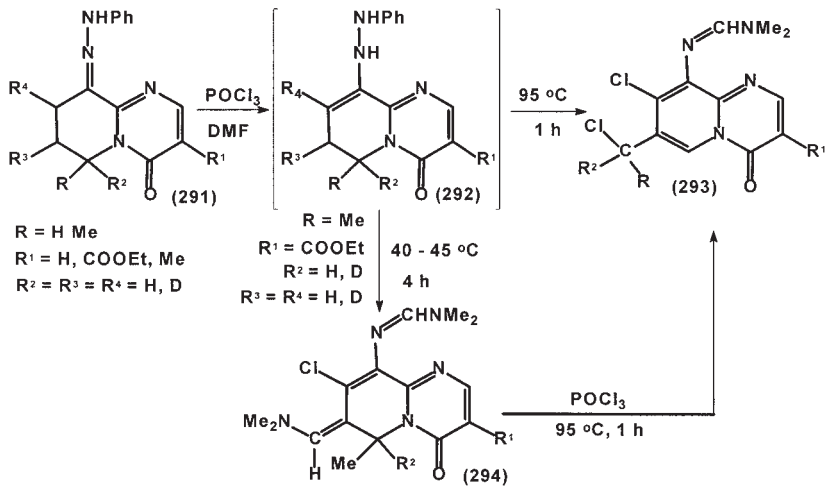
Whereas FVT of 3-methyl derivative of **131** at 700–830 °C (10^{-4} mbar) afforded 1,3-dimethyl-4-hydroxy-1,2-dihydro-1,8-naphthyridin-2-one, FVT

of **132** (R = H, Me, Ph) resulted in the formation of 2-amino-, 2-(methylamino)-, 2-(phenylamino)pyridines and C_3O_2 (00JCS(P2)1841).

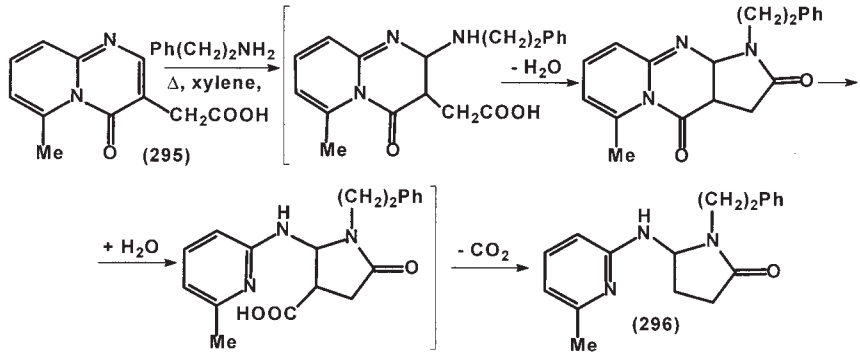
Heating 6-bromo- and 6-chloro-2-halomethyl- (99JHC1065) and 6-bromo-, 6-chloro- and 6-fluoro-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (00JMC2814) in phenyl ether at 220 °C for 10 min yielded the appropriate 7-halo-1,8-naphthyridin-4-ols. 6-Amino-2-trifluoromethyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one was transformed into 7-amino-2-trifluoromethyl-1,4-dihydro-1,8-naphthyridin-4-one in 90% yield (98EJM383).



Fischer indolization of 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones **289** by heating in 85% phosphoric acid, or in PPA yielded 7,12-dihydropyrimido[1′,2′:1,2]pyrido[3,4-*b*]indol-4(6*H*)-ones **290** (96JHC799, 99MI12, 00MI22). From the 3-ester and 3-carboxylic acid derivatives **289** (R^1 = COOEt, COOH) and decarboxylated products **290** (R^1 = H) were obtained.



Heating 9-hydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **291** in a mixture of $POCl_3$ and DMF at 95 °C gave 8-chloro-7-(chloromethyl)-9-[(dimethylaminomethylene)amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **293** via 9-hydrazino-6,7-dihydro-4*H* derivatives **292**. At lower temperature 9-[(dimethylaminomethylene)amino]-7-dimethylaminomethylene-8-chloro-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **294** (R = H, D) were obtained from the 6-methyl-3-ester derivative and its 6,7,8-deuterio derivative **291** (R = Me, R^1 = COOEt, R^2–R^4 = H, D). These derivatives were transformed into **293** (R^2 = H, D) by heating in $POCl_3$. Optically active **291** (R = Me, R^1 = COOEt, R^2–R^4 = H) afforded optically active 6,7-dihydro-4*H* **294** (R^2 = H), but optically inactive 4*H*-pyrido[1,2-*a*]pyrimidine **293** (R = Me, R^1 = COOEt, R^2 = H). Similarly ethyl 9-(*N*-phenyl-*N*-methylamino)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate gave 9-[*N*-(4-formylphenyl)-*N*-methylamino]-7-dimethylaminomethylene-6-methyl-6,7-dihydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates in a mixture of $POCl_3$ and DMF at lower (20–25 °C) and higher (95–100 °C) temperatures, respectively. 9-(Ethoxycarbonylmethyl)-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **158** (but not 9-ethoxycarbonylmethylene-6,7,8,9-tetrahydro derivative **157**) was also transformed into ethyl 9-(ethoxycarbonylmethyl)-7-(1-chloroethyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (99T10221).

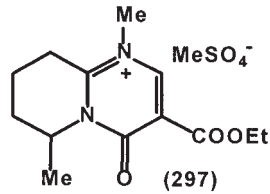


Reaction of 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetic acid (**295**) with phenylethylamine in boiling xylene afforded ring-transformed product **296** (98ACH515).

Heating 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-diazonium tetrafluoroborate and its 8-methyl derivative in alcohol at 60–90 °C for 15 min to 5 h gave alkyl 1-(2-pyridyl)- and 1-(4-methyl-2-pyridyl)-1*H*-1,2,3-triazole-4-carboxylates (00H(53)1793).

10. *Miscellaneous*

Diorganotin(IV) complexes (**109**) were prepared from 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with Me_2SnCl_2 and Ph_2SnCl_2 in dry $CHCl_3$ (96MI4). Different complexes of 2-methyl-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 8-nitro derivative were prepared with Cu(I)Cl, Cu(II)Cl_2, Ni(II)Cl_2, Co(II)Cl_2, Mn(II)Cl_2, and Ag(I)NO_3 in EtOH (00MI23). Complexes of 2,4-dimethyl-9-hydroxypyrido[1,2-*a*]pyrimidinium salt were obtained with Pr(III), Nd(III), Sm(III), and Eu(III) ions in acetone (00MI24).



(297)

9*a*-Ethoxy-9-hydroxy-1,6-dimethyl-1,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylate **123** was isolated from a solution of rimazolium (**297**) in 2 N NaOH solution, standing for 30 min at room temperature (97H(45)2175).

Reaction of perhydropyrido[1,2-*a*]pyrimidine with BrCN in the presence of MgO in a 1:1 mixture of $CHCl_3$ and MeOH at 40 °C resulted in the formation of the ten-membered 6-methoxy-3,4,7,8,9,10-hexahydro-1,5-diazecine-1,5-(2*H*,6*H*)-dicarbonitrile. Similar reaction of perhydropyrido[1,2-*a*]pyrimidin-2-one led to the nine-membered 6-methoxy-4-oxo-2,3,4,5,6,7,8,9-octahydro-1*H*-1,5-diazonine-1-carbonitrile (99AJC1131).

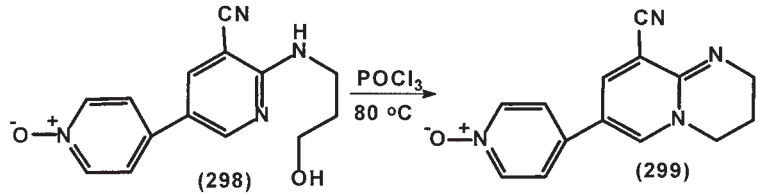
Two polymorphic forms of 3-{2-[4-(6-fluorobenzisoxazol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**137** R = H) were prepared (99MIP1). Racemic 9-hydroxy-2-methyl-3-{2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1,2,3,6-tetrahydro-1-pyridyl]ethyl}-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was resolved into its (*R*)- and (*S*)-isomers (00MIP10).

Free radical polymerization of *anhydro*-(2-hydroxy-3-[(3-vinylphenyl)-methyl]-1-phenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide in DMF at 60 °C for 2 days in the presence of 2,2′-azoizobutyronitrile led to a mesoionic polymer (00MI26).

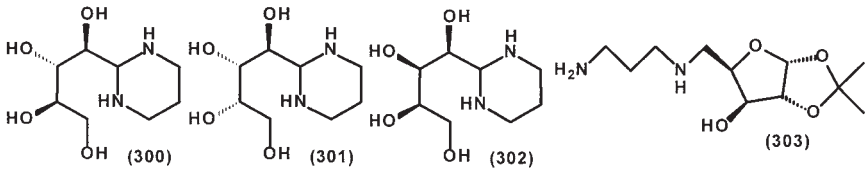
C. Synthesis

1. *By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0 (α)]*

Cyclization of 3-cyano-2-[(3-hydroxypropyl)amino]-5-(4-pyridyl)pyridine-1′-oxide (**298**) in $POCl_3$ yielded 9-cyano-7-(4-pyridyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyrimidine 1′-oxide (**299**) (94EJM175). After heating 3-cyano-4-trifluoromethyl-6-phenyl-2-[(3-hydroxypropyl- and 3-hydroxybutyl)-amino] pyridines in boiling $POCl_3$ for 1 h, the product was treated with aqueous NH_4OH to yield 6-phenyl-8-trifluoromethyl-9-cyano-3,4-dihydro-2*H*-pyrido-[1,2-*a*]pyrimidine and its 4-methyl derivative (01CHE329).

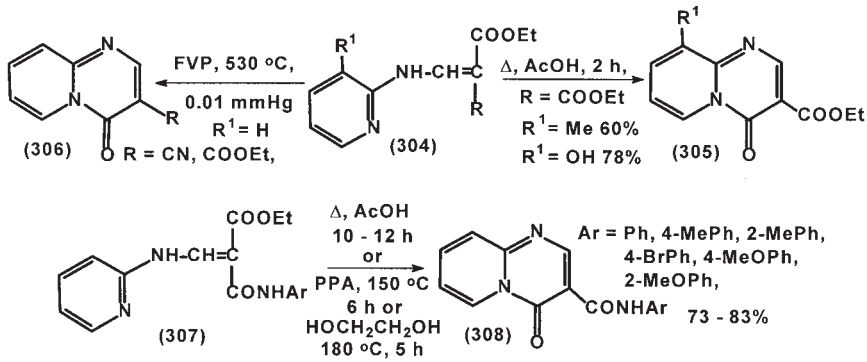


7,8,9-Trihydroxyperhydropyrido[1,2-*a*]pyrimidines **112**, **113**, **115** were obtained by the cyclization of 2-substituted perhydropyrimidines **300**–**302**, obtained in the reactions of 1,3-propanediamine and D-xylose, L-arabinore and D-ribose, respectively, with Ph_3P and CCl_4 in the presence of NEt_3 in DMF at ambient temperature in 22–40% yields (98JOC391, 98T5097). Perhydropyrido[1,2-*a*]pyrimidine **112** was also prepared in crude form, containing dehydrated impurity, by the cyclization of compound **303** with a saturated aqueous solution of SO_2 and with a 1:2 mixture of 1 N HCl in THF (98JOC391).

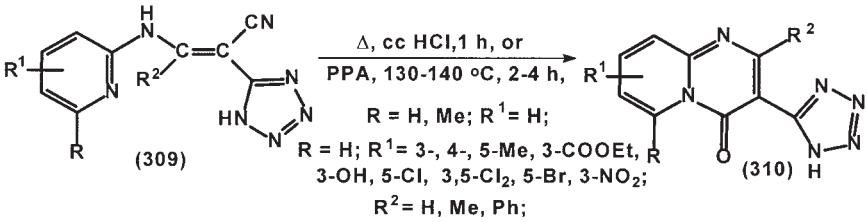


Heating diethyl (2-pyridylamino)methylenemalonates **304** (R = COOEt, R^1 = Me, OH) in AcOH afforded 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **305** (R^1 = Me, OH) (96JHC1041). Flash vacuum thermolysis of 2-substituted 3-(2-pyridylamino)acrylates **304** (R = CN, COOEt, R^1 = H) through a packed silica tube (530 °C, 0.01 mmHg) gave 3-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **306** (R = CN, COOEt) (94AJC1263). Ethyl 7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (79%) was

obtained together with ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (5%), when diethyl [(6-methyl-2-pyridyl)amino]methylenemalonate was pumped at a rate 14 g/min through a stainless steel coil heated in a fluidized sand bath at 380 °C (00MI14). Heating isopropylidene (2-pyridylamino)-methylenemalonates at 200 °C gave 4-oxo-4*H*-pyrido [1,2-*a*]pyrimidin-4-ones (00CHE754).

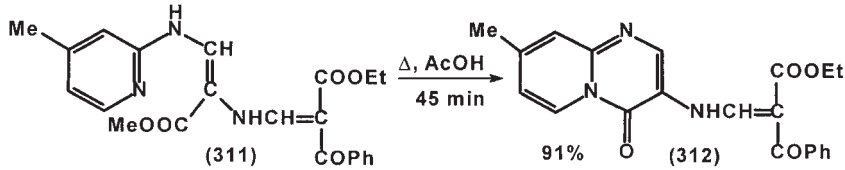


Cyclization of *N*-aryl-2-(ethoxycarbonyl)-3-(2-pyridylamino)acrylamides **307** in AcOH, and in PPA, or in ethylene glycol afforded *N*-aryl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic amide **308** (94KGS629, 95KFZ(5)39).

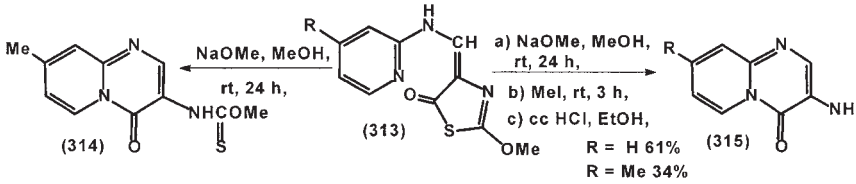


Cyclization of ethyl 3-[(9-methyl-2-pyridyl)amino]-2-cyanoacrylate on treatment with $AlCl_3$ and NaN_3 gave a 2 : 1 mixture of 3-(1*H*-tetrazol-5-yl)-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and ethyl 4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate in 48 and 24% yields, respectively (95CPB683). 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **310** were prepared by the cyclization of 3-(2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylnitrile **309** in boiling conc. HCl, or in PPA at 130–140 °C (93MIP3). The 6-methyl derivative **309** (R = Me, R^1 = H) could be cyclized only by the PPA method. Treatment of ethyl 3-(3-methyl-2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylate with 2 N KOH in boiling *i*-PrOH for 2 h gave pemirolast (**7**) in 95% yield (98H(48)775). Cyclization under acidic conditions, such as aqueous HCl or H_2SO_4 were unsuccessful.

Alkyl 3-(2-pyridylamino)-3-alkoxycarbonylacrylates cyclized into alkyl 4-oxo-4*H*-pyrido[1,2-a]pyrimidine-2-carboxylates either spontaneously or by the action of silica gel (00TL5837).

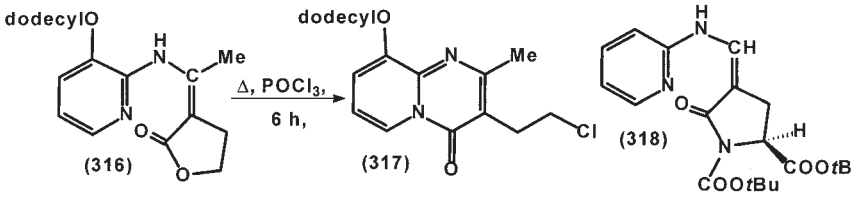


Cyclization of methyl 2-[2-benzoyl-2-ethoxycarbonyl-1-vinyl)amino]-3-[(4-methyl-2-pyridyl)amino]acrylate (**311**) afforded the 3-amino-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **312** (97JHC1511).



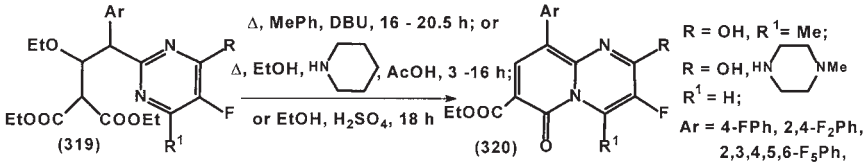
Cyclization of 4-[(2-pyridylamino)methylene]-2-methoxythiazolin-5(4*H*)-one **313** (R = Me) in the presence of NaOMe gave 3-(methoxythiocarbonylamino)-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one **314**. When the reaction mixtures were subsequently treated with MeI, and the evaporated reaction mixtures with conc. HCl in EtOH, 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **315** were obtained (94JHC125).

9-Dodecyloxy-3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **317** was obtained by cyclization of 3-{1-[(3-dodecyloxy-2-pyridyl)amino]ethylidene}-4,5-dihydro-2(3*H*)-furanone (**316**) in boiling $POCl_3$ (95MIP4).

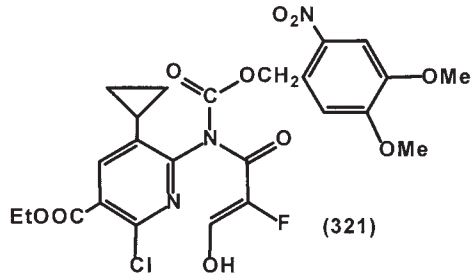


Heating 1,5-di(*tert*-butoxycarbonyl)-3-[(2-pyridylamino)methylene]pyrrolidin-2-one (**318**) in boiling EtOH in the presence of K_2CO_3 gave 2-(*tert*-butoxycarbonylamino)-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)propionate (**190**) in 55% yield (95TL7503, 97JCS(P1)1297).

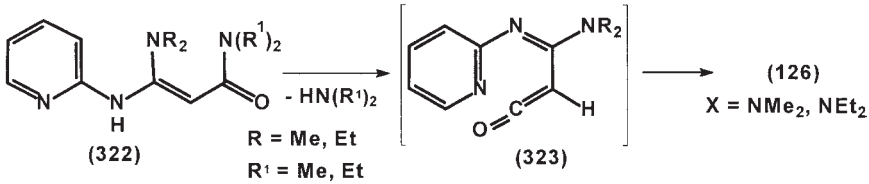
Cyclization of ethyl *N*-(2-pyridyl)-2-methyl)- and *N*-(5-chloro-2-pyridyl)-malonamates in a mixture of $POCl_3$ and PPA at 130 °C gave 2-chloro-3-methyl- and 2,7-dichloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in 26 and 61% yields, respectively (00BMC751).



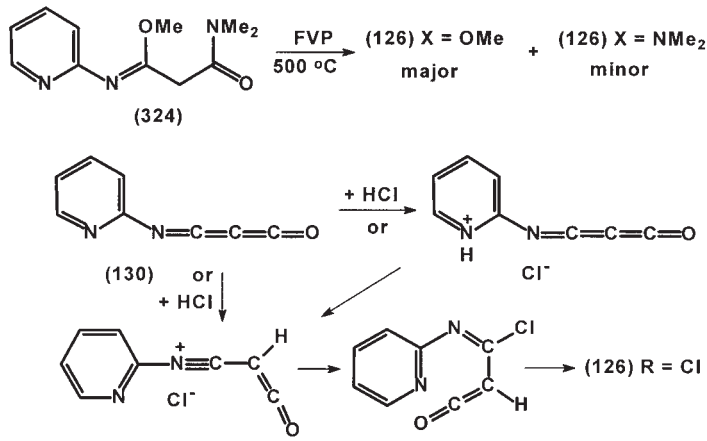
Cyclization of 3-aryl-2-ethoxy-3-(5-fluoro-2-pyrimidinyl)propane-1,1-dicarboxylates **319** either in boiling toluene in the presence of DBU under a Dean-Stark condenser, or in boiling EtOH in the presence of catalytic amount of piperidine and AcOH, or in the presence of conc. H_2SO_4 gave 9-aryl-3-fluoro-6-oxo-6*H*-pyrido[1,2-*a*]-pyrimidine-7-carboxylates **320** (95MIP1, 96JMC3070, 96MIP4, 96USP5580872).



It was claimed that cyclization of ethyl 2-chloro-5-cyclopropyl-6-{[(*N*-(4,5-dimethoxy-2-nitrophenyl)methoxy)carbonyl]-*N*-(2-fluoro-3-hydroxy-1-oxo-2-propen-1-yl)amino}nicotinate (**321**) in boiling aqueous dioxane in the presence of K_2CO_3 overnight yielded 1-{[(4,5-dimethoxy-2-nitrophenyl)methoxy]carbonyl}-9-cyclopropyl-3-fluoro-2-oxo-2,6-dihydropyrido[1,2-*a*]pyrimidine-7-carboxylate (**160**) (95MIP1, 96MIP4, 96USP5580872).



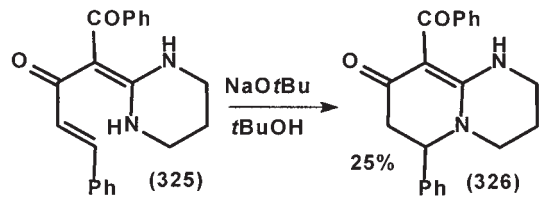
Heating amidoamidine derivatives **322** [obtained from 2-pyridylimino-propadienone **130** with dialkylamine] gave imidoylketenes **323**, which



Scheme 14

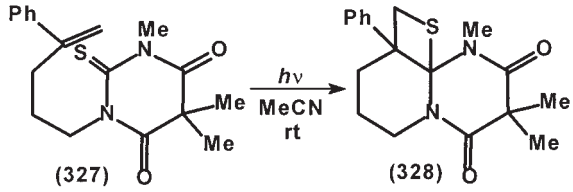
subsequently cyclized to 2-dialkylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **126** (X = NMe_2, NEt_2). The formation of pyrido[1,2-*a*]pyrimidin-4-ones started at 40 °C (99JCS(P2)1087). Flash vacuum thermolysis of 2-aminopyridine derivative **324** at 500 °C gave a mixture of 2-methoxy- and 2-dimethylamino-4*H*-pyrido[1,2-*a*]pyrimidinones (**126**, X = MeO, NMe_2). 2-Pyridyliminopropadienone (**130**), obtained by FVT of **126** (X = Cl), reacted very efficiently with HCl on warm-up to yield the starting 2-chloro derivative **126** (X = Cl) (Scheme 14).

Treatment of perhydropyrimidide **325** with NaO*t*-Bu gave 1,2,3,4,6,7-hexahydro-8*H*-pyrido[1,2-a]pyrimidin-8-one **326** (00MI25).

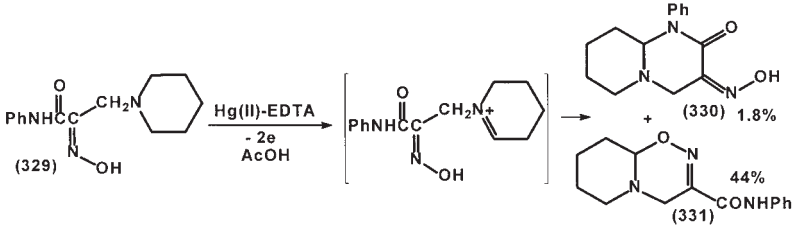


2. *By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0 (β)]*

Photocyclization of *N*-(4-phenyl-4-pentenyl)monothiobarbiturate (**327**) afforded a mixture of 1,2,3-trimethyl-9-phenyl-1,2,3,6,7,8-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione and tricyclic nitrogen bridgehead compound **328** (96H(42)117).

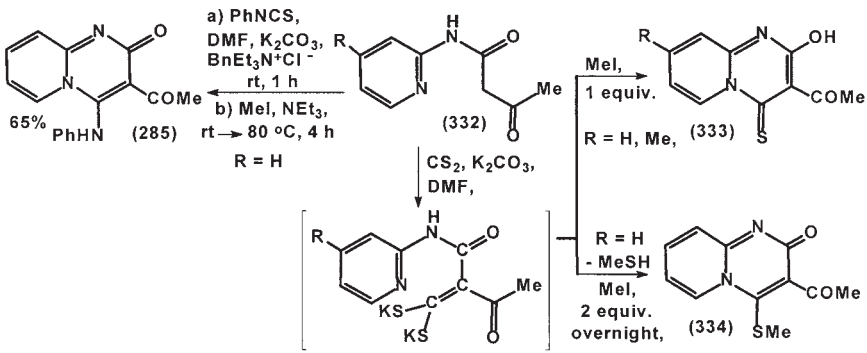


Dehydrogenation of piperidine derivative **329** with Hg(II)–EDTA reagent afforded a mixture of perhydropyrido[1,2-*a*]pyrimidin-2-one **330** and pyrido[1,2-*c*][1,2,5]oxadiazine **331** (99ZN(B)632).



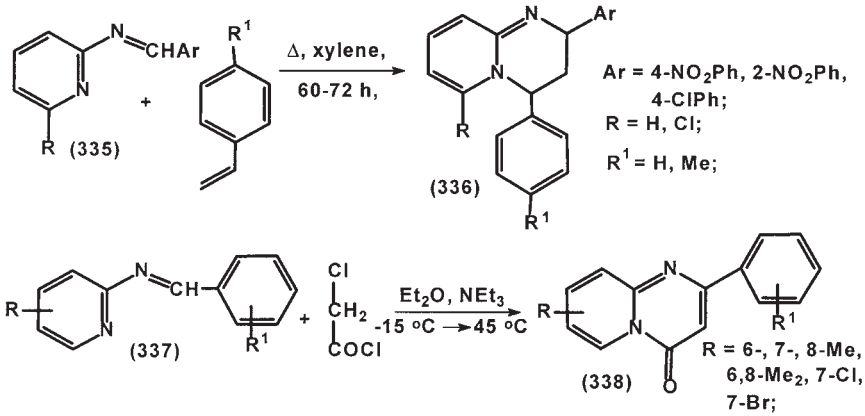
3. *By Formation of Two Bonds from [5+1] Atom Fragments*

3-Acetyl-4-phenylamino-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**285**) was obtained when *N*-(2-pyridyl)acetoacetamide **332** (R = H) was first treated with PhNCS in the presence of K_2CO_3 and $BnEt_3NCl$, then with MeI and NEt_3, and then the reaction mixture was heated rapidly to 80 °C (95MI2). Reaction of *N*-(2-pyridyl)acetoacetamides **332** with CS_2 in the presence of K_2CO_3 and a catalytic amount of $BnEt_3NCl$, then with 1 or 2 equiv of MeI afforded 3-acetyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidine-4-thiones **333** and 3-acetyl-4-methylthio-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**334**), respectively (96MI22).

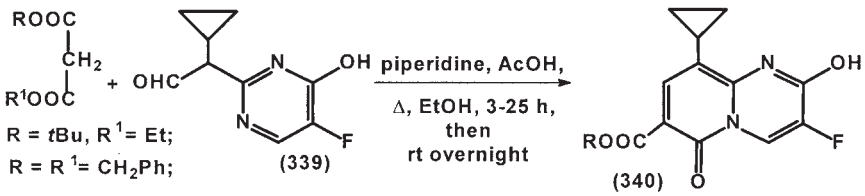


4. *By Formation of Two Bonds from [4+2] Atom Fragments*

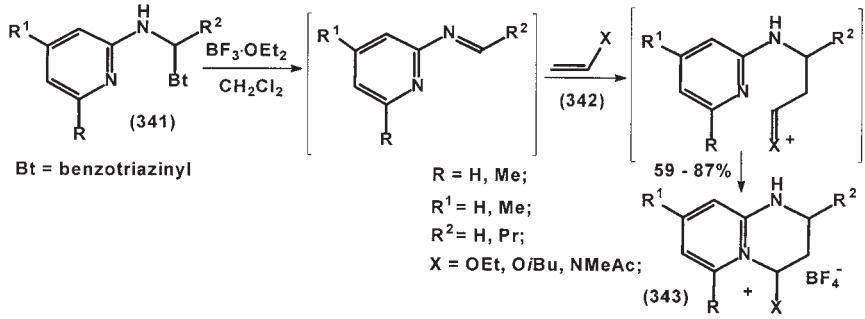
Reaction of 2-(arylmethyleneamino)pyridines **335** and styrenes in the presence of hydroquinone afforded 2,4-diaryl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **336** by means of an inverse electron demand Diels–Alder reaction (95MI10). Reaction of 2-(benzylideneamino)pyridines **337** and chloroacetyl chloride gave 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **338** (97JMC2266).



9-Cyclopropyl-3-fluoro-2-hydroxy-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylates **340** were obtained in the reaction of 2-cyclopropyl-2-(5-fluoro-4-hydroxy-2-pyrimidinyl)acetaldehyde (**339**) and ethyl, *tert*-butyl and dibenzyl malonates in the presence of piperidine and AcOH (95MIP1, 96JMC3070, 96MIP4, 96USP5580872).



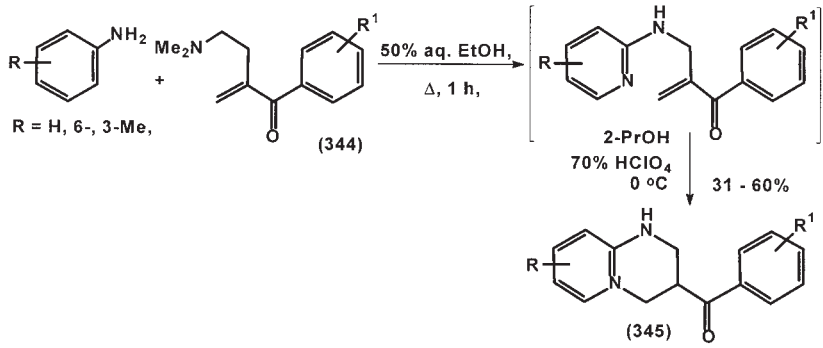
Reaction of 2-[(benzotriazol-1-yl)alkylamino]pyridines **341** with open-chain electron-rich alkenes **342** in the presence of $BF_3 \cdot Et_2O$ gave 4-substituted 1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidinium tetrafluoroborates **343** (98S704).



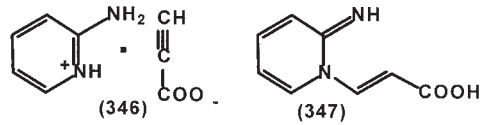
3,9-Dicyano-2,4,8-triphenyl-7-phenylsulfonyl-6*H*-pyrido[1,2-*a*]pyrimidine-6-thione was obtained in the reaction of 6-amino-1-benzoyl-5-cyano-4-phenyl-3-phenylsulfonylpyridin-2(1*H*)-one and benzylidenemalononitrile in the presence of piperidine in boiling dioxane for 4 h in 59% yields (98M1049).

5. *By Formation of Two Bonds from [3+3] Atom Fragments*

Cyclocondenzation of 2-amino-3-hydroxypyridinium perchlorate with benzoylacetone in boiling EtOH afforded 2-methyl-4-phenylpyrido[1,2-*a*]pyrimidinium perchlorate in 23% yield (94KFZ(10)23).

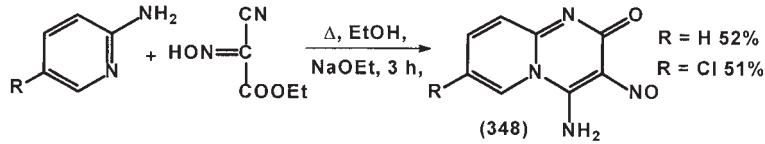


Treatment of a residue, obtained after the evaporation of the reaction mixtures of 2-aminopyridines and enone Mannich bases **344** with 70% $HClO_4$ gave 3-aroyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidinium perchlorates **345** (98SL263). Reactions in AcOH afforded a complex reaction mixture with lower overall yields.



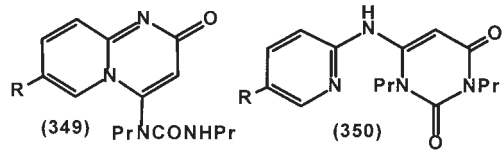
Heating the crystalline salt 2-aminopyridinium propiolate (**346**) at 100 °C in the solid state led to a 10:9 mixture of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one and (*E*)-3-(2-imino-1,2-dihydro-1-pyridyl)acrylic acid (**347**). Analysis of differental scanning calorimetry data shows unambiguously that the reaction takes place in the solid state. An endothermic peak at 81.1 °C corresponds to a solid state reaction, and a peak at 122–123 °C is attributed to melting. The product ratio of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one and **347** is 1:2.5 at 60 °C, and 1:1.4 at 80 °C (94MI12).

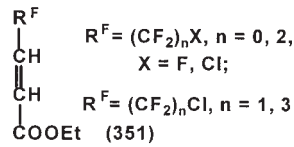
Reaction of 2-cyano-3-(4-methoxyphenyl)acroyl chloride and 2-aminopyridine in boiling benzene in the presence of NEt_3 for 5 h gave a 2:1 mixture of 3-cyano-4-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and 2-{[2-cyano-3-(4-methoxyphenyl)acroyl]amino}pyridine (01SUL151).



Cyclocondensation of 2-aminopyridines and ethyl cyano(hydroxyimino)acetate in the presence of NaOEt gave 4-amino-3-nitroso-4*H*-pyrido[1,2-*a*]pyrimidin-2-ones **348** (95JHC1725).

Reaction of 2-aminopyridine and 6-chloro-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione in THF in the presence of NaH at room temperature overnight gave a mixture of 4-[*N*-(propylaminocarbonyl)-*N*-propylamino]-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**349**) and 6-(2-pyridylamine)-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione (**350**, R = H) (94JHC81). Only the non-cyclized product **350** (R = Cl) was obtained from 5-chloro-2-aminopyridine.

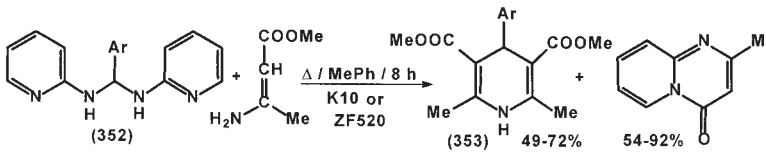




Reaction of 2 equiv of 2-aminopyridines with 2-hydropolyfluoroalk-2-anoates **351** in MeCN in the presence of NEt_3 at 90 °C for 50 h afforded a mixture of the isomeric 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **110** and **111**. Reaction of 3 equiv of 2-amino-pyridines and 2-hydropolyfluoroalk-2-enoates **351** in MeCN in the presence K_2CO_3 could be accelerated by ultrasonic irradiation (125 W). 2-Amino-6-methylpyridine yielded only 2-substituted 6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **111** (R = 6-Me), whereas 2-amino-5-bromopyridine gave a mixture of 7-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**111**, R = 7-Br, $R^F = CF_2Cl$) and 2-(chloro,difluoromethyl)-6-bromoimidazo[1,2-*a*]pyrimidine-3-carboxylate in 44 and 8% yields, respectively (97JCS(P1)981). Reactions in the presence of K_2CO_3 in MeCN at 90 °C for 60 h afforded only imidazo[1,2-*a*]pyrimidine-3-carboxylates.

Cyclocondensation of 2-iminopiperidine and 3-aryl-2-propynylnitriles in THF or 5% MeCN/THF afforded 4-aryl-2-imino-6,7,8,9-tetrahydro-2*H*- and 2-aryl-4-imino-6,7,8,9-terahydro-4*H*-pyrido[1,2-*a*]pyrimidines in 70–98% and 2–30% yields, respectively (00OL3389). When the reactions were carried out in the presence of 2 equiv of NaHMDS the product ratio was reversed.

From the reaction mixture of 2-aminopyridine and perfluoro-2-methylpent-2-ene in MeCN a 9:1 mixture of 2,4-difluoro-2-pentafluoroethyl-3-trifluoromethyl-4*H*- and isomeric 2,4-difluoro-4-pentafluoroethyl-3-trifluoromethyl-2*H*-pyrido[1,2-a]pyrimidine (64%), and 2-pentafluoroethyl-3-trifluoromethyl-4*H*-pyrido[1,2-a]pyrimidine-4-one (20%) was isolated (00JFC105).

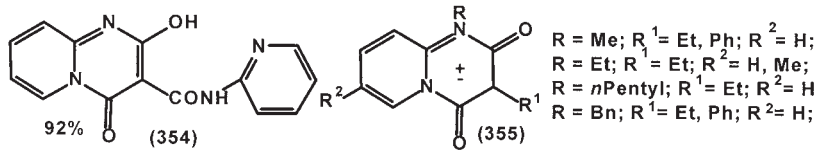


Reaction of 1 mole of aminals **352** with 4 mol of methyl 3-aminocrotonate in the presence of the solid acids montmorillonte clay (K_{10}) and ZF520 zeolite as strong Brönsted acidic catalysts, gave 1,4-dihydropyridines **353** and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (99MI8).

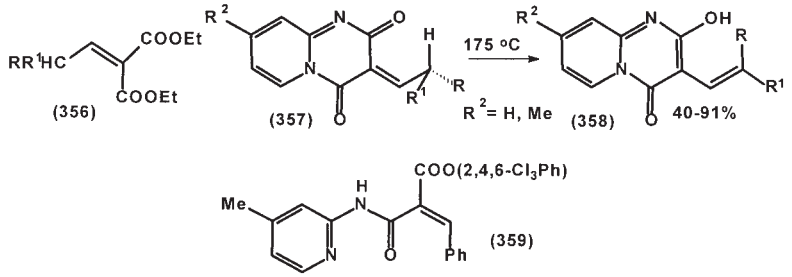
Reaction of 2-aminopyridine with dimethyl 2-methylmalonate in the presence of some drops of conc. HCl at 150 °C for 1 h (96EUP733633), and with diethyl 2-(1-decyl)malonate at 120 °C for 5 min (94JCR(S)206) gave 2-hydroxy-3-methyl- and 2-hydroxy-3-(1-decyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in 2.2% and 7.5% yields, respectively. Reaction of 3-benzyl-2-aminopyridine and diethylmalonate at 190–200 °C for 4 h yielded 9-benzyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (01MIP9). Cyclocondensation

of 2-amino-5-bromopyridine and diethyl arylmalonates at 180 °C overnight under nitrogen yielded 3-phenyl- and 3-(3-thienyl)-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (97BRP2307177). Cyclocondensation of 2-amino-pyridines with diethyl 2-{[4-(2-cyanophenyl)phenyl]methyl}malonate at 180 °C gave 2-hydroxy-3-{4-[(2-cyanophenyl)phenyl]methyl}-4*H*-pyrido[1,2-*a*]pyrimidines (94BMCL183) Reaction of 3-(2-substituted ethoxy)-2-aminopyridines and bis(2,4,6-trichlorophenyl)malonate in boiling acetone afforded 2-hydroxy-9-(2-substituted ethoxy)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (01MIP8).

Anhydro-(2-hydroxy-7-chloro-3-propyl- and -3-allyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidinium)hydroxydes were prepared in the reaction of 5-chloro-2-aminopyridine and the appropriate diethylmalonates near at 175 °C for 3.5 h, or in boiling diethylbenzene for 1 h (93MIP4). Heating a 1 : 2 molar ratio of 2-aminopyridine and trialkyl methanetricarboxylates in boiling bromobenzene for 10 h afforded alkyl 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates (99JHC237). When 2 : 1 molar ratio of 2-aminopyridine and trialkyl methanetricarboxylate was heated at 200 °C in a melt for 20 min *N*-(2-pyridyl)-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**354**) was obtained.



Cyclocondensation of 2-(alkylamino)- and 2-(benzylamino)pyridines with bis(2,4,6-trichlorophenyl) 2-ethyl- (99BCJ503, 00BMC1917), and 2-phenylmalonates (99BCJ503) at 160–190 °C in a melt for 5–10 min, and with diethyl 2-substituted malonates (99BCJ503) in boiling tetralin for 2–6 h afforded mesoionic *anhydro*-(2-hydroxy-1,3-disubstituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidiniun)hydroxides **355** in 24–90% yields. Reaction of 4-[2-(4-isopropyl-1,3-thiazol-2-yl)-1-ethenyl]-2-aminopyridine and bis(2,4,6-trichlorophenyl)malonate in boiling xylene for 12 h gave 8-substituted 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (01MIP1). Cyclocondensation of 2-anilinopyridine with 2-benzyl- and 2-[(3-vinylphenyl)methyl]malonic acids in the presence of 2 mol equiv of dicyclohexylcarbodiimide and a catalytic amount of hydroquinone monopropyl ether in CH_2Cl_2 at 0 °C, then 25 °C for 3 h gave *anhydro*-(2-hydroxy-3-benzyl- and -3-[(3-vinylphenyl)methyl]-1-phenyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidinium)hydroxydes in 87 and 67% yields, respectively (00MI26).



Reaction of 2-aminopyridine and its 4-methyl derivative and diethyl alkylidenemalonates **356** at 175 °C for 1.5–2.5 h yielded 3-vinyl derivatives **358**, after the isomerization of the exocyclic double bond in **357** (99ACS901). Reaction of 2-amino-4-methylpyridine and bis(2,4,6-trichlorophenyl) benzylidenemalonate in the presence of NEt_3 afforded only noncyclised product **359**. 2-Aminopyridine and its 4-methyl derivative with diethyl benzylidene- and hexylidenemalonates at 190 °C did not give cyclized products (99ACS901, 99MI29).

Cyclocondensation of 2-aminopyridines with ethyl acetoacetate at 100 °C (93IJC(B)978, 95KFZ(2)40), with ethyl (het)aroylacetates at 125 °C (97JMC2266, 97JMC3049, 98MIP3, 99JMC4081), with ethyl 4-methoxyacetoacetate at 80–85 °C (93MI2) in PPA yielded 2-methyl-, 2-hetaryl- and 2-methoxymethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, respectively. From the reaction mixture of 6-substituted 2-aminopyridines (6-Me, 6-F, 6-Cl, 6-Br) and ethyl benzoylacetate and its *o*-, and *p*-fluoro derivatives, 2-aryl-6-substituted 4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones (14–15%, Knorr product) and 1-(6-substituted-2-pyridyl)-3-aroyl-4-aryl-4-hydroxy-1,2-dihydropyridin-4-ones (3–12%, Conrad-Limpach product) could be isolated (99JHC1123).

Cyclocondensation of 2-amino-6-bromopyridine and 4-chloroacetoacetate in PPA at 100 °C for 4 h afforded a mixture of 2-chloromethyl-, 2-bromomethyl-6-bromo-, and 2-chloromethyl-, 2-bromomethyl-6-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in 84% yield (99JHC1065). The pyrido-[1,2-a]pyrimidin-4-ones were separated by preparative reversed phase HPLC. The pure 2-bromomethyl-6-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from 2-amino-6-bromopyridine with ethyl 4-bromoacetoacetate in 63% yield. Reaction of 2-aminomethylpyridines and ethyl 4-chloroacetoacetate in PPA at 110 °C gave 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (95FES69, 01H(55)535).

9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared in the reaction of 2-amino-3-benzyloxypyridine and ethyl acetoacetate at 60 °C, then at 100 °C for 3 h in 22% yield (96MIP1). Reaction of 2-amino-3-hydroxypyridine and ethyl 2-methylacetoacetate in a 1:2 mixture of

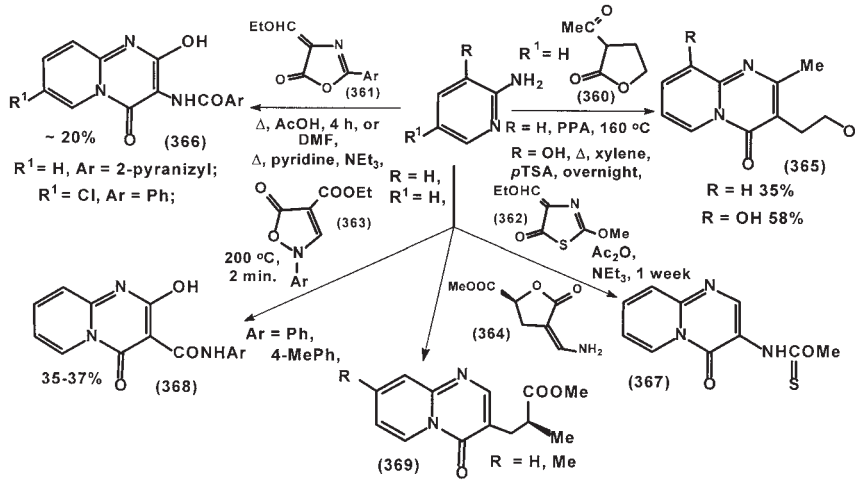
PPA and AcOH at 100 °C for 4 h gave 9-hydroxy-2,3-dimethyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one in 24% yield (96EUP733633). Reaction of 2-aminopyridine and ethyl 2-acetoxyacetoacetate in boiling EtOH gave 2-methyl-3-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 47% yield (94KFZ(10)23).

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were also prepared in the reaction of 2-aminopyridines and ethyl 3-methoxy-2-butenoate in PPA at 80–85 °C for 3 h (93MI2).

Reaction of 2-amino-3,4,5,6-tetrahydropyridine and ethyl 2-methyl-, 2-propargyl-benzoylacetates in EtOH at room temperature for 3 weeks gave 2-phenyl-3-methyl- and -3-propargyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones (94EUP579425). Reaction of 2-iminopiperidine and methyl 4,4,4-trifluoro-2-methylacetoacetate in boiling CH_2Cl_2 for 3 days gave 2-trifluoromethyl-3-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (01T2689).

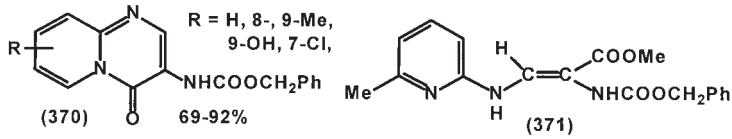
Reaction of 2-aminopyridine and its 3-, 4-, 5-, and 6-methyl derivatives with 3-chloro-3-trifluoromethyl-3-ethoxycarbonyl- and -2-cyanoacrylnitrils in $CHCl_3$, sometimes in the presence of NEt_3, afforded 4-oxo- and 4-imino derivatives of 2-trifluoromethyl-3-cyano-4*H*-pyrido[1,2-*a*]pyrimidines, respectively (00MI27).

Cyclocondensation of 4-substituted 2-aminopyridines and ethyl 3-dimethylamino-2-[2-(4-methoxybenzyl)tetrazol-5-yl)acrylate in boiling EtCOOH for 4 h afforded 8-substituted [2-(4-methoxybenzyl-2*H*-tetrazol-5-yl)]-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (01MIP1).

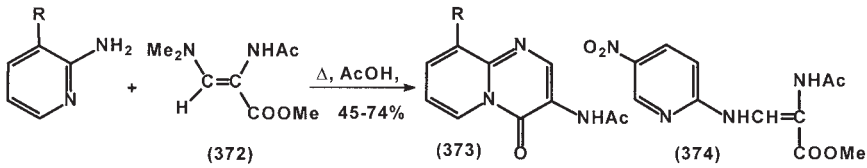


Cyclocondensation of 2-aminopyridines with 2-acetylbutyrolactone (**360**) in PPA (94MIP8) or in xylene in the presence of *p*TSA (95MIP4, 96MIP2)

with 4-ethoxymethylene-2-(het)aryl-5(4*H*)-oxazolone (**361**) in AcOH, in boiling DMF or in boiling pyridine in the presence of NEt_3 (93H(35)955, 99H(50)315); with 4-ethoxymethylene-2-methoxy-4,5-dihydro-5-thiazolone (**362**) in Ac_2O in the presence of NEt_3 at room (94JHC125); with ethyl 2-aryl-5-oxo-2,5-dihydroisoxazole-4-carboxylates (**363**) (93JHC33), and with (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**364**) in boiling AcOH in the presence of NaOAc (00JHC703) afforded 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **365**–**369**, respectively. When **364** was reacted with 2-aminopyridines in boiling AcOH only condensation products were obtained (00JHC703).

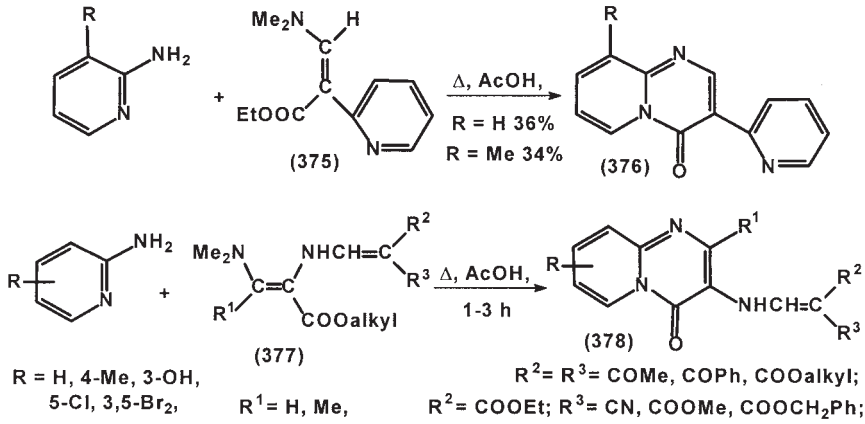


Cyclocondensation of 2-aminopyridines with methyl 3-(*N*,*N*-dimethylamino)-2-(benzyloxycarbonylamino)acrylate in boiling AcOH for several hours gave 3-(benzyloxycarbonylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **370** (99CCC177, 00MI33). 2-Amino-6-methylpyridine afforded only condensation product **371**.



Reaction of 2-aminopyridines and methyl 3-(*N*,*N*-dimethylamino)-2-acetylaminoacrylate (**372**) in boiling AcOH yielded 3-acetylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **373** (97JHC247). From 2-amino-5-nitropyridine only a condensation product **374** was obtained. Similarly 3-(pyrazinylcarbonylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained in the reaction of 2-aminopyridine and methyl 3-(*N*,*N*-dimethylamino)-2-(pyrazinylcarbonylamino)acrylate in boiling DMSO for 4 h in 17% yield (99H(50)315). Reaction of 2-amino-pyridines and 3-(*N*,*N*-dimethylamino)-2-(2-pyridyl)acrylate **375** yielded 3-(2-pyridyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **376** (93JHC1253). Cyclocondensation of 2-aminopyridines and 3-(*N*,*N*-dimethylamino)-2-(substituted amino)acrylates **377** yielded 3-(substituted amino)-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones **378** (95JHC921, 97H(45)2349,97HCA2418,97JHC813,97JHC1511,98ACH613,98H(47)1017, 98H(49)133, 98JHC1275). In the case of 2-amino-5-nitropyridine only the

substitution of the *N*,*N*-dimethylamino group occurred to give a condensation product (95JHC921).



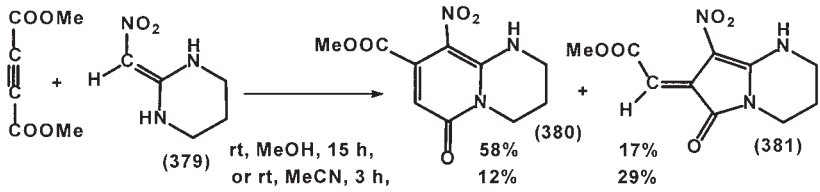
Reaction of 2-aminopyridine with ethyl 2-cyano-3-ethoxy-3-methyl-, -3-ethyl-, -3-phenylacrylates and ethyl 2-ethoxycarbonyl-3-ethoxy-3-methyl-, -3-phenylacrylates in boiling xylene yielded 2-substituted 4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles and -3-carboxylates (99MI7). Similar reactions of 2-aminopyridine with 2-cyano-3-ethoxyacrylonitrile and its 3-methyl, 3-ethyl, -3-phenyl derivatives in boiling MeCN afforded 4-imino-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carbonitrile and its 2-substituted derivatives.

Cyclocondenzation of 4-(*E*)-2-(4-isopropyl-1,3-thiazol-2-yl)-1-ethenyl)-2-aminopyridine and ethyl ethoxymethylenemalonate in boiling toluene for 2 h gave ethyl 8-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate (01MIP1). Reaction of 2-amino-4-methylpyridine and diethyl *N*,*N*-dimethylaminomethylenemalonate in boiling AcOH for 90 min gave ethyl 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate in 35% yield (96JHC1041). Cyclocondensation of 2-amino-3-methylpyridine and ethoxymethylenemalononitrile gave 9-methyl-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (**199**) in 91% yield (95CPB683). It was stated that cyclocondensation of 2-amino-3,5-dicyano-4-phenyl-6-phenylthiopyridine and ethyl ethoxymethylenecyanoacetate in boiling AcOH for 5 h gave ethyl 7,9-dicyano-4-imino-8-phenyl-6-phenylthio-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate in 70% yield (94MI5).

Cyclocondensation of 2-aminopyridine and its 3-, 4-, and 5-methyl derivatives with ethyl 2-(bismethylthiomethylene)cyanoacetate in boiling BuOH for 5 h afforded 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles in 55–87% yields (96FES781).

Cyclocondensation of 2-iminopiperidine hydrochloride with an *E–Z* isomeric mixture of ethyl 2-cyano-3-methylsulfanyl-3-(1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)acrylate in DMF in the presence of DBU at 100 °C gave 2-substituted 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (01EUP1074549).

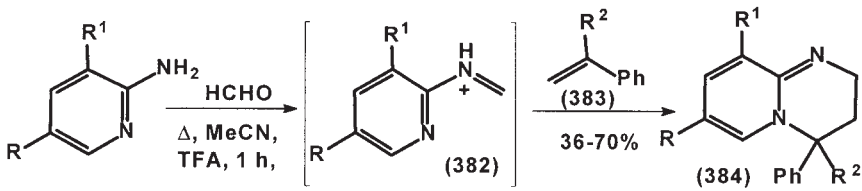
Cyclocondensation 2-{[2-cyano-2-(2-pyridyl)ethenyl]amino}-3-(dimethylamino)acrylates and 2-aminopyridines in boiling AcOH for 1–1.5 h afforded 3-{[2-cyano-2-(2-pyridyl)ethenyl]amino}-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in low yields (01H(55)705, 01JHC869).



Cyclocondensation of 2-(nitromethylene)perhydropyrimidine (**379**) and dimethyl acetylenedicarboxylate yielded a mixture of 9-nitro-1,2,3,4-tetrahydro-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidin-8-carboxylate **380** and a pyrrolo[1,2-*a*]pyrimidine-7-ylideneacetate **381** (93BCJ2118). Their ratio depends on the reaction circumstances.

6. *By Formation of Three Bonds from [3+2+1] Atom Fragments*

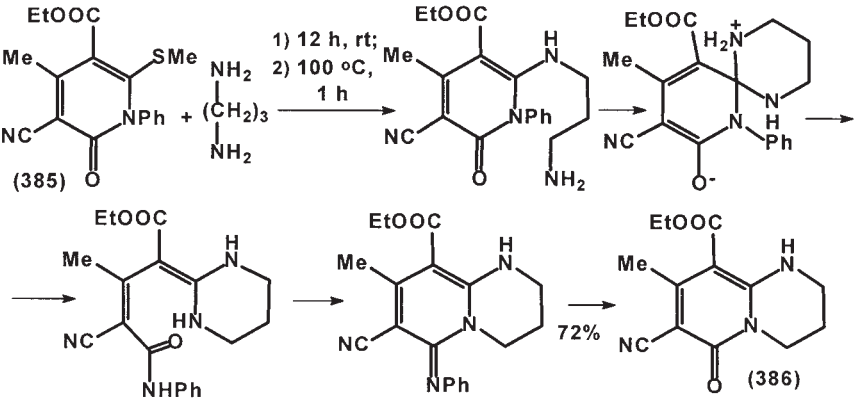
Reaction of 2-aminopyridines with formaldehyde and electron rich styrenes **383** permitted the synthesis of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **384** (96TL2615). First imines **382** formed; they are involved in a formal aza-Diels–Alder reaction to give compounds **384**.



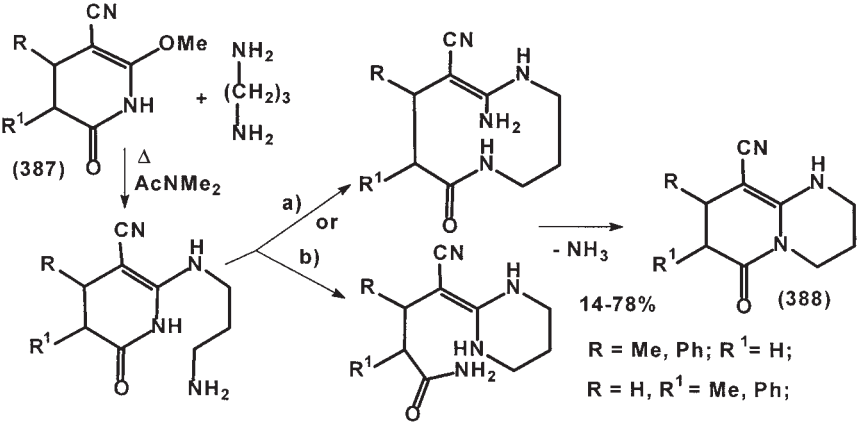
Pemirolast (**7**) was prepared in 68% yield in a one pot reaction of 2-amino-3-methyl-pyridine, malononitrile and $HC(OEt)_3$ and NaN_3 in AcOH at 90 °C for 2 h, then the reaction mixture was treated with conc. HCl at 90 °C for another 2 h (98H(48)775).

7. *Rearrangement*

Reaction of 1,3-propanediamine and 3-cyano-4-methyl-6-methylthio-1-phenyl-2-oxo-1,2-dihydropyridine-5-carboxylate **385** yielded 7-cyano-8-methyl-6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-a]pyrimidine-9-carboxylate (**386**) (94JHC393).

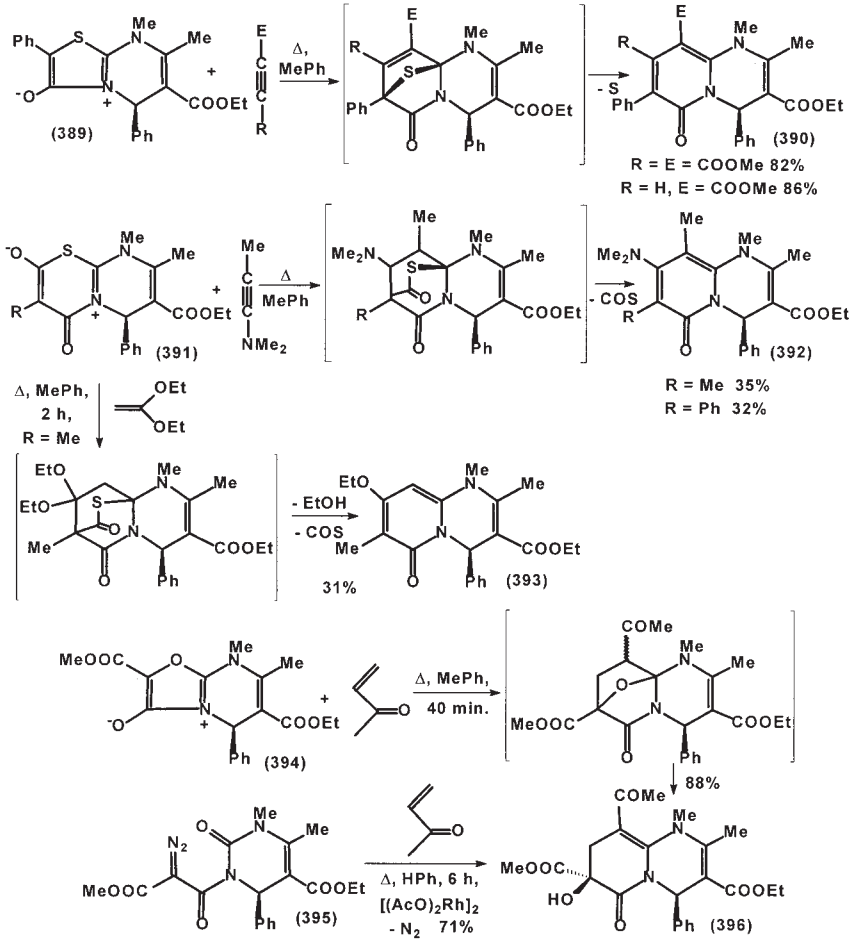


Reaction of 5-cyano-6-methoxy-1,2,3,4-tetrahydropyridin-2-ones **387** with 1,3-propanediamine in boiling *N*,*N*-dimethylacetamide gave 9-cyano-1,2,3,4,7,8-hexahydro-6*H*-pyrido-[1,2-*a*]pyrimidin-6-ones **388** either via route *a* or via route *b* (95H(41)2173).



Dipolar cycloadditions of dihydropyrimidine-fused mesomeric betaines **389**, **391** and **394** with different dipolarophiles afforded 6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **390**, **392**, **393** and **396** (97JOC3109).

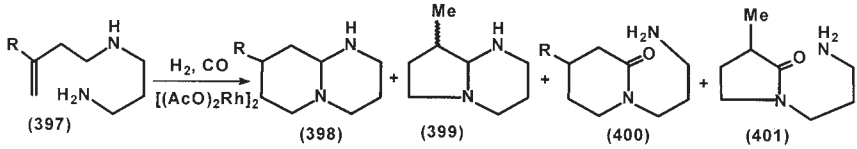
Pyrido[1,2-*a*]pyrimidine-3,7-dicarboxylate **396** was also obtained in the reaction of diazo compound **395** and methyl vinyl ketone in boiling benzene in the presence of a catalytic amount of ruthenium acetate.



8. *Miscellaneous*

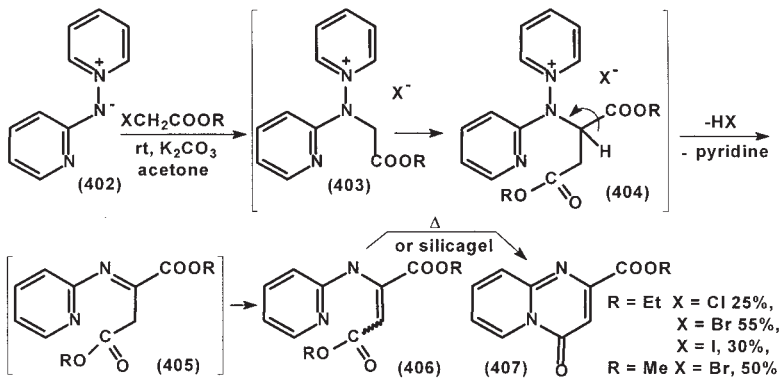
Rhodium catalyzed reaction of *N*-butenyl-1,3-propanediamines **397** with a mixture of H_2 and CO gave usually a mixture of hydroformylated **398** and **399** and carbonylated products **400** and **401** in the presence of a phosphite [PPh_3, PBu_3, $P(C_6H_{11})_3$, $P(o\text{-tol})_3$] (97TL4315, 97T17449). When the hindered biphosphite, BIPEPHOS, and a 9:1 or 1:1 mixture of H_2 and

CO were used only perhydropyrido[1,2-*a*]pyrimidine (**398**, R = H) formed from compound **397** (R = H).

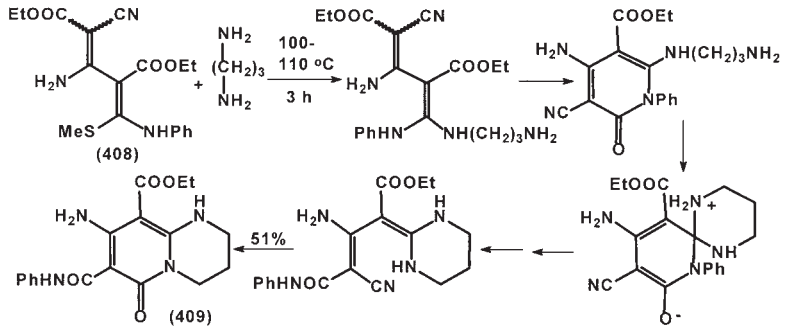


Reaction of pyridinium-*N*-(2-pyridyl)amidine (**402**) and alkyl haloacetates in the presence of K_2CO_3 afforded a mixture of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates **407** and 2-aminopyridine derivatives **406** through intermediers **403**–**405**, as depicted in Scheme 15 (00TL5837). Compound **406** could be cyclized on the action of heat or silica gel into **407**. The best yield was achieved in the case of ethyl bromoacetate.

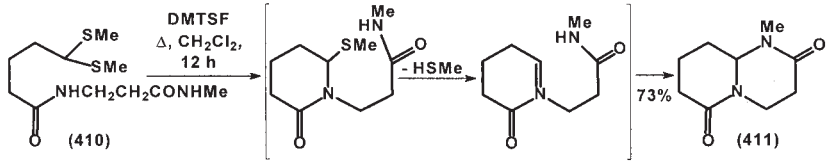
Reaction of 1,3-propanediamine and a mixture of α and β isomers of 5-bromo-5-deoxy-D-xylofuranose in H_2O for 10 min gave 7*R*-(7α,8β,9α9aα)-7,8,9-trihydroxyperhydropyrido[1,2-*a*]pyrimidine (**112**, R = H) in 27% yield (99T6759). Reaction of 5-bromo-5-deoxy-D-xylofuranose and *N*-methyl-1,3-propanediamine in H_2O at room temperature afforded a 5:1 mixture of 1-methyl **117** and 5-methyl **118** derivatives of 7,8,9-trihydroxyperhydropyrido[1,2-*a*]pyrimidine **112** (R = H). When this reaction was carried out in the presence of 3 moles of NEt_3 the product ratio of **117** to **118** was 1:2. The influence of NEt_3 on the product ratio may be a consequence of it scavenging HBr and freeing the more basic and more nucleophilic methylamino group for participation in the displacement reaction.



Scheme 15

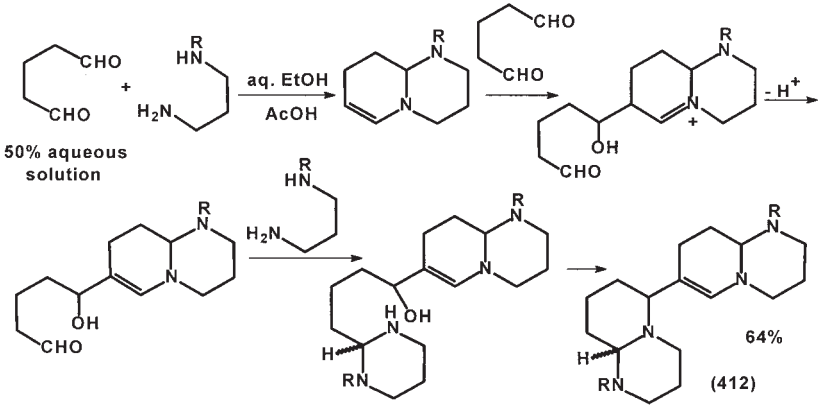


Reaction of 3-amino-2-cyano-4-[(phenylamino)(methylthio)methylene]-2-pentenedioate (**408**) with a large excess of 1,3-propanediamine afforded ethyl 6-imino-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**409**) as depicted in Scheme 16 (95JHC477).



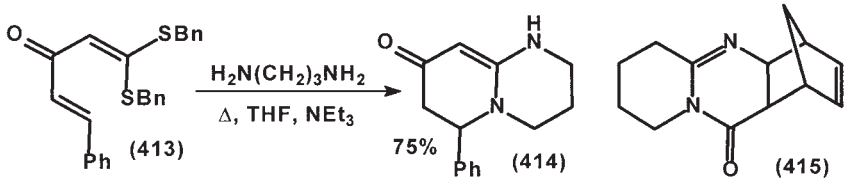
Scheme 16

Heating thioacetal **410** in the presence of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) yielded 1-methylperhydropyrido[1,2-*a*]pyrimidine-2,6-dione (**411**) (00JOC235).



A diastereomeric mixture of 1-alkyl-7-(1-alkylperhydropyrido[1,2-*a*]-pyrimidin-6-yl)-1,2,3,4,8,9-hexahydro-9*a*-pyrido[1,2-*a*]pyrimidines **412** was obtained in the reaction of glutaraldehyde and *N*-alkyl-1,3-propanediamines in the presence of a drop of AcOH at 0 °C, then at ambient temperature for 13 h (96H(43)2487).

Reaction of di(benzylthio)acetal **413** and 1,3-diaminopropane in the presence of a catalytic amount of NEt_3 afforded 1,2,3,4,6,7-hexahydro-8*H*-pyrido[1,2-*a*]pyrimidin-8-one **414** (00MI25).



Retro Diels–Alder reaction of nitrogen bridgehead compound **415** at 100 °C afforded 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and cyclobutadiene (97SC195).

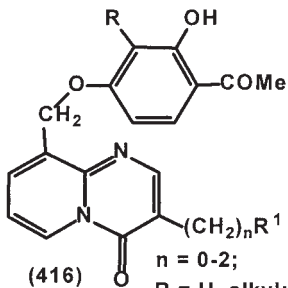
D. Applications and Important Compounds

Neurotropic and antistress properties of 2,4-dimethylpyrido[1,2-*a*]pyrimidinium perchlorate were compared with those of piracetam (95MI7). 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one binds selectively to rat A_3 receptors with a K_i value of 48 μM. No affinities were observed to rat A_1 and A_2 receptors (96MI17). 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid and -3-carbonitrile did not exhibit significant antibacterial activities (97MI6).

2-(4-Methyl-1-piperazinyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one exhibited *in vitro* platelet aggregation inhibitory activities on human platelet aggregations induced by ADP, collagen and A23187 (93FES1225). 2-Piperazino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one inhibited dose-dependently aggregation both in platelet rich plasma and in washed platelets, exerting its maximal power in the presence of collagen, ADP and platelet activating factor (97MI21). The structure and antiplatelet activity relationship of a series of 2-(substituted amino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their congeners and isosteric analogs was analyzed by comparative molecular field analysis (COMFA) (00BMC751). Inhibitory activities of mesoionic **355** were investigated on ADP-induced human platelet aggregation (00BMC1917). The gastroprotective activities of a series of *N*-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides were

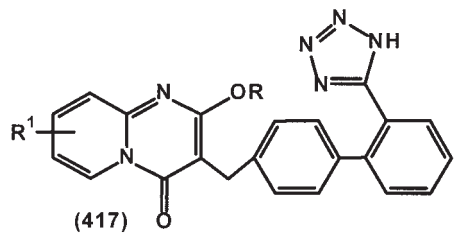
studied. The most active derivative was 6-methyl-*N*-cyclopentyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (92MI1). The mechanism of action of the cytoprotective effect of *trans*-6,9*a*-H-1,6-dimethyl-4-oxo-1,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (CHINOIN-127) was investigated (92MI2). Analgetic activity of 2-(substituted amino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles was reported (95MI9). Cytotoxic activity of diorganotin(IV) complexes of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **109** was tested (96MI4).

The antiallergic activity of pemirolast (**7**) were investigated on different *in vitro* and *in vivo* models (93MI3, 94MI2, 94MI7, 94MI9, 95MI1, 95MI12, 95MI15, 95MI16, 96MI18, 96MI21, 97MI17, 98MI12). Pemirolast did not inhibit neuronal dopamine up-take into the rat striatal synaptosomes (98MI6). Interaction of **7** and theophilline was investigated under steady-state conditions in healthy male volunteers (94MI4). The preventive effects of **7** on restenosis after percutaneous transluminal coronary angioplasty were investigated on humans (98MI15). Treatment of inflammatory bowel and liver diseases with **7** was patented (95JAP(K)95/69895, 95JAP(K)95/101863). A meta-analysis of clinical trials of antihistamines, among them **7**, was performed to access the risk–benefit ratio of this therapeutic class in asthma (97MI23). Compositions, containing **7** among others, were patented for the treatment of the common cold (97JAP(K)97/52849) and as a compound of ophthalmic compositions (01JAP(K)01/187728). Pemirolast was patented as an arteriosclerosis depressant (95MIP6). Stabilized aqueous solutions of **7** were patented (96JAP(K)96/92093, 96USP5527802). Antiallergic activity of AS-35 (**8**) was investigated on different models (94AF754, 94MI11, 94MI13, 00MI19). AS-35 (**8**) was claimed for the treatment of inflammatory intestinal diseases (94MIP2). Orally administrable compositions of antiallergic 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **416** were patented (93MIP5).



(416)

n = 0-2;
R = H, alkyl;
R^1 = COOH, 5-tetrazolyl;

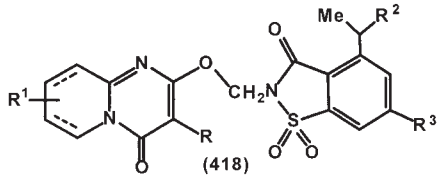


(417)

R = alkyl;
R^1 = H, 7-, 8-, 9-Me,
7-CHOH, 7-COOEt;

2-Alkoxy-3-{4-[2-(5-tetrazolyl)phenyl]phenylmethyl}-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **417** exhibited potential angiotensin II receptor antagonistic activities (94BMCL183).

2-[4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]oxymethylsaccharin derivatives **418** exhibited human leukocyta elastase inhibitory activities (94EUP626378, 95USP5378720). 2-Substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**419**) is a potent human leukocyta elastase inhibitors (K_i 1.79 μM) (96USP5512576). The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one moiety was included in leukotriene antagonist 2-ethynylthiazole derivatives (98JAP(K) 98/195063)



Biochemical and pharmacological properties of pirenperone (**9**) (94AF269, 95MI4, 95MI6, 95MI8, 96MI8, 97MI10, 97MI16, 97MI20, 99MI5, 99MI21), ocaperidone (**13**) (94AF269, 95MI14, 96MI8, 96MI23, 97MI5, 98BJP1655, 00MI2, 00MI18), and seganserin (**15**) (95MI5, 96MI8, 98MI5) were investigated. Pirenperone partially blocked (±)-3,4-methylenedioxymethamphetamine discrimination (00MI31). Applications of **9** and risperidone (**11**) for the treatment of circadian rhythms were patented (98MIP4). Among other serotonin antagonists, **9** and **11** were patented for use in a dermatological composition for treating sensitive skin (98MIP7). Metrenperone (**10**), a selective $5HT_2$ receptor antagonist, was investigated as a possible drug to alleviate respiratory distress associated with experimentally induced Pasteurella haemolytica pneumonia in feedlot calves (96MI20). The effect of **10** on systematic and pulmonary hemodynamics was determined in conscious 7 to 15-day-old calves after they were intratracheally inoculated with Pasteurella haemolytica (96MI16). Three dosage regimens of **10** were compared to inhibit the 5-HT-induced pulmonary dysfunction in cattle (93MI1). Among other 5-HT_2 and D_2 receptor antagonists, **11** and **13** were patented for treating mental disease associated with cerebrovascular disorders (96CP2167004). The binding of **11** and **13** to D_3 receptors in the rat brain was studied (96MI19). Covalent conjugates of **11** and **13** with a fatty acid were patented for the treatment of schizophrenia (99MIP5).

Risperidone (**11**) is a new type of an atypical antipsychotic with relatively pronounced effects on negative symptoms and low extrapyramidal side

effects. Its preclinical (00MI42), animal (96MI9), and clinical pharmacology, metabolism (00MI30), pharmacokinetics (96MI9), pharmacodynamics, pharmacoeconomics (00MI12, 00MI32, 00MI34, 01MI5), pharmacogenetics (00MI15), toxicology (96MI9), clinical development and clinical applications (00MI42), extrapyramidal side effects, safety use and usage in the treatment of schizophrenia, dementia (00MI21) and in geriatric patients and its side effects were extensively reviewed (94MI1, 95MI11, 95MI13, 96MI1–96MI3, 96MI5, 96MI7, 96MI8, 96MI10–96MI15, 97MI1, 97MI2, 97MI8, 97MI9, 98MI1, 98MI3, 99MI9, 99MI16–99MI19, 99MI24, 00MI3–00MI10, 00MI17). Possible induction of mania and hypomania of olanzepine and **11** was discussed (00MI36). Cardiac safety parameters of **11** were compared with those of olanzepine (01MI6). The advantages and disadvantages of the medications of different atypical antipsychotics, including **11**, for schizophrenia (01MI15), pharmacology and toxicology of atypical antipsychotics, including **11** (01MI12), were reviewed. In the treatment of refractory schizophrenia **11** was less effective than clozapine (00MI43). Bodyweight gain after treatment with **11** (01MI7), the possible role of **11** in the treatment of autism (01MI8), its optimal dosing (01MI9), and priapism side effect of **11** (01MI10) were reviewed. A summary of the uses of **11** in the emergency treatment of psychosis (00MI44), in the treatment of bipolar disorders (00MI45), and in the treatment of psychosis and agitation in elderly patients (00MI46) has been presented.

Different pharmaceutical formulations of **11** were developed and patented (94MIP3, 95MIP2, 95MIP3, 95USP5453425, 96MIP3, 97MIP5, 97MIP6, 97USP5616587, 98EUP830864, 98MIP6, 98USP5792477, 99MI1, 99MI4, 00MIP9).

Risperidone (**11**) was also included among a α1-adrenergic receptor antagonists to study a quantitative structure–activity relationship (99BMC2437). A pharmacophore model for atypical antipsychoties, including **11**, was established (00MI41). An increased plasma level of **11** and 9-hydroxyrisperidone (**12**) was observed in combination with paroxetine (01MI13). The effect of vanlafaxine on the pharmacokinetics of **11** was reported (99MI13).

Preparations of aqueous suspensions of submicron **12** fatty acid esters were patented (99MIP4). Risperidone was used and patented in combination therapies (99MIP8, 99MIP9, 00MIP5, 00MIP6, 01MIP7). Risperidone was applied in an ophthalmic formulation (01JAP(K)01/97865). Preparation of microparticles of **11** and **12** was patented (01MIP2, 01MIP3, 01USP6264987). Absorption, metabolism and excretion of **11** in rats, dogs (94MI6) and humans (93MI4) were studied. The long-term stability of **11** and **12** in plasma was studied (99MI20). The regional brain distribution of **11** and its 9-hydroxy main metabolite **12** was investigated

in the rat (94MI3, 98MI9). The *in vivo* pharmacological profile (94MI8) and *in vitro* and *in vivo* receptor binding (96MI5) of **12** were studied. The role of cytochromes P450 2D6 in the metabolism of **11** and **12** was investigated (99MI3, 99MI14, 99MI15, 99MI22, 99MI23). Pharmacokinetic interaction of **11** with CYP450 isoenzymes was investigated (01MI14). Risperidone drug interactions were evaluated (01MI3). Different antipsychotic drugs, including **11** and **12**, were investigated to bind to nine different receptors of postmorten human brain (00LS29).

The treatment of psychoses with enantiomers of 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-9-sulfonic acid and **12** was patented (99MIP6, 99MIP7). Pamoate acid salt of **11** was prepared and patented (94MIP7).

3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one was used in the synthesis of antiallergic tricyclic triazolobenzazepine derivatives (99MIP3). 8-[2-(4-*i*-Propyl-2-thienyl)ethenyl]- and 8-[(4-*i*-propryl-2-thienyl)methoxy]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids were patented for the treatment of preventing and/or treating microbial infectious diseases (01MIP1).

Potential antidepressant activity of lusaperidone (**14**) and its derivatives were investigated on α1, α2A, α2B and α2C receptor binding tests (00BMCL71). Hydrophilic controlled release formulations of **14** were developed and patented (00MIP8).

3,4,6,7,8,9-Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was used as deblockable latent catalysts for Michael addition-based polyurethane coatings (97MI4), and its usage in the preparation of a fuel barrier laminate was patented (01MIP6). Its salt with trimellitic anhydride as a curing catalyst for epoxy resin compounds with good storage stability for scaling semiconductor devices (98JAP(K)98/53588), and its pyromellitic acid as a hardening accelerator in the manufacture of epoxy materials for hybrid powdered coatings (95EUP663385) were patented.

1-(Dichloroacetyl)-3,3,9*a*-trimethylperhydropyrido[1,2-*a*]pyrimidin-6-one was applied in herbicidal compositions as a sefaner (99EUP901752).

Among other bicyclic amidine catalysts, 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was also applied in the preparation of β-alkoxy nitriles from α,β-unsaturated nitriles and alcohols (99GEP 19803515). The azido group could be smoothly converted into a trifluoroacetylamido group by treatment with $(CF_3CO)_2$ in the presence of Ph_3P and 2,3-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one under Ar in THF (99HCA2380).

V. Benzologs of Pyrido[1,2-a]pyrimidine

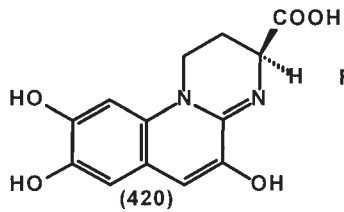
A. Structure

1. *Thermodynamic Aspects*

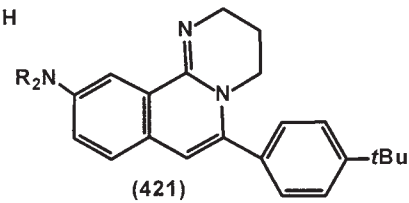
The lipophilicity (R_M value) and specific hydrophobic surface area of 11*H*-pyrido[2,1-*b*]quinazolin-11-one and its isomeric 6*H*-pyrido[1,2-*a*]quinazolin-6-one were determined by reversed-phase thin-layer chromatography (98MI4).

2. *Circular Dichroism*

The absolute configuration of C-3 of the chromophore **4** of an isopyoverdin was determined as *S* from the CD spectrum (Cotton effect +242 nm, −290 nm, +358 nm) of **420** obtained from isopyoverdin by acidic hydrolysis (01T1019).



(420)



(421)

3. *Theoretical Calculations*

Bond orders, charges on the atoms in 11*H*-pyrido[2,1-*b*]quinazolin-11-one and its protonated form were calculated by quantum chemical calculations by the semiempirical AM1 method. According to the results, the equilibrium conformation of the ring in 11*H*-pyrido[2,1-*b*]quinazolin-11-one is planar, while 1*H*-pyrimido[1,2-*a*]quinolin-1-one adopts a conformation close to a half-chair due to the unfavorable interactions between the oxygen atom of the carbonyl group and the ring C-10 atom in the *peri*-position (97MI22).

4. *Infrared Spectroscopy*

IR Spectra of the hydrochloride of 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolines and their $ZnCl_2$ complexes were investigated in the stretching vibration region of N^+H (2000–3500 cm^{-1}) (97MI18, 99MI25).

5. *NMR Spectroscopy*

Chromophore **1** of pyoverdin siderophores (99MI27, 99MI28, 00ZN(C)153, 00ZN(C)323, 00ZN(C)671, 00ZN(C)857, 01TL5849), and chromophore **4** of isopyoverdin (01T1019) were characterized by ^{1}H and ^{13}C NMR data.

6. *X-ray Investigations*

The structures of 5-ethyl-11-methyl-9-oxo-5,11-dihydro-9*H*-pyrido[2,1-*b*]-quinazoline-8-carboxylic acid (00K669), the chromophore **4** of isopyoverdin siderophores (01T1019), and that of 5,5*a*,6,7,8,9-hexahydro-11*H*-pyrido [2,1-*b*]quinazoline (99SL1383) were justified by X-ray analysis.

B. Reactivity

1. *Hydrogenation*

Catalytic debenzylation of 10-(dibenzylamino)-6-(4-*tert*-butylphenyl)-3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline **421** ($R = PhCH_2$) over a 5% Pd/C catalyst under hydrogen at atmospheric pressure in acidified EtOH at ambient temperature afforded the 10-amino derivative **421** ($R = H$) (98JMC1050).

2. *Oxidation*

Ozonolysis of 6-(phenylmethylene)-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]-quinazolin-11-one in CH_2Cl_2 gave 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]-quinazoline-6,11-dione (01H(55)1555).

Ozonolysis of 5,8,9-trihydroxy-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-3-carboxylic acid (**420**), obtained from isopyoverdin isolated from Pseudomonas putida BTP1 by acidic hydrolysis, gave L-2,4-diaminobutyric acid, which confirmed the hypothesis that heterocyclic chromophores **1** and **4** of pyoverdin and isopyoverdin, respectively, could have the same precursor, and the configuration at C(3) should be *S* (97ZN(C)549).

3. *Reactivity of Ring Carbon Atoms*

Condensation of 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one and PhCHO in boiling Ac_2O for 48 h yielded a 6-phenylmethylene derivative (01H(55)1555).

4. *Reactivity of Substituents Attached to Ring Carbon Atoms*

The halogen atoms of 2-iodo- and 3-bromo-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamides were replaced by (het)aryl groups on treatment with (het)arylboronic acids in the presence of $[Ph_3P)_4]Pd$ and 2 M Na_2CO_3 in toluene at 120–125 °C (98MIP1, 98MIP2, 99USP5908840, 99USP5914327). Instead of (het)arylboronic acids 4-(tributylstannyl) pyridine (98MIP2, 99USP5908840) and phenyl trimethyltin (98MIP1, 99USP5914327) were also applied.

Reaction of 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazoline-6,11-dione and $PhNHNH_2$ in EtOH afforded 6-phenylhydrazono derivative (01H(55)1555).

N-Substituted 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamides were prepared from 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic acids and amines in the presence of $(i\text{-Pr})_2EtN$ and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate in CH_2Cl_2 (98MIP1, 98MIP2, 99USP5908840, 99USP5914327).

(*tert*-Butyldimethylsilyl)oxy and *N*-*tert*-butoxycarbonylamido groups on a substituent in position 9 of 11*H*-pyrido[2,1-*b*]quinazolin-11-one were converted into hydroxy and amino groups by treatment with 3 N–6 N HCl at room temperature (99USP5914327).

A 3-amino-*N*-[2-chloro-4{[(3-hydroxyphenyl)methyl]aminocarbonyl} benzoyl-L-alanine substituted Wang resin was *N*-acylated with 2-methoxy-11-oxo-11*H*-pyrido[2,1-*b*]-quinazoline-8-carboxylic acid in *N*-methylpyrrolidone in the presence of 1-hydroxy-7-azabenzotriazole and diisopropylcarbodiimide (00MIP2). The product was cleaved from the resin by treatment with 50% TFA in a mixture of CH_2Cl_2 and MeOH.

The amino group of 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline **421** (R = H) was acylated with different isocyanates and phenyl isothiocyanate (98JMC1050).

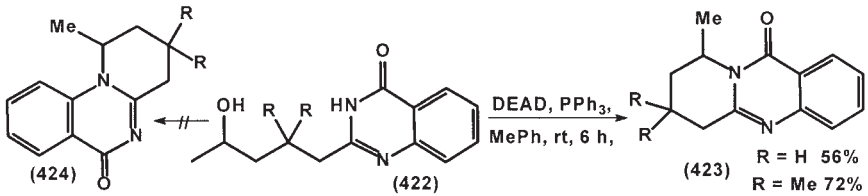
5. *Miscellaneous*

A pyoverdin, containing chromophore **1**, was coupled with different antibacterial fluoroquinoline-3-carboxylic acids (01JMC2139).

C. Synthesis

1. *By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0 (α)]*

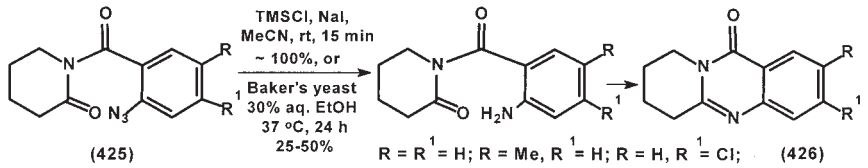
Cyclization of 2-(4-hydroxypentyl)quinazolin-4(3*H*)-ones **422** under Mitsunobu's conditions afforded only linearly fused 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **423** without angularly fused 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]quinazolin-6-ones **424** (98CPB928).



3-Methyl-1*H*-pyrimido[1,2-a]quinolin-1-one was obtained by heating isopropylidene 2-[1-(2-quinolylamino)ethylidene]malonate in EtOH at 20 °C (00MI40).

2. *By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0 (β)]*

5,5*a*,6,7,8,9-Hexahydro-11*H*-pyrido[2,1-b]quinazoline alkaloid was obtained in 70% yield when 1-(2′-nitrobenzyl)-2-cyanopiperidine was reduced with Zn in acidified EtOH at 78 °C (99SL1383). 6,7,8,9-Tetrahydro-11*H*-pyrido[2,1-b]quinazolin-11-ones (**426**) were synthesized by azidoreductive cyclization of *N*-(2-azidobenzoyl)-2-piperidones **425** using TMSCl-NaI and bakers' yeast (01JOC997).

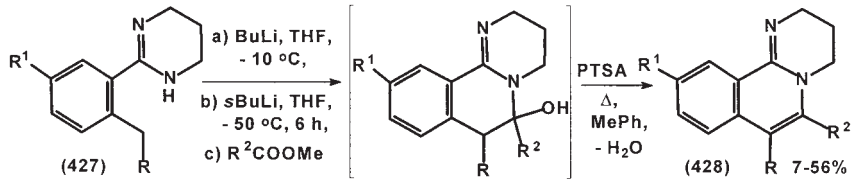


Oxidative cyclization of 1-[(2′-aminocarbonyl)phenyl]piperidine and its 4′-substituted derivatives with $Hg(OAc)_2$–EDTA reagent afforded 1,2,3,4-tetrahydro-6*H*-pyrido[2,1-*b*]quinazolin-6-one and its 3-substituted derivatives in 36–82% yields (99ZN(B)1577). Similarly, (*E*)-2-(piperidin-2-yl)benzaldoximes gave 2,3,4,4*a*-tetrahydro-1*H*-pyrido[1,2-*a*]quinazolin-5-oxide and

its 3-substituted derivatives, which were sometimes accompanied by over-oxidized, ring-opened (*E*)-2-(2-oxopiperidin-1-yl)benzaldoximes.

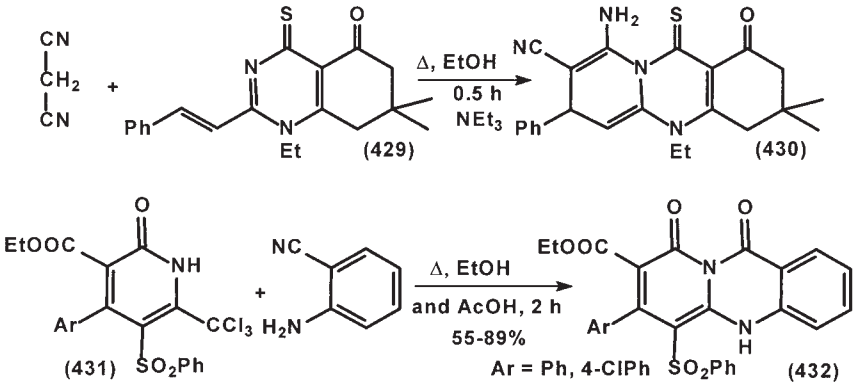
3. *By Formation of Two Bonds from [5+1] Atom Fragments*

Lithiation of 2-(2-alkylphenyl)-1,2,3,4-tetrahydropyrimidines **427** with 1.3 M BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, then with 1.3 M *s*-BuLi, followed by the addition of a carboxylic acid methyl ester, and treatment of the reaction mixture with *p*TSA afforded 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinolines **428** after chromatographic work-up (98JMC1050).



4. *By Formation of Two Bonds from [4+2] Atom Fragments*

Reaction of malononitrile and quinazolinone **429** in the presence of three drops of NEt_3 yielded pyrido[2,1-*b*]quinazolinone **430** (97MI7). 9,11-Dioxo-5,9-dihydro-11*H*-pyrido[2,1-*b*]quinoline-8-carboxylates **432** were prepared in the reaction of anthranilonitrile and 2-piperidones **431** in boiling EtOH in the presence of AcOH (00JCS(P1)3686, 00PS133).

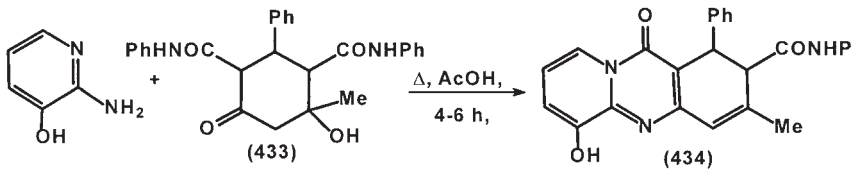


5. *By Formation of Two Bonds from [3+3] Atom Fragments*

Cyclocondensation of 2-chloronicotinic acid with 2-amino-5-iodobenzoic acid and methyl 2-amino-4-bromobenzoate in boiling EtOH in the presence of conc. HCl for 18 h gave the 2-iodo and 3-bromo derivatives of 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic acid (98MIP1, 98MIP2, 99USP5908840, 99USP5914327).

Reaction of 2-aminopyridine and 2,3,4,5,6-pentafluoro- and 5-nitro-2-fluorobenzoyl chloride in CH_2Cl_2 in the presence of $(i\text{-Pr})_2EtN$ at room temperature afforded 1,2,3,4-tetrafluoro- and 8-nitro-11*H*-pyrido[2,1-*b*]-quinazolin-11-ones, respectively (01TL1851).

The reaction of methyl anthranilate and 3-amino-2-chloropyridine in 1,2,4-trichlorobenzene in the presence of KO*t*-Bu at 50 °C gave 5,11-dihydro-6*H*-pyrido[2,3-*b*]benzodiazepin-6-one and 6-amino-11*H*-pyrido[2,1-*b*]quinazolin-11-one as a by-product (99BMCL3031).

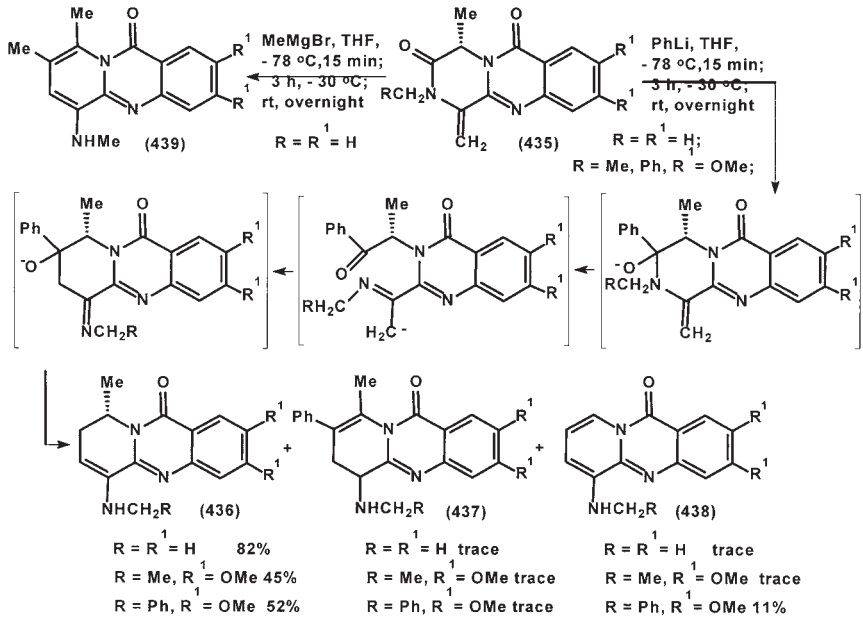


Reaction of 2-amino-3-hydroxypyridine and cyclohexanone **433** in boiling AcOH yielded *N*,1-diphenyl-6-hydroxy-3-methyl-11-oxo-1,2-dihydro-11*H*-pyrido[2,1-*b*]quinazoline-2-carboxamide (**434**) (98MI2, 99USP5908840, 99USP5914327).

Cyclocondenzation of 2-aminoquinoline and isopropylidene 2-(1-methylthioalkylidene)malonates on SiO_2 under microwave irradiations afforded 3-substituted (3-methylthio, 3-methyl, 3-ethyl, and 3-phenyl) 1*H*-pyrimido[1,2-*a*]quinolin-1-ones (00MI40).

6. *Ring Transformation*

Reaction of 1-methylene-1,2,3,4-tetrahydro-5*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**435**) with PhLi and MeMgBr in THF at −78 °C gave a mixture of 11*H*-pyrido[2,1-*b*]-quinazolin-11-ones **435**–**439** (01T1987).



7. *Miscellaneous*

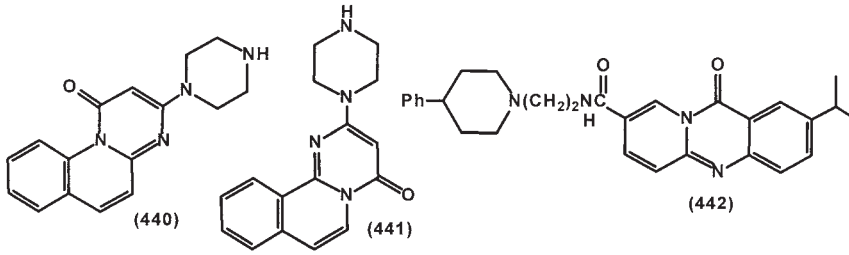
11-(4-Fluorophenyl)-11-hydroxy-2,3,4,11-tetrahydro-6*H*-pyrimido[1,2-*b*]-isoquinolin-6-one was obtained in the reaction of 1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-1-carboxamide and 1,3-diaminopropane in boiling toluene (01BMCL339).

(3*S*)-5,8,9-Trihydroxy-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-3-carboxylic acid and (**420**) and its (1*S*)-1-carboxylic acid isomer were isolated from isopyoverdins (97ZN(C)549, 01T1019) and pyoverdins (99MI27), respectively, after acidic hydrolysis in 3 M HCl for 5 days at 110 °C.

D. Applications and Important Compounds

Different pyoverdins contain a (1*S*)-8,9-dihydroxy-5-amino-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-1-carboxylic acid **1** chromophore (99MI27, 99MI28, 99ZN(C)1021, 00MI38, 00MI39, 00MI47, 00ZN(C)146, 00ZN(C)153, 00ZN(C)323, 00ZN(C)857, 01MI2, 01MIP4, 01TL5849). 5-Amino-8,9-dihydroxy-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-3-carboxylic acid moiety **4** was also identified as a chromophoric moiety of certain

isopyoverdins (99ZN(C)1021, 01T1019, 01ZN(C)303). Chromophores **1** and **4** are formed from the same precursor (01T1019).



3,4-Dihydro-2*H*-pyrimido[2,1-*a*]isoquinolines **421** inhibited the FcεRI-mediated activation of mast cells (98JMC1050). 3-Piperazino-1*H*-pyrimido[1,2-*a*]quinolin-1-one (**440**) and 2-piperazino-4*H*-pyrimido[2,1-*a*]isoquinolin-4-one (**441**) inhibited platelet aggregation in a concentration dependent manner (97MI15). The *in vitro* platelet aggregation inhibitory activities of 3-(cyclic amino and disubstituted amino)-1*H*-pyrimido[1,2-*a*]quinolin-1-ones and 2-(cyclic amino and diethylamino)-4*H*-pyrimido[1,2-*a*]quinolin-4-ones were investigated on human platelet aggregations induced by ADP collagen, and A23187 (00BMC751). 11*H*-Pyrido[2,1-*b*]quinazolin-11-one (**442**) was screened for anticancer activity (98MI14). 6-(2-Methoxyphenyl)-3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline exhibited good inhibition of melanocortin-4 receptors (01MIP5). *N*-Methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinazolin-7-carboxamide did not exhibit any MAO A and B inhibitory activities (97JMC2466).

The use of 11*H*-pyrido[2,1-*b*]quinazolin-11-ones in an organic electroluminescent device was patented (99JAP(K)99/74080). 2*H*-Pyrimido[2,1-*a*]isoquinolin-7-ols were patented as multi-functional fuel and lube additives (97USP5646098).

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