REACTION OF CARBENES WITH PYRIMIDINES AND ISOQUINOLINE DERIVATIVES. APPROACHES TO THE SYNTHESIS OF MODIFIED NUCLEOSIDES AND ALKALOIDS*.

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Reactions of carbenes[1] with the olefinic function of heterocyclic systems is of potential interest in the derivitisation and ring-expansion of the heterocycles[2]. In the case of nitrogen heterocycles, the course of the reaction is expected to be significantly influenced by (a) the basicity of the nitrogen atom(s) and (b) their location with respect to the double bond, in addition to other factors. Of particular interest is the reaction (with carbenes) of nitrogen heterocycles which contain a potential enamine functionality. Recent developments in this specific area are the subject of the present discussion.

Reactions of carbenes with enamines have been extensively investigated in this laboratory[3a-d]. The general reactivity-pattern, that emerges from these and related studies[4-28], shows the primary product to be a carbene adduct (cyclopropane derivative) which, depending upon the nature of the substituents on the carbene[6,8,12,13,20,22,23,30,31], the steric and functional environment of the ename nitrogen[3d,4-7,17-28] and the stereochemistry of the adduct[18], can be isolated as such, or undergoes diverse types of transformations to secondary products. This is illustrated by the reactions described in Fig. 1.

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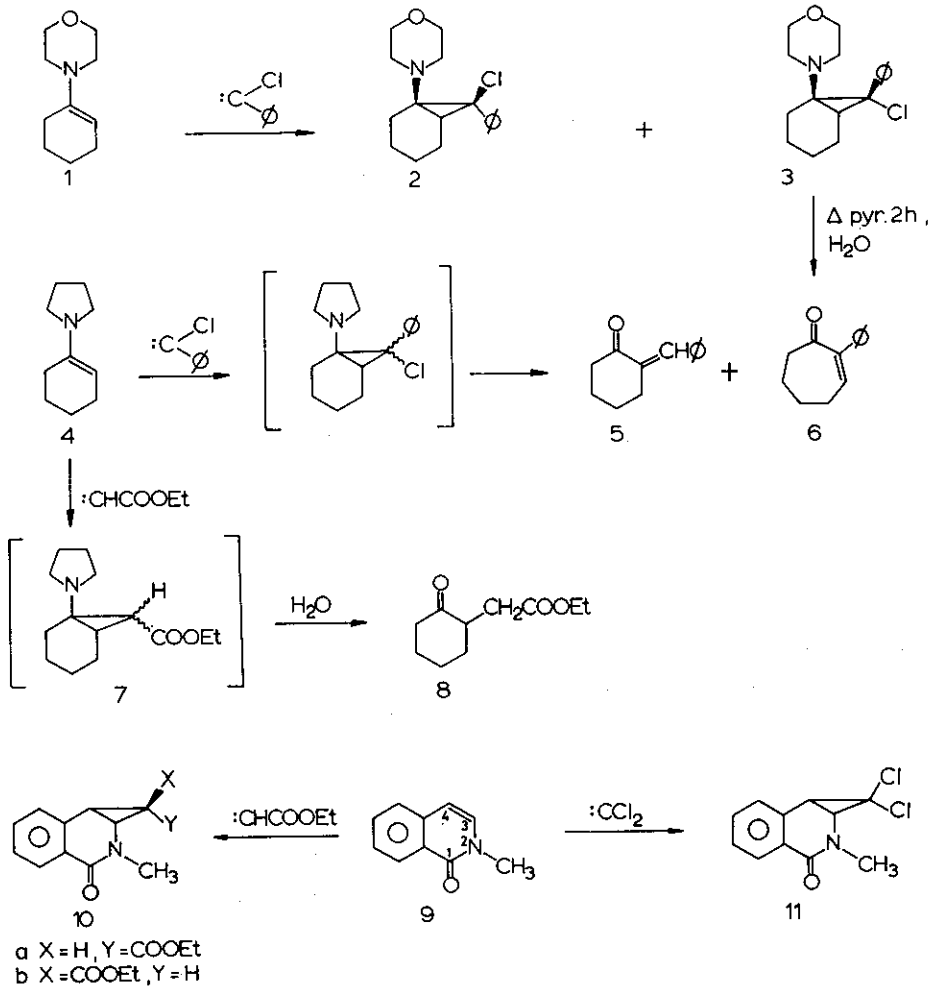

1
2
3
Δ pyr. 2h ,
H_2O
4
5
6
:CHCOOEt
7
8
CH_2COOEt
9
$:CCl_2$
10
11
a X = H, Y = COOEt
b X = COOEt, Y = H

Fig. 1

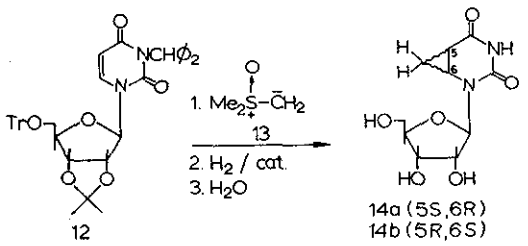
The morpholino enamine 1 reacts with phenylchlorocarbene to yield the isomeric adducts 2 and 3[18]. While the corresponding pyrrolidino enamine 4 gives no cyclopropane adduct; after hydrolysis, a mixture of α,β-unsaturated ketones 5 (major) and 6 (minor product) could be isolated[3a,19,22]. The difference in the behaviour of 1 and 4 can be ascribed to the differences in the basicities and the ring-sizes of the base components of the enamines. Change of the reactivity pattern with variation of the base-component has also been observed in the reaction of enamines with other electrophiles[32,33]. Stereochemistry of the primary adducts (2 and 3) controls further reaction, involving a three-ring opening, in accordance with the orbital symmetry rules[34,35]. Thus, heating of the endo-chloro adduct 3, in pyridine, followed by hydrolysis, results in its quantitative conversion to 6. Under identical conditions, the exo-chloro isomer 2 is totally unaffected[18].

The reaction of enamine 4 with a carbene carrying an electronegative substituent, e.g. ethoxycarbonylcarbene, leads to the isomeric amino-cyclopropane esters (7; exo-COOEt and endo-COOEt), which undergo a spontaneous ring-opening and , under hydrolytic conditions, give γ-ketoester 8[3a]. The intermediacy of the primary adduct 7 has been adduced from a study of the reaction of methylene and dichlorocarbene with β-amino-α,β-unsaturated esters [20-22]. In contrast, a latent enamine function reacts to give stable aminocyclopropane ester adducts (10a,b), if the free-electron pair on the nitrogen is delocalized by an adjacent electronegative group. This is seen in the reaction of isoquinolinone 9 with ethoxycarbonylcarbene and dichlorocarbene (Fig. 1)[36].

Synthesis and Structure of Pyrimidine-Carbene Adducts.

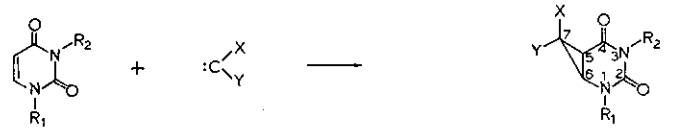
Novel types of transformations of pyrimidines are of interest in view of their potential application to the synthesis of new classes of modified nucleosides. The reactions of nucleo-bases have been recently surveyed

by TsO[37]. The C(5)=C(6) bond of the pyrimidine bases (uracil, thymine, cytosine) undergoes dimerization[38], photochemical cycloadditions[39,40] and reactions with halogens[41], bisulfite anion[42], permanganate[43] and tetrahydrofuran[44]. Attempts to add the methylene moiety, generated from iodomethylzinc iodide, to 1,3-dialkyluracil, were reported to be unsuccessful[45]. However, it was possible to convert the uridine derivative 12 to the corresponding cyclothymidine system 14[55] by reaction with ylid 13[45].



The 5'-diphosphate of 14 (a+b) undergoes polynucleotide phosphorylase catalyzed copolymerization with ADP, IDP, CDP and UDP[46].

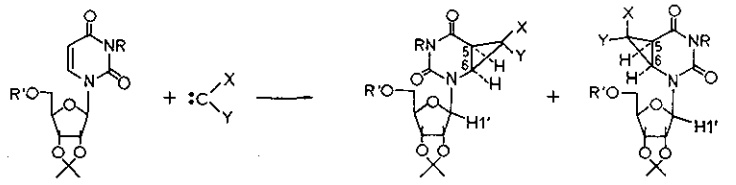
On the basis of theoretical calculations and photoelectron spectral data, it has been pointed out that uracil and thymine can be regarded as a combination of an enamine and a dicarboxamide system[47]. The nucleophilic character of the N(1)-C(6)=C(5) system in the pyrimidines is, however, suppressed owing to both the electron-withdrawing group on the enamine-nitrogen and the carbonyl function adjacent to the double bond. Addition of carbenes to pyrimidines has, to the best of our knowledge, not been described in the literature. Dichlorocarbene, generated from the more conventional sources like chloroform (base-catalyzed α-dehydrohalogenation[48-51]), or sodium trichloroacetate (thermal decomposition)[52], does not react with 1,3-dialkylated uracil derivatives. On the other hand,



	R_1	R_2		X	Y
15a	CH_3	CH_3	2a	Cl	Cl
b	$PhCH_2$	$PhCH_2$	2b	Br	Br
c	$PhCH_2OCH_2$	CH_3	2c	Cl	F
d	$PhCH_2OCH_2$	$PhCH_2$	2d	H	COOEt
e	$PhCH_2CH_2CH_2$	CH_3			

	X	Y	R_1	R_2
17a	Cl	Cl	$PhCH_2$	$PhCH_2$
b	Br	Br	$PhCH_2$	$PhCH_2$
c	Cl	F	$PhCH_2$	$PhCH_2$
d	F	Cl	$PhCH_2$	$PhCH_2$
e	COOEt	H	CH_3	CH_3
f	H	COOEt	CH_3	CH_3
g	COOEt	H	$PhCH_2$	$PhCH_2$
h	H	COOEt	$PhCH_2$	$PhCH_2$
i	COOEt	H	$PhCH_2OCH_2$	CH_3
j	H	COOEt	$PhCH_2OCH_2$	CH_3
k	COOEt	H	$PhCH_2CH_2CH_2$	CH_3
l	H	COOEt	$PhCH_2CH_2CH_2$	CH_3
m	COOEt	H	$PhCH_2OCH_2$	$PhCH_2$
n	H	COOEt	$PhCH_2OCH_2$	$PhCH_2$

Fig. 2



18 R = Me , R' = Ac
19a R = $CH\phi_2$, R' = $C\phi_3$
19b R = $CH\phi_2$, R' = Ac

	Ⓐ (5S,6S)		Ⓑ (5R,6R)	
20	X	Y	R	R'
21	Cl	Cl	CH_3	Ac
22	Br	Br	CH_3	Ac
23	Cl	Cl	$CH\phi_2$	$C\phi_3$
24	Cl	F	CH_3	Ac
25	F	Cl	CH_3	Ac
26	Cl	F	$CH\phi_2$	Ac
27	F	Cl	$CH\phi_2$	Ac

Fig. 3

the latter readily undergo addition of dihalocarbenes- produced via the phenyl(trihalomethyl)mercury compounds[53] - or ethoxycarbonylmethylene[54] - generated from ethyl diazoacetate (Cu catalyst) - at the C(5)=C(6) double bond, to yield the corresponding 1:1 adducts. The results of these reactions are described in Fig. 2[25]. The reaction can be extended to uridine derivatives and constitutes a general procedure for the synthesis of substituted cyclothymidines. As expected, owing to the chirality of the sugar moeity in the nucleoside, addition of symmetrically substituted carbenes to uridines (18, 19a,b; Fig. 3) leads, in each case, to a mixture of diastereomeric products (5S,6S, A; 5R,6R, B)[25]. A similar reaction of unsymmetrical carbenes gives two diasteromeric pairs, corresponding to geometrical isomerization of the substituents at C(7)[55] (Fig. 3)[25]. The compounds within the diastereomeric series A and B have been correlated by their CD spectra; A-isomers exhibiting a negative maximum in the range 248-262 nm, while corresponding B-isomers showed a positive maximum in the same range. The absolute stereochemical assignments of the adducts (20A,B - 26A,B) is based upon X-Ray crystallographic analysis of the crystalline adduct 20B[25]. The computed structure of 20B (Fig. 4) establishes its configuration as 5R,6R.

The configurational assignments of the diastereomers, obtained in our work, were correlated with those made for the cyclothymidines 14a,b, prepared by Witkop et al.[45]. This was achieved by the conversion of 21A and 21B via hydrolysis and subsequent $(nBu)_3SnH$ reduction, to the corresponding cyclothymidines, and examination of their ORD spectra. Comparison of the signs of the Cotton effects of the latter and 14a,b showed that 21A (5S,6S) and 21B (5R,6R) were relatable to 14a (5S,6R) and 14b (5R,6S), respectively. Since the assignments made by us are based upon X-Ray data, the aforementioned correlations establish, unambiguously, the assignments of Kunieda and Witkop[45].

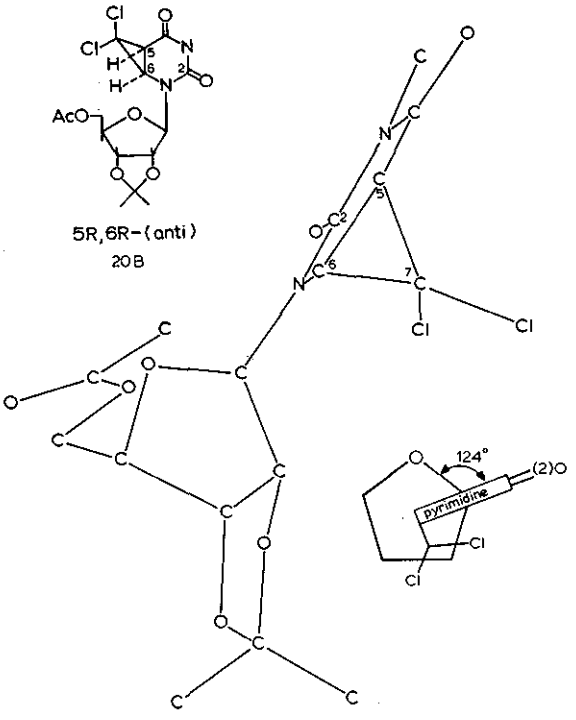


Fig 4

The nucleosides of the A and B series are characterized by a difference in the conformation about the glycosidic bond[25]. This feature is revealed by the ^{1}H-NMR spectra of the compounds. The chemical shifts of the C(1') protons in diastereomers A and B lie in the ranges δ 5.58 - 5.62 and 6.03 - 6.16, respectively. The low field shift of C(1')-H in the B series can be ascribed to the deshielding effect of the C(2)=O group in the anti-conformer. The A-series can, therefore, be assigned the syn-conformation. These conformational assignments receive support from the X-Ray structure of 20B (Fig. 4), which shows an anti-orientation of the pyrimidine, with respect to the ribose moiety. The conformational preference of the diastereomers is, obviously, a consequence of the steric interactions - between the base and the sugar - involving the C(7)-halogens

In the absence of the halogens the signals of the C(1')-protons in the diastereomers (14a and 14b) exhibit very similar chemical shifts[45].

Transformations of Pyrimidine-Carbene Adducts.

A transformation of pyrimidine-carbene adducts which is of potential synthetic interest, especially in the preparation of base-modified nucleosides, is the cleavage of the C(5)-C(6) bond, whereby a new heterocyclic (diazepine) system is produced. For the ethoxycarbonylcarbene-uracil adducts, a ring-opening under influence of an acid catalyst holds the promise of the desired type of conversion. It was, however, recognized that the trigger for such a reaction could involve the protonation of either the C(4)=O function or the ester carbonyl. The former protonation process would be expected to result in ring expansion[20,56], while the latter would give an uracil derivative (Fig. 5). When the isomers 17e and 17f were heated in DME, in the presence of p-toluenesulfonic acid, the only isolable product, in both cases, was the uracil ester 27a. Heating in a 10% solution of HCl resulted in the conversion of 17e,f to the acid 27b, quantitatively. Basic hydrolysis of 17e and 17f (NaOH, ethanol/water) led to the formation of the isomeric crystalline disodium salts (28)[45], which have been isolated and identified. This hydrolytic cleavage is reversible, since acidification of the isomeric salts (28) gives the acids corresponding to the starting esters (17e,f).

It was anticipated that the dihalocarbene-uracil adducts should undergo a ring expansion of the original pyrimidine moiety, by extrusion of the endo-halogen, in accordance with the expected disrotatory ring-opening of cyclopropane derivatives[34,35].

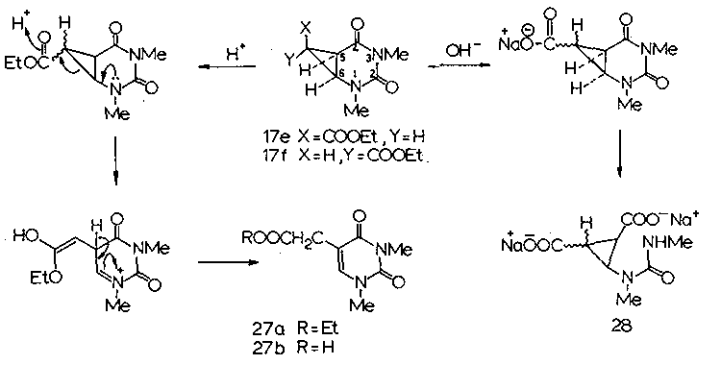


Fig. 5

The presence of the nitrogen [N(1)] should, in fact, facilitate the reaction, by delocalizing the charge developed in the ionization step (Fig. 6). It should be noted, however, that a non-stereospecific ring-opening of bicyclic systems containing a cyclopropane moiety has been observed in special cases where unique structural features [5,22,31,27a,b] or reaction conditions[18] influence the course of the reaction. The general scheme for the transformation is given in Fig. 6.

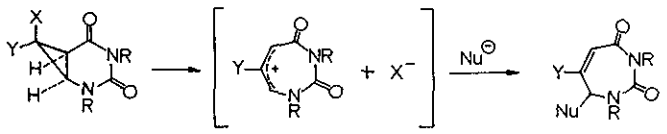


Fig.6

In accord with the aforementioned line of reasoning, the dihalocarbene adducts 17a and 17b (Fig. 7) give the dioxodiazepines 29a and 29b, respectively, when heated with methanol in a sealed tube (130°)[58]. Under similar conditions, the endo-chloro adduct 17c is converted to a mixture of 29e and 30; whereas, significantly, the exo-chloro isomer (17d) is recovered totally unchanged. The fluoro compound 17c is converted into the expected diazepine derivative 29c, if the reaction is carried out by heating (reflux) in a benzene solution containing a limited amount (2 eq.) of methanol. That 29c is the primary product of the sealed tube reaction, is demonstrated by the fact that it is quantitatively converted to 29e upon treatment with methanol, in the presence of catalytic quantities of a base or acid. The latter reaction presumably involves an initial nucleophilic addition of the alcohol to the α,β-unsaturated system, in 29c, which is followed by elimination of the fluoride ion. In support of this explanation, heating of 17c in t-butanol resulted in fluorodiazepine 29d, in quantitative yield. A further nucleophilic attack by the bulky t-butanol, (to 29d), in a reaction analogous to that of 29c, with methanol, is hindered on steric grounds. The formation of 30 deserves comment. Mechanistic considerations suggested that the product could

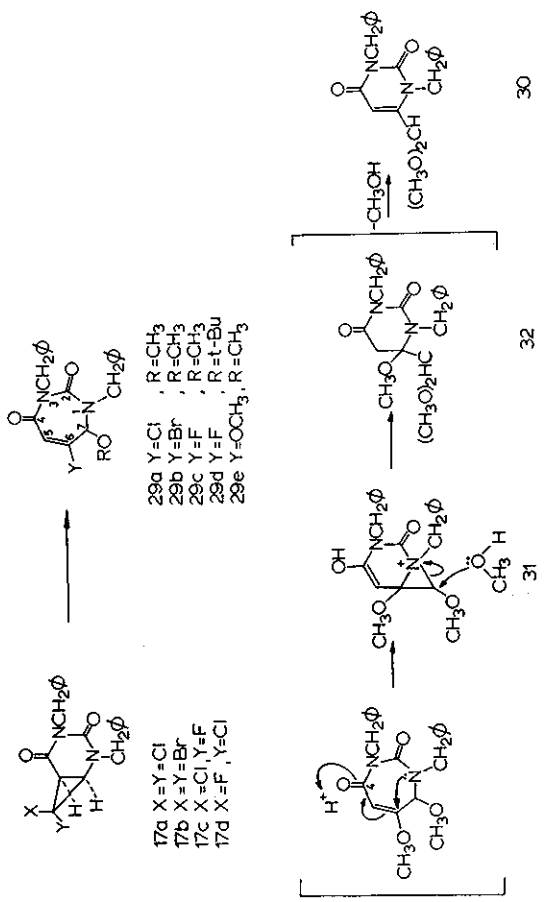

17a X=Y=Cl
17b X=Y=Br
17c X=Cl, Y=F
17d X=F, Y=Cl
29a Y=Cl, R=CH3
29b Y=Br, R=CH3
29c Y=F, R=CH3
29d Y=F, R=t-Bu
29e Y=OCH3, R=CH3
31
32
30

Fig.7

arise from an acid-catalyzed contraction of 29e, via intermediates 31 and 32 (Fig. 7). It should be pointed out that transformation of 17c to 29c is accompanied by the generation of one equivalent of hydrochloric acid, which could serve as the catalyst for the last mentioned reaction. This has been established in two ways: (a) by showing that 29e is quantitatively converted into 30, upon refluxing in methanol in the presence of p-toluenesulfonic acid, and (b) by completely suppressing the formation of 30, during the conversion 17c ⟶ 29e, by using one equivalent of triethyl amine. The difference in behaviour of the isomers 17c and 17d shows that the reaction is subject to stereoelectronic control and thereby constitutes strong support for a mechanism involving a synchronous chloride elimination and ring-opening.

The ring-expansion reaction of uracil-carbene adducts can be conveniently applied to analogous systems derived from uridine derivatives. Heating of the adducts 20A,B, 21A,B and 23A,B in t-butanol (110^0, sealed tube) resulted in the formation of, besides side-products , to be discussed in the sequel, the expected diazepine nucleosides 33a-c (Fig. 8)[59]. The endo-fluoro diastereomers (24A,B) were inert under the described reaction conditions; wholly in accordance with the mechanistic considerations of ring-opening, metioned earlier. The chemical shifts of the C(1')-protons in nucleosides 33a-c lie in the range δ 5.46 - 5.59, indicating, by analogy with the spectral data of adducts 20B-26B, that the former possess a syn- conformation. This conclusion is consistent with the expectation that the bulky t-butoxy substituent would tend to be outside the domain of the ribose moiety. It should be mentioned that while the ring-expansion process can, in principle, lead to a pair of diastereomeric diazepine nucleosides [epimeric about C(7)], we have been able to find only one product, in each of the reactions with t-butanol[60]. The stereochemistry about C(7) has thus far not been elucidated.

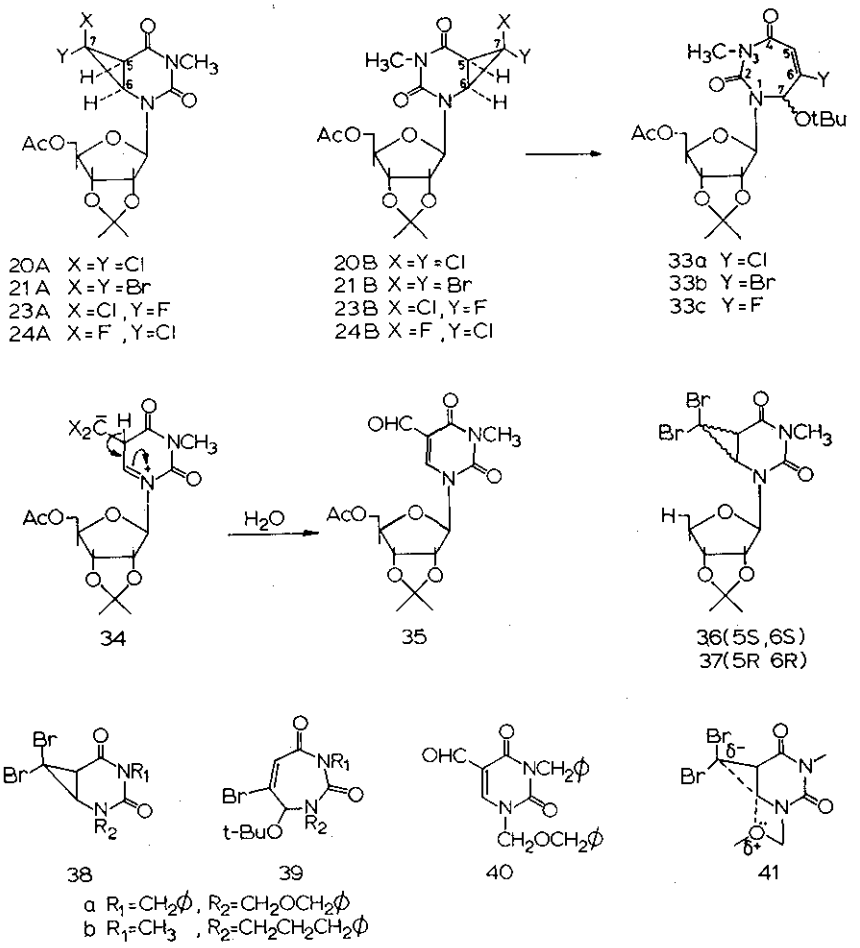

20A X=Y=Cl
21A X=Y=Br
23A X=Cl, Y=F
24A X=F, Y=Cl
20B X=Y=Cl
21B X=Y=Br
23B X=Cl, Y=F
24B X=F, Y=Cl
33a Y=Cl
33b Y=Br
33c Y=F
34
35
36(5S,6S)
37(5R 6R)
38
39
40
41
a R1=CH2φ, R2=CH2OCH2φ
b R1=CH3, R2=CH2CH2CH2φ

Fig. 8

As indicated earlier, the reactions of 20A,B and 21A,B do not lead exclusively to the diazepine nucleosides. In addition, the uridine aldehyde 35 is also isolated from the reaction mixtures. The formation of 35 can be accounted for by invoking a C(6)-C(7) cleavage, leading to intermediates op type 34, which yield the aldehyde upon hydrolysis. Noteworthy is the observation that the ratio of 33:35 formed from each diastereomer, - within the pair - is significantly different; the diastereomers with the syn-conformation giving a preponderance of the diazepine product. A possible role of the C(5')-acetate group, in promoting the C(6)-C(7) bond fission - to give 35 - was eliminated by showing that the same trend in the diazepine/aldehyde ratio was observed, when the diastereomeric 5'-deoxy adducts 36,37 were subjected to ring-expansion. That the riboside ring-oxygen may play a part in assisting C(6)-C(7) bond breaking is suggested by model studies involving dibromocarbene adducts 38a,b. Heating 38a in t-butanol (110^0, Et_3N, 4h) does give a mixture of 39a and 40 (Fig. 8). On the other hand, a comparative reaction of 38b while resulting in 39b, did not show the aldehyde 40 in the reaction mixture. Although participation of the oxygen electrons would require an energetically unfavoured four-membered ring (41), such an interaction would explain the preponderant formation of the aldehyde derivative in the reaction of the anti- conformer of the uridine-carbene adducts.

Isoquinolinone-Carbene Adducts.

The results of the investigation of the pyrimidine-carbene adducts have prompted the study of the reaction of carbenes with other heterocyclic compounds. A heterocyclic system, of interest, which bears resemblance to the uracil derivatives, is isoquinolinone 9 (Fig. 1). Addition of carbenes to 9 can be visualized as a potential approach to benzazepines and 4-substituted isoquinoline derivatives. The latter can, in their own turn, serve as precursors of polyheterocyclic compounds,

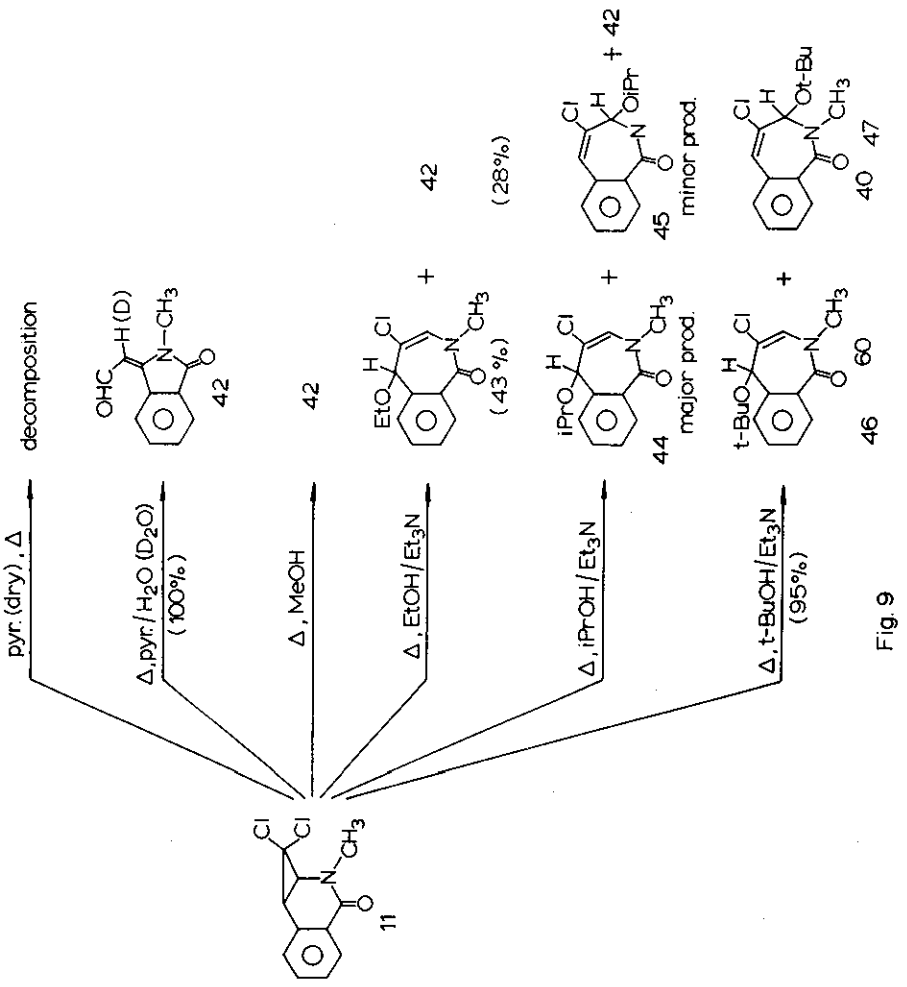
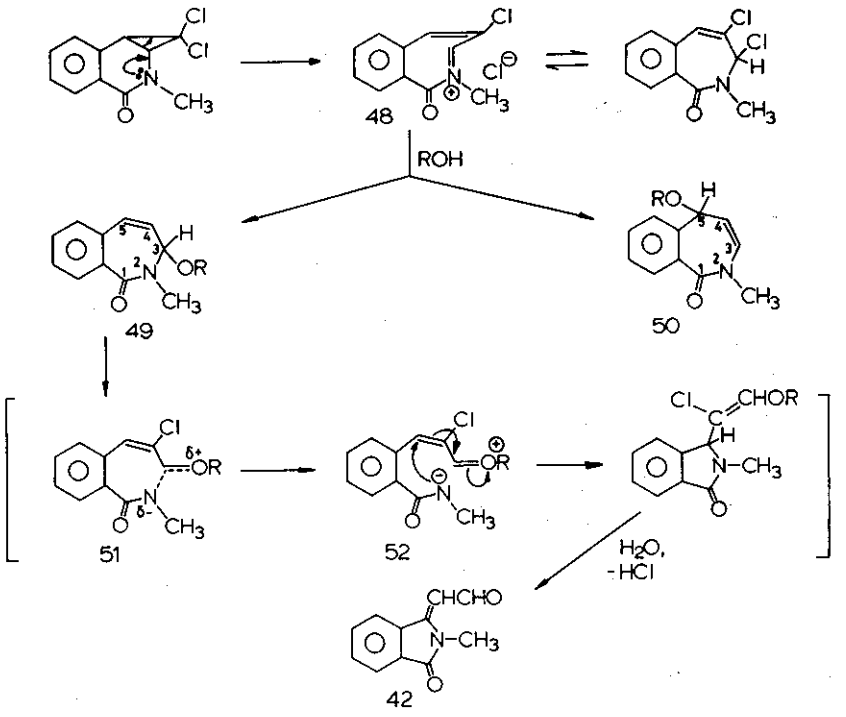

pyr. (dry), Δ
decomposition
Δ, pyr./H2O (D2O)
(100%)
42
Δ, MeOH
42
Δ, EtOH/Et3N
42
(43%)
Δ, iPrOH/Et3N
44
major prod.
+ 42
45
minor prod.
Δ, t-BuOH/Et3N
(95%)
46
60
40
47
11

Fig. 9

including alkaloids. An objective in our work, in this connection, was the development of a facile approach to the synthesis of physiologically important phenanthridine alkaloids[61-63]. N-methylisoquinolinone 9 reacts with $:CCl_2$ and :CHCOOEt to give the corresponding addition products in very good yields [10a + 10b (90%); 11 (82%)] Fig. 1[36]. The best results are obtained when the dichlorocarbene is prepared by the procedure described by Makosza[49,51] and the ethoxycarbonylcarbene[54] is generated by heating 9 with ethyl diazoacetate, without solvent, at 125° in presence of copper catalyst. In the case of the last reaction, refluxing in toluene in the presence of bis(acetylacetonato)-Cu (II) complex[54] (catalytic quantities), gives comparable results.

In Fig. 9, the results of thermal transformation of 11, in various solvents, are described. The products are significantly dependent upon the nature of the solvent employed. In water and methanol, none of the *ring-expanded system - expected by analogy to the transformation of the* pyridine-carbene adducts - is isolated; the only product formed being the isoindole derivative 42. In contrast to these results, the sterically bulky alcohols do give rise to the formation of progressively larger amounts of benzazepine derivatives, in addition to 42. As an extreme case, t-butanol gives exclusively a mixture of benzdiazepines 46 and 47. The formation of 42 can be rationalized in terms of the mechanistic scheme described in Fig. 10. The expected intermediate 48 is quenched by the solvent to the corresponding benzazepinones 49 and 50, of which 49 can undergo ring-opening (51) and subsequent ring-closure (52) on the path towards 42. The role of the bulk of R in the alcohol can be best understood by a closer inspection of the transition-state (51) for the ring-opening process. During the latter, bond-fission between N(2)-C(3) is concerted with the change in hybridization, from sp^3 to sp^2, of C(3). A stereo-projection of the transition-state (53, Fig. 10) reveals that the OR group buttresses against the chlorine atom on one hand and


Cl
Cl
N
CH3
O
48
ROH
H
OR
49
RO
50
δ+
δ-
51
52
CHOR
H2O,
-HCl
CHCHO
42

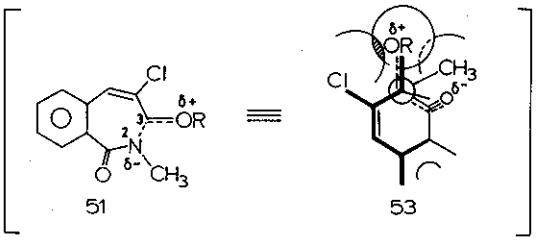

Cl
δ+
OR
δ-
CH3
51
53

Fig. 10

possesses a gauche interaction with the N(2)-CH_3, on the other. With increase in size of R, these interactions destabilize the transition-state so that the ring-opening process is suppressed. It is noteworthy that in reactions with ethanol and isopropyl alcohol the major products correspond to the 5-alkoxy isomers 50 (R=Et, iPr) which are stable towards the ring-opening reaction (51).Consistent with the argument based upon steric factors, while in the isopropanol reaction a minor quantity of 45 is reatined, the t-butanol reaction results in significant amounts of the related isomer 47.

The aforementioned results and the proposed mechanistic considerations suggested that a facile procedure for the transformation of 11 to stable benzazepine derivatives would require the quenching of the intermediate carbenium ion (48, Fig. 10) with a nucleophile, which would intrinsically prohibit the ring-opening (observed with alcohols). Heating of 11 in DME, followed by reduction with $NaBH_4$ yielded a mixture of 54 and 55 (Fig. 11). The formation of 55 can be explained in terms of reduction of the enamine function in 56, under the conditions of the reaction. The ethoxycarbonylcarbene adducts of 9, namely 10a,b, were recognized as valuable intermediates for the synthesis of 4-substituted quinolinones. Although transformation of 10a,b to ester 57 (Fig. 12) can be accomplished by heating the isomers without a solvent - the exo-ester 10b requiring a higher temperature - a more convenient method for the same conversion, consists in refluxing solutions of either of the isomeric esters, in EtOH/HCl, for 16 hours. Under these conditions the yields of 57 are quantitative. The conversion of 57 to a suitable precursor of benzphenanthridine derivatives followed the sequence: 57 ⟶ 58 (alkylation with veratryl bromide, -50°, THF/HMPT) ⟶ 59 (DDQ, decalin). While the last oxidation can lead to E and Z isomers, in our hands only the E-isomer has thus far been isolated.

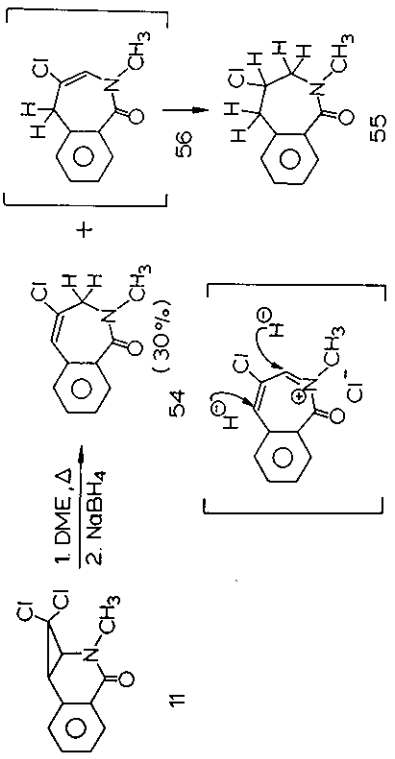


Fig. 11

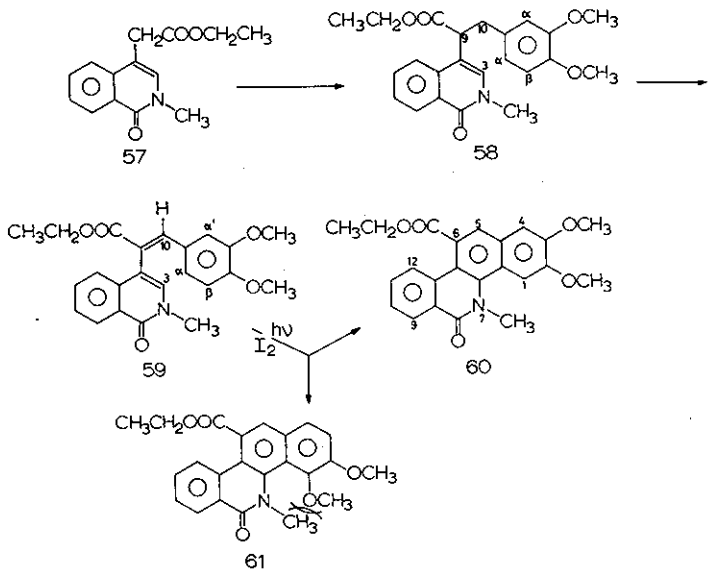


Fig. 12

Photolysis of 59 in benzene (Rayonet reactor, 300 nm lamps) in the presence of iodine, gives a mixture of benzphenanthridines 60 and 61 (85%), which can be separated by chromatography.

The synthesis of naturally occurring benzphenanthridine alkaloids, utilizing the aforementioned sequence, is being undertaken. It should be mentioned that the approach to the synthesis of the alkaloids, developed in our studies, compares favourably with other methods which have been reported recently[62-66]. Attempts to add carbenes of the type ArCOCH:, to 9, with the purpose of reducing the number of steps in the synthetic sequence, have so far proved unsuccessful.

Acknowledgement.

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