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PYRROLES AND RELATED COMPOUNDS—IX*

SYNTHESES AND PROPERTIES OF CERTAIN PYRROKETONES

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Abstract—The adducts (IV) of phosphoryl chloride and 2-dimethylaminocarbonylpyrroles condense smoothly with pyrroles having a free 2-position, and subsequent hydrolysis gives 2,2′-dipyrrolylketones (V) in good yield. In these ketones the two pyrrole nuclei are conjugated through the carbonyl group, and their concomitant dipolar character (cf. IX) is reflected in spectra, basicity and ready reduction by diborane. A 5-methyl group in such pyrroketones can be chlorinated stepwise by t-butyl hypochlorite (cf. XVa and c).

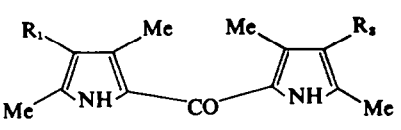
LINKING pyrrole rings by methylene groups has been the subject of previous papers in this series. While efficient methods have been found for joining two diversely substituted pyrrole nuclei,[1,2] it has become evident that unambiguous syntheses of porphyrins cannot be achieved by repetition of the process, after the fashion of porphyrin biosynthesis, because the methylene group is often easily displaced by an electrophile.[1,3] This displacement is inhibited by electron-withdrawing substituents and therefore we turned our attention to synthetic routes including a carbonyl link.[4] This paper is concerned with the necessary starting materials, 2,2′-dipyrrolylketones (abbreviated to "pyrroketones" by Hans Fischer). Later papers will describe new porphyrin syntheses[5] based on pyrroketones.

Pyrroketones have been reviewed,[6] and in the meantime two more methods of preparation have been devised. Both have rather limited scope, one being based on simultaneous synthesis of the two pyrrole rings[7] and the other on oxidation of pyrromethane-5,5′-dicarboxylic esters with lead dioxide and lead tetra-acetate.[8] As pyrromethanes are readily accessible, the latter method is attractive but the two ester substituents appear to be necessary; we had independently tried unsuccessfully to oxidize 5-benzyloxycarbonyl-3,4′-diethyl-4,3′,5′-trimethylpyrromethane[1] with alkaline permanganate, sodium peroxide, sodium periodate, or dimethyl sulphoxide. Another possibility was the Hoesch synthesis, but attempts to employ this were also unsuccessful.[9]

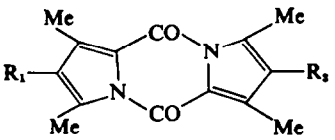
* Part VIII: *Tetrahedron* **21**, 2913 (1965).

[1] A. Hayes, G. W. Kenner and N. R. Williams, *J. Chem. Soc.* 3779 (1958).
[2] A. H. Jackson, G. W. Kenner and D. Warburton, *J. Chem. Soc.* 1328 (1965).
[3] J. Ellis, A. H. Jackson, A. C. Jain and G. W. Kenner, *J. Chem. Soc.* 1935 (1964).
[4] This point was made independently by G. P. Arsenault, E. Bullock and S. F. MacDonald, *J. Amer. Chem. Soc.* **82**, 4384 (1960).
[5] A. H. Jackson, G. W. Kenner, G. McGillivray and G. S. Sach, *J. Amer. Chem. Soc.* **87**, 676 (1965).
[6] H. Fischer and H. Orth, *Die Chemie des Pyrrols* Vol. I; pp. 361–377. Akademische Verlag, Leipzig (1934).
[7] A. Treibs and K. H. Michl, *Liebigs Ann.* **577**, 129 (1952).
[8] J. M. Osgerby and S. F. MacDonald, *Canad. J. Chem.* **40**, 1585 (1962).
[9] Unpublished work by Dr. D. Warburton.

The earlier, more general methods for synthesis of pyrroketones[10] depend on acid chlorides. Aluminium chloride was used in several Friedel-Crafts reactions, which gave yields of about 30%.[10] We thought the catalyst might be superfluous, and indeed 4,4′-diethoxycarbonyl-3,5,3′,5′-tetramethylpyrroketone (Ia) was obtained in 80% yield from 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carbonylchloride and 4-ethoxycarbonyl-3,5-dimethylpyrrole. However, under the same conditions in boiling benzene,



I



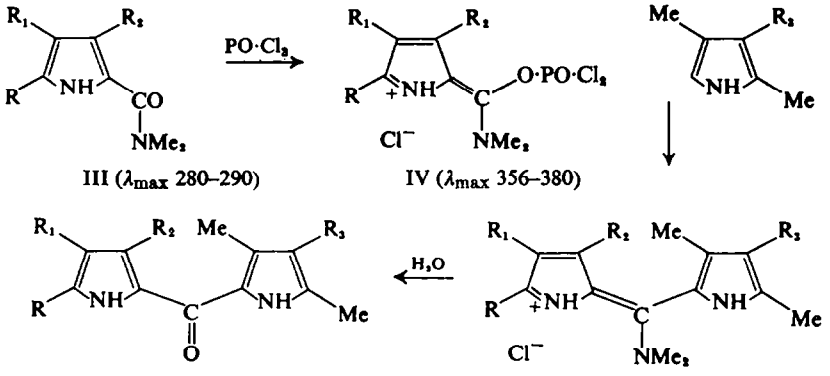
II

a, $R_1 = R_2 = CO_2Et$
b, $R_1 = R_2 = COMe$
c, $R_1 = Et$, $R_2 = CO_2Et$

the analogous 4-acetylpyrroles gave a low yield of the pyrrocoll (IIb) instead of the ketone Ib. The pyrrocolls IIa and IIb were the major products of reactions in pyridine solution; in basic media the acidity of the NH group in a ring bearing a further carbonyl group becomes dominant. An alternative route to symmetrical pyrroketones is from phosgene and the Grignard derivative of the pyrrole.[10] Presumably this proceeds through the acid chloride, and we were able to prepare an unsymmetrical ketone (Ic) by both possible routes of this type. Conversion of the Grignard reagent into the cadmium derivative made a slight improvement and another unsymmetrical pyrrroketone (Va) was prepared thus, but the method is rather unattractive.

A very satisfactory general method for preparing pyrroketones has now been found in an adaptation of the Vilsmeier synthesis of aldehydes,[11] which has been widely applied to pyrroles. It has also been used[12] for the preparation of some 4-dimethylaminophenyl ketones from dimethylaniline, which is comparable to many pyrroles in reactivity towards electrophilic substitution. In the pyrrole series formation of the phosphoryl chloride complex (IV) from the amide (III) can be conveniently followed by disappearance of one ultraviolet absorption (at 282 mμ for IIIa) and appearance of a new band (at 378 mμ for IVa). There was a marked difference between the behaviour of the amide containing a benzyloxycarbonyl group (IIIa) and that of the fully alkylated amide (IIIb). The latter was readily converted to the complex (IVb, λ_{max} 380 mμ) by one mole of phosphoryl chloride in ethylene chloride, but reaction was incomplete in the former case unless the solvent was entirely phosphoryl chloride or heating was prolonged. Subsequent reaction with a trialkylpyrrole was marked by bathochromic shift of the absorption (to 402 mμ for VIa, 408 mμ for VIb and VIc). Finally hydrolysis to the pyrroketone was followed by hypsochromic shift of the absorption (to 348 mμ for Va, 364 mμ for Vb and Vc). Aqueous sodium acetate was effective in the first instance (Va from VIa), but aqueous sodium carbonate had to be used when the electron-withdrawing benzyloxycarbonyl group was absent; aqueous

[10] H. Fischer and H. Orth, *Liebigs Ann.* **489**, 62 (1931); **502**, 237 (1933).
[11] A. Vilsmeier and A. Haack, *Ber. Dtsch. Chem. Ges.* **60**, 119 (1927).
[12] H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta* **42**, 1659 (1959).



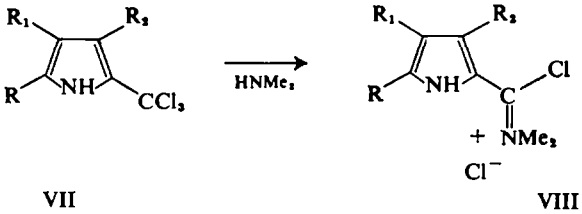
III (λ_{max} 280–290) IV (λ_{max} 356–380)

V (λ_{max} 345–370) VI (λ_{max} 400–410)

a, R = CO_2Bzl, R_1 = Me, R_2 = R_3 = Et
b, R = R_2 = Me, R_1 = R_3 = Et
c, R = R_2 = Me, R_1 = Et, R_3 = $(CH_2)_2CO_2Me$
d, R = CO_2H, R_1 = Me, R_2 = R_3 = Et
e, R = H, R_1 = Me, R_2 = R_3 = Et

sodium acetate merely converted the second salt (VIb) into its free base, which remarkably also has maximum absorption at 408 mμ.[13] The pyrroketones Ia and Ic were also prepared satisfactorily by this method. Subsequently it has been applied to many pyrroketones containing three or four pyrrole nuclei, and yields in the region of 80% have generally been obtained by careful attention to two points;[14] (i) the reaction mixtures should be as concentrated as possible and (ii) during the coupling stage hydrogen chloride should be swept out by a stream of dry nitrogen (otherwise the pyrrole reagent becomes sequestered as its hydrochloride). Some of the yields given in this paper could be increased by incorporation of these improvements. An attempt to employ an amide containing a formyl group (III; R = CHO, R_1 = Me, R_2 = Et) was unsuccessful, because the amide gave a dark red solution when mixed with one mole of phosphoryl chloride.

The amides, required as starting materials for syntheses of pyrroketones, were prepared either from the acid chlorides or from the trichloromethylpyrrole (VII) and the amine in benzene solution with subsequent hydrolysis. The latter route is frequently convenient because the crude trichloromethylpyrrole, prepared from the methylpyrrole

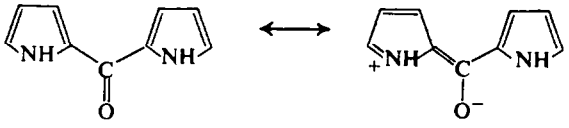


VII VIII

[13] Dr. G. S. Sach (work to be published) had already found that a pyrrolenine, isolated from a Vilsmeier aldehyde synthesis, absorbed at 350 mμ, both as the free base and its hydrochloride. Another closely related case can be found in the work of J. H. Atkinson, R. Grigg and A. W. Johnson, *J. Chem. Soc.* 893 (1964), and J. H. Atkinson and A. W. Johnson, *Ibid.* 2614 (1965). A comprehensive spectral study of Schiff's bases has appeared [R. A. Jones, *Austral. J. Chem.* **17**, 894 (1964)], but they do not exist as pyrrolenines.

[14] Dr. G. S. Sach is responsible for these improvements. Later papers of this series will describe these syntheses.

and sulphuryl chloride, can be used directly. Presumably two of the chlorine atoms are displaced by the amine, and then the resulting imido-chloride derivative (VIII) is hydrolysed. The pyrrolidide analogous to IIIa was used successfully but without any advantage, while an attempted preparation of Va from the piperidide was unsuccessful Attempts to substitute toluene-*p*-sulphonyl chloride, diphenylphosphoryl chloride, or phosphorus pentachloride for phosphoryl chloride were unsuccessful.



IX

The properties of pyrroketones are largely determined by the mesomeric contributions of the two dipolar structures, e.g. IX. Thus, the IR absorption is at remarkably low frequency, ca. 1580 cm^{-1} in chloroform depending on substituents.[15] Furthermore reaction with hydrazine and its derivatives is only achieved under forcing conditions,[6] whereas monopyrrylketones react normally. Perhaps the most striking phenomena are the UV spectra and basicity. The principal absorption band is at ca. 350 mμ (depending on substituents) compared with ca. 300 mμ for simple 2-acylpyrroles,[16] and it is shifted to ca. 420 mμ (e.g. Va) with some intensification by addition of strong acid to a solution in an organic solvent. The absorption of the pyrroketones (Vb) and (Vc) is shifted to even longer wavelengths (ca. 440 mμ) in acidic media. The dissociation constant of the conjugate acid has not been measured, but trifluoroacetic acid (2% in CH_2Cl_2) is sufficiently strong to protonate pyrroketones whereas acetic acid is not. Assuming that the proton is added to the oxygen atom, the conjugate acid of a pyrroketone is a *meso*-hydroxypyrromethene salt, which would be expected to absorb light above 400 mμ.[17] Altogether pyrroketones can be usefully regarded as vinylogues of urea and likened to tropone, in having a strongly polarized, basic carbonyl group through which π-bonds are conjugated.

Reduction of the carbonyl group in pyrroketones, an important step on our schemes of porphyrin synthesis, is greatly influenced by its dipolar character. One pyrroketone (Ia), containing two electron-withdrawing substituents, was reduced by potassium borohydride in boiling methanol to the corresponding pyrromethane. but, in general, pyrroketones are inert under these conditions, although Dr. D. B. Bigley found that the pyrroketone Va is slowly reduced by sodium borohydride in boiling 2-propanol. Brown and Subba Rao[18] have shown that the reactivity of carbonyl compounds towards diborane is the reverse of the usual order, typified by attack of borohydride. Diborane attacks polarized carbonyl groups most easily, because the initial step is coordination with the oxygen atom, as in formation of an oxonium salt. We therefore

[15] The unsubstituted pyrroketone absorbs at 1597 cm^{-1}. [H. Rapoport and C. D. Wilson, *J. Amer. Chem. Soc.* **84**, 630 (1962)], and the low frequency of absorption in substituted pyrroketones has already been remarked.[8] Much earlier the same effect on Raman spectra was reported [G. B. Bonino, R. Manzoni-Ansidei and P. Pratesi, *Z. physikal. Chem.* **25B**, 348 (1934)].

[16] G. H. Cookson, *J. Chem. Soc.* 2789 (1953); U. Eisner and P. H. Gore, *Ibid.* 922 (1958).

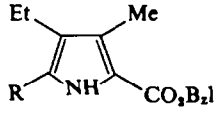
[17] The corresponding *meso*-chloropyrromethene salts absorb at about 505 mμ (observations by Mr. K. M. Smith, Liverpool).

[18] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **82**, 681 (1960).

expected that pyrroketones would form conjugates with the general structure X, and that these would decompose to the pyrromethenes (XI), which would be reduced

X XI

further. When gaseous diborane was passed into a solution of Va in tetrahydrofuran, reduction was complete in 40 min and less than 5% of the intermediate pyrromethene could be detected by its UV spectrum during the reduction. A separate experiment showed that the pyrromethene rapidly formed a borane complex (λ_{max} 435 mμ), which then decayed. The final product from reduction of either the pyrroketone or the pyrromethene was a borane complex (ν_{max} ca. 2300 cm^{-1}) of the pyrromethane. This was best decomposed by brief treatment with boiling methanol, and the pyrromethane could be isolated in 79% yield from the pyrroketone (Va). Many examples of this general reaction will be given in subsequent papers. In order to evaluate its scope in synthesis, the behaviour of a series of simple pyrroles, having different functional groups, was examined. The formylpyrrole (XIIa) was eventually reduced to the



XII

a, R = CHO
b, R = CH_2OH
c, R = CH_3
d, R = CO_2H
e, R = $CO{\cdot}NMe_2$
f, R = $CH_2\overset{+}{N}(Me_2)\overset{-}{B}H_3$
g, R = CH_2Cl
h, R = $CHCl_2$

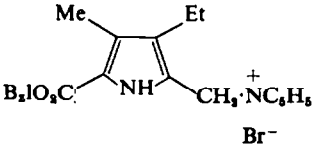
corresponding methylpyrrole (XIIc), but the intermediate hydroxymethylpyrrole (XIIb) could be obtained in good yield by limiting the time of reaction. Similar elimination of the oxygen atom has been observed during reduction of carbonyl groups by diborane in aromatic compounds containing electron-releasing substituents,[19] and the foregoing reduction of pyrroketones to pyrromethanes is analogous. The dimethylamide (XIIe) unexpectedly gave a mixture of XIIb, XIIc, and the very stable borane complex (XIIf) of the dimethylaminopyrrole. A reasonable mechanism can be written for elimination of the dimethylamino group as a complex with borane, and, in accord, the extent of this elimination is increased by a greater proportion of diborane, The simple reduction of amides by diborane without elimination of the amino-group has recently been reported,[20] and elimination is obviously dependent on electron-release by the pyrrole ring.

The pyrroketone system is rather stable towards catalytic hydrogenation, and hence the benzyl ester Va is easily converted into the corresponding acid (Vd). This appeared to undergo thermal decarboxylation, but the two-step process of alkaline iodination and hydrogenolysis was used to obtain the pure product (Ve). Neither

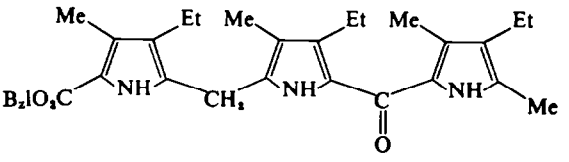
[19] K. M. Biswas, L. E. Houghton and A. H. Jackson, *Tetrahedron* **22**, Suppl. I, 261 (1966), following paper; similar reactions with lithium aluminium hydride have also been observed [E. Leete and L. Marion, *Canad. J. Chem.* **31**, 775 (1953); E. Leete, *J. Amer. Chem. Soc.* **81**, 6023 (1959); R. L. Hinman and S. Theodoropoulos, *J. Org. Chem.* **28**, 3052 (1963)].

[20] H. C. Brown and P. Heim, *J. Amer. Chem. Soc.* **86**, 3566 (1964).

this compound nor the acid (Vd) gave a positive reaction in Ehrlich's test: instead the yellow colour of the oxonium salt appeared. The concentration of acid may be critical, because Osgerby and MacDonald[8] report positive Ehrlich reactions for several 5,5'-unsubstituted pyrroketones, prepared by alkaline decarboxylation. They remark, however, that these compounds failed to undergo many of the usual electrophilic substitutions, and we ascribe this inertia to formation of oxonium complexes. Otherwise the acid Vd behaves normally, for example in undergoing iodination under alkaline conditions. Its dissociation constant is normal (apparent pK_{MCS} 6·62),[21] and correspondingly[2] its lithium salt couples with a pyridinium salt (XIII) to form a tripyrrolic compound (XIV).

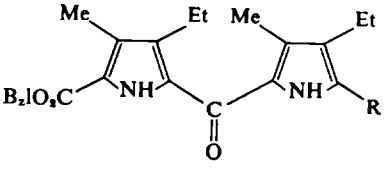


XIII



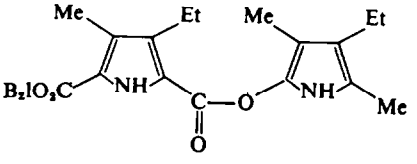
XIV

Conversion of the 5'-methyl group in pyrroketones, such as Va, into a reactive functional group, e.g. chloromethyl, as in XVa, was essential for one of our porphyrin syntheses,[5] and therefore this step was investigated in the case of Va. Analogous



XV

a, R = CH_2Cl
b, R = CH_2OEt
c, R = $CHCl_2$
d, R = CHO



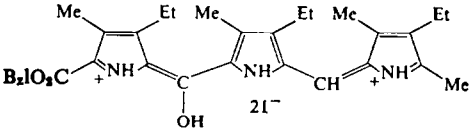
XVI

brominations have been achieved with pyrroketones containing two acyl substituents,[9] but we could not isolate any bromomethyl derivative from Va although some must have been produced, as the reaction mixture yielded 18% of the corresponding ethoxymethyl derivative (XVb) on ethanolysis. Probably bromination was accompanied by fission of the pyrroketone system, a reaction which is dominant in the case of Vb.[6] Seeking a milder, selective halogenating agent, we turned to t-butyl hypochlorite and we examined its action on a simple pyrrole, XIIc. Reaction was too vigorous at room temperature in carbon tetrachloride or ether and it was too slow at −5°, but at 3° it proceeded rapidly and efficiently. Either the monochloro (XIIg) or the dichloro (XIIh) compound could be obtained by adding the appropriate amount of hypochlorite, and the third stage of chlorination could be achieved by finally raising the temperature to 20°. Illumination of the reaction mixtures did not have a noticeable effect. The method was also successful with the pyrroketone (Va) although a mixture of ether and tetrahydrofuran had to be used. The monochloro derivative (XVa) was obtained in 82% yield, and it could be further chlorinated in ethereal solution to XVc in 90% yield; direct double chlorination was less successful, perhaps because some of the t-butyl hypochlorite was destroyed by the tetrahydrofuran. Alternatively the dichloromethyl

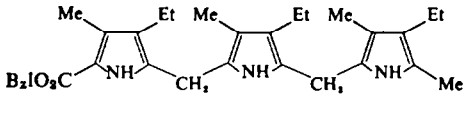
[21] Measured in 2-methoxyethanol; cf. W. Simon and E. Heilbronner, *Helv. Chim. Acta* **38**, 508 (1955).

derivative (XVc) was obtained directly from Va by treatment with 2·2 equivalents of sulphuryl chloride and catalytic amounts of dibenzoyl peroxide. When mono-chlorination of Va was attempted with t-butyl hypochlorite in chloroform containing alcohol stabiliser, reaction was very rapid, even at −6°, but it took the course of a Baeyer-Villiger oxidation. The structure (XVI) of the product was shown particularly clearly by the mass spectrum (Experimental). This unexpected reaction is similar to the brominative fission[6] mentioned above. In absolute chloroform monochlorination of Va with t-butyl hypochlorite gave the expected monochloro product (XVa), though in lower yield than in tetrahydrofuran.

The formyl pyrroketone (XVd) appeared to have considerable potentialities in porphyrin synthesis. It was prepared from the dichloromethyl compound (XVc) by treatment with dimethylamine in dry benzene and subsequent hydrolysis, a reaction which is essentially similar to the preparation of amides mentioned earlier. Condensation of XVd with 2,4-dimethyl-3-ethylpyrrole by means of hydriodic acid yielded the



XVII



XVIII

crystalline dihydriodide XVII, whereas reaction with hydrobromic acid gave the crystalline monohydrobromide. Potassium borohydride in aqueous methanol reduced XVII to XVIII, identified with material prepared by a different route.[1] We had expected reduction solely of the pyrromethene system following the pattern of model experiments (Experimental), and this would have given an isomer of XIV. The reduction of the pyrroketone system may have been due to some liberation of borane, or it may be related to the hydroborating power of sodium borohydride in acetic acid,[22] but a simple pyrroketone (Va) was unaffected by this reducing agent. Neither the condensation of the aldehyde, XVd, to XVII nor the reduction to XVIII proceeded in good yield, and therefore it is not surprising that attempts to exploit such reactions in more complex cases were unrewarding. Hydrogenolysis of XVd afforded the carboxylic acid, which underwent self-condensation in presence of hydriodic acid but only to linear compounds instead of a macrocycle.

EXPERIMENTAL

Monopyrrolic Compounds

Benzyl 5-chloromethyl-4-ethyl-3-methylpyrrole-2-carboxylate

A solution of t-butyl hypochlorite[21] (1·54 ml; 1 mole) in CCl_4 (10 ml) was added during 10 min to a stirred solution of benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (3·3 g) in CCl_4 (125 ml), which had been cooled to 3°. Immediately afterwards the starch-iodide reaction was negative. When the solution was concentrated to 25 ml, the *chloromethylpyrrole* crystallized in colourless needles (3·5 g; 93%), m.p. 105–107°. (Found: C, 66·1; H, 6·1; N, 4·9. $C_{16}H_{18}ClNO_2$ requires: C, 65·9; H, 6·2; N, 4·8%.) A similar reaction in dry ether (200 ml) gave an 80% yield.

[21] J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 595 (1963).
[22] H. M. Teeter and E. W. Bell, *Organic. Syntheses* IV, 125 (1963).

Benzyl 5-dichloromethyl-4-ethyl-3-methylpyrrole-2-carboxylate

A solution of t-butyl hypochlorite (1·5 ml; 2 moles) in dry ether (15 ml) was added during 10 min to a stirred solution of benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (1·5 g) in dry ether (70 ml), cooled to 3°. After a further 10 min the starch-iodide reaction was negative. Evaporation gave a dark brown oil, which gradually solidified. Recrystallization (charcoal) from light petroleum (b.p. 40–60°) afforded the *dichloromethylpyrrole* (1·6 g; 80%) as colourless needles, m.p. 102°. (Found: C, 59·4; H, 5·2; N, 4·1. $C_{16}H_{17}Cl_2NO_2$ requires: C, 58·9; H, 5·3; N, 4·3%.)

Benzyl 5-dimethylaminomethyl-4-ethyl-3-methylpyrrole-2-carboxylate

Dimethylamine was passed into a solution of benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (6·5 g) in dry benzene (100 ml) until it was saturated. The residue left by evaporation was taken up in CH_2Cl_2 (100 ml), which was washed with 10% Na_2CO_3 aq (2 × 100 ml), H_2O (twice), and dried ($MgSO_4$). Evaporation and recrystallization (charcoal) from light petroleum (b.p. 40–60°) afforded the *dimethylaminomethylpyrrole* (3·45 g; 60%) as clusters of colourless needles, m.p. 73°. (Found: C, 72·1; H, 8·1; N, 9·5. $C_{18}H_{24}N_2O_2$ requires: C, 72·0; H, 8·1; N, 9·3%.)

5-Benzyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carbonylchloride

5-Benzyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylic acid (0·50 g) was dissolved in $SOCl_2$ (4 ml) by gentle warming for 30 min. Evaporation gave the crystalline acid chloride, which was recrystallized from light petroleum (b.p. 40–60°) in colourless needles, m.p. 76°. This material was used in the following four experiments.

Methyl 5-benzyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylate

The foregoing acid chloride dissolved in dry MeOH when it was warmed gently. Dilution with water afforded the *methyl ester*, which was recrystallized from light petroleum (b.p. 60–80°), m.p. 76°. (Found: C, 67·5; H, 6·5. $C_{17}H_{19}NO_4$ requires: C, 67·8; H, 6·4%.)

5-Benzyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxanilide

The foregoing acid chloride reacted violently with aniline. The neutral product was extracted by ether, which was washed with dilute HCl, and the gum obtained by evaporation of the ether was crystallized from ether–light petroleum (b.p. 40–60°) in colourless needles of the *anilide*, m.p. 87°. (Found: C, 73·2; H, 6·6; N, 7·7. $C_{23}H_{24}N_2O_3$ requires: C, 72·9; H, 6·1; N, 7·7%.)

Benzyl 4-ethyl-3-methyl-5-pentamethyleneamidopyrrole-2-carboxylate

Sulphuryl chloride (4·7 ml) was added dropwise during 90 min to a stirred solution of 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (5 g) in dry ether (70 ml) at 0°. The solution was kept overnight at 0° and then evaporated under red. press. The sticky residue was taken up in benzene (100 ml) and then treated with piperidine (19 ml). The mixture was stirred for 10 min and then washed with water and dil HCl. The *piperidide*, obtained by evaporation of the benzene, crystallized very slowly, and it was recrystallized from light petroleum (b.p. 60–80°) in colourless prisms (2·4 g, 35%), m.p. 107°. (Found: C, 71·1; H, 7·3; N, 7·9. $C_{21}H_{26}N_2O_2$ requires: C, 71·1; H, 7·4; N, 7·9%.)

Benzyl 4-ethyl-3-methyl-5-tetramethyleneamidopyrrole-2-carboxylate

This *pyrrolidide* was obtained in 31% yield by a preparation analogous to the preceding one, and it had m.p. 88°. (Found: C, 70·5; H, 7·3; N, 8·4. $C_{20}H_{24}N_2O_2$ requires: C, 70·6; H, 7·1; N, 8·2%.)

2-Dimethylamido-3-ethyl-4-methylpyrrole

(a) *By direct decarboxylation.* 5-Dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylic acid (1·6 g)[2] was kept at 240° (N_2) and then distilled at 230°/15 mm. The resulting colourless oil rapidly crystallized and recrystallization from light petroleum (b.p. 60–80°) gave colourless prisms of the *amide* (1·18 g, 90%), m.p. 133°. (Found: C, 66·4; H, 9·0; N, 15·6. $C_{10}H_{16}N_2O$ requires: C, 66·6; H, 9·0; N, 15·5%.)

(b) *Through 2-dimethylamido-3-ethyl-5-iodo-4-methylpyrrole.* A solution of I_2 (5·65 g) in MeOH (30 ml) was added gradually to a well stirred, warm solution of 5-dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylic acid (5 g) and $NaHCO_3$ (5·67 g, 3 eq) in MeOH (ca 110 ml) and water (ca. 15 ml).

The *iodopyrrole* (5·7 g; 83%) was obtained in colourless prisms by recrystallization from aqueous MeOH of the solid precipitated when the solution was poured into water, and recrystallization from light petroleum (b.p. 60–80°) gave colourless needles, m.p. 160°. (Found: C, 39·1; H, 5·1; N, 8·8. $C_{10}H_{15}IN_2O$ requires: C, 39·2; H, 4·9; N, 9·0%.)

Hydrogenation of the foregoing iodopyrrole in EtOH, in which sodium acetate trihydrate was suspended, at 20° and 2 atm with 10% Pd–C gave 2-dimethylamido-3-ethyl-4-methylpyrrole, which was recrystallized from light petroleum (b.p. 60–80°) in colourless prisms, m.p. 131° (85%).

Alternatively a solution of the iodopyrrole in MeOH was boiled for 20 min with excess KBH_4, and the product (91% after recrystallization) was isolated by ether extraction after the reaction mixture had been poured into water.

2-Dimethylamido-3-ethyl-5-formyl-4-methylpyrrole

A solution of the phosphorylchloride–dimethylformamide complex (3·4 g; 3 mole) in CH_2Cl_2 (10 ml) was added during 10 min to a stirred solution of 2-dimethylamido-3-ethyl-4-methylpyrrole (0·9 g) in CH_2Cl_2 (50 ml). After 1 hr the solution was boiled for 1 hr. A solution of sodium acetate trihydrate (25 g) in water (50 ml) was added and the mixture was boiled with vigorous stirring for 1·5 hr. The *formylpyrrole* was obtained by extraction with CH_2Cl_2, which was washed with Na_2CO_3 aq and water, and it was recrystallized from benzene–light petroleum (b.p. 40–60°) in colourless needles (0·72 g, 69%), m.p. 141°. (Found: C, 63·7; H, 7·8; N, 13·7. $C_{11}H_{16}N_2O_2$ requires: C, 63·4; H, 7·7; N, 13·5%.)

2-Dimethylamido-4-ethyl-3,5-dimethylpyrrole

Phosgene gas was passed into a solution of 3-ethyl-2,4-dimethylpyrrole (8 g) in dry ether (125 ml) until the initially formed buff precipitate had dissolved. Evaporation gave a brown solid, which was dissolved in benzene (200 ml). Dimethylamine gas was passed into the solution until it was saturated, and then the neutral product was isolated. Recrystallization from light petroleum (b.p. 60–80°) gave the *dimethylamide* (8·6 g, 70%) as colourless prisms, m.p. 117°. (Found: C, 67·9; H, 9·1; N, 14·1. $C_{11}H_{18}N_2O$ requires: C, 68·0; H, 9·3; N, 14·4%.)

Ethyl 5-dimethylamido-2,4-dimethylpyrrole-3-carboxylate

This *dimethylamide* was obtained from the corresponding acid chloride[10] as in the preceding experiment. Recrystallization from light petroleum (b.p. 40–60°) gave colourless needles (64%), m.p 114°. (Found: C, 60·8; H, 7·5; N, 11·7. $C_{12}H_{18}N_2O_3$ requires: C, 60·5; H, 7·6; N, 11·8%.)

4-(2'-Methoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylic acid

This *carboxylic acid* was obtained from its benzyl ester[1] by hydrogenation at 20° and 1 atm in tetrahydrofuran, containing a little triethylamine, with 10% Pd–C. Recrystallization from AcOEt gave colourless prisms (98%), m.p. 131° dec. (Found: C, 58·7; H, 6·7; N, 6·2. $C_{11}H_{15}NO_4$ requires: C, 58·7; H, 6·7; N, 6·2%.)

Pyrromethanes and Pyrromethenes

Benzyl 3,4'-diethyl-4,3',5-'trimethylpyrromethene-5-carboxylate

(i) 4-Ethyl-3,5-dimethylpyrrole-2-carboxylic acid (prepared by catalytic hydrogenation of the corresponding benzyl ester) (1·29 g) and benzyl 4-ethyl-5-formyl-3-methylpyrrole-2-carboxylate (1·36 g) suspended in EtOH (5 ml) were treated with conc HBr (0·75 ml). The mixture was swirled gently until all the solid had dissolved to give a bright orange solution and heat was evolved. On cooling a red-brown solid separated and was collected and recrystallized from $CHCl_3$–light petroleum (b.p. 40–60°) to give the *pyrromethene hydrobromide* (2·0 g, 86%) as red-brown prisms, m.p. 175°. (Found: C, 62·5; H, 6·4; N, 5·7. $C_{24}H_{29}BrN_2O_2$ requires: C, 63·0; H, 6·3; N, 6·1%.) An equally good yield of the same product may be obtained by using cryptopyrrole in the preparation in place of the carboxylic acid.

The free base was obtained by passing ammonia gas into a warm solution of the hydrobromide (1·2 g) in MeOH (20 ml). After cooling the orange solid which had separated out was collected and recrystallized from MeOH to give the *pyrromethene free base* (0·82; 85%) as orange prisms, m.p. 90°. (Found: C, 76·5; H, 7·7; N, 7.3: $C_{24}H_{28}N_2O_2$ requires: C, 76·5; H, 7·4; N, 7·4%.) λ_{max} (ε_{max}): 409 mμ (31,400) (EtOH); 485 (52,700) (EtOH + HCl).

(ii) Benzyl 3,4'-diethyl-4,3',5-trimethylpyrromethane-5-carboxylate (300 mg) in dry ether (50 ml) at 3° was treated dropwise with t-butyl hypochlorite (0·12 ml; 1 equiv) in dry ether (10 ml) during 10 min with stirring. An orange crystalline solid separated out during the addition, and a starch-iodide test immediately after the addition was negative. The orange pyrromethene hydrochloride was filtered off and converted into the free base as above. Yield: 170 mg, 66%, m.p. 91°.

Benzyl 3,4'-*diethyl*-4,3',5'-*trimethylpyrromethane*-5-*carboxylate*

With Dr. G. S. Sach. The corresponding pyrromethene hydrobromide (3·5 g) in MeOH (100 ml) was treated with solid $NaBH_4$ (2·0 g) and warmed on the water bath until the orange colour was discharged. Water was then added and the product extracted into ether and dried ($MgSO_4$). After evaporation of the solvent the residue was crystallized from aqueous MeOH (or light petroleum (b.p. 60–80°)) to give the required pyrromethane (3·0 g, 90%) as prisms, m.p. 123°. The identity of the product was confirmed by mixed m.p. and spectroscopic comparisons with authentic material.

Diethyl 3,3',5,5'-*tetramethylpyrromethane*-4,4'-*dicarboxylate*

(i) Diethyl 3,3',5,5'-tetramethylpyrromethene-4,4'-dicarboxylate hydrochloride (420 mg) suspended in MeOH (200 ml) was heated under reflux with excess KBH_4 for 30 min and the product worked up as above. The required methane (360 mg, 94%) was crystallized from MeOH and formed colourless prisms, m.p. 223°. (Lit.[24,25] m.p. 223°).

(ii) Diethyl 3,3',5,5'-tetramethylpyrroketone-5,5'-dicarboxylate (200 mg) in MeOH (50 ml) was treated with excess KBH_4 (500 mg) and the mixture heated under reflux for 1 hr. Water (50 ml) was then added and most of the MeOH was evaporated under red press. The product separated as an almost colourless solid, and was recrystallized from aqueous MeOH to give the pyrromethane (120 mg, 60%) as colourless prisms m.p. 223°. The identity of the product was confirmed by comparison with the sample prepared as in (i), and by its synthesis from ethyl 2,4-dimethylpyrrole-3-carboxylate and formaldehyde.[24,25]

Ethyl 3,4'-*diethyl*-3',4,5'-*trimethylpyrromethane*-5-*carboxylate*

Ethyl 4-ethyl-5-formyl-3-methylpyrrole-2-carboxylate (4·0 g) and cryptopyrrole (2·35 g) were suspended in saturated methanolic HCl (30 ml) and warmed gently on the water bath for 5 min. The deep red solution obtained was made just alkaline with 2N NaOH, sodium dithionite (4·0 g) added and the solution stirred vigorously for 1 hr. The colourless solution was neutralized with dil HCl and most of the MeOH removed by distillation under red press. The solid, which had separated, was collected and recrystallized from aqueous MeOH to give ethyl 3,4'-diethyl-3',4,5'-trimethylpyrromethane-5-carboxylate (4·6 g, 75%) as colourless needles, m.p. 139°.

Pyrroketones and Pyrrocolls from Acid Chlorides

4,4'-*Diethoxycarbonyl*-3,5,3',5'-*tetramethylpyrroketone* (Ia)

4-Ethoxy-3,5-dimethylpyrrole-2-carbonyl chloride was obtained from 3-ethoxycarbonyl-2,4-dimethylpyrrole (0·50 g) in anhydrous ether by the action of phosgene. This crystalline solid was suspended in dry benzene (80 ml), to which a second portion (0·50 g) of 3-ethoxycarbonyl-2,4-dimethylpyrrole was added. The mixture was heated under reflux for 30 min, and the pyrroketone (80%), m.p. 221°,[10] was obtained by concentration and then recrystallization from MeOH.

4,4'-*Diethoxycarbonyl*-3,5,3',5'-*tetramethylpyrrocoll* (IIa)

3-Ethoxycarbonyl-2,4-dimethylpyrrole (1·0 g) was converted into 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carbonyl chloride, which was dissolved in dry pyridine (5 ml) and added to another portion of the same pyrrole (1·0 g) in dry pyridine (15 ml). The mixture was warmed on a steam bath for 20 min before being cooled and poured into water containing a little HCl. The precipitated *pyrrocoll* was recrystallized from MeOH in colourless needles (0·71 g, 30%), m.p. 280°. (Found: C, 62·3; H, 5·5; N, 7·0. $C_{30}H_{32}N_2O_6$ requires: C, 62·2; H, 5·7; N, 7·25%.) ν_{max} (CO) in nujol: 1730, 1710 cm^{-1}.

[24] O. Piloty and E. Stock, *Ber. Dtsch. Chem. Ges.* **47**, 1124 (1914).
[25] W. Küster, *Z. physiol. Chem.* **121**, 141 (1922).

4,4'-Diacetyl-3,3',5,5'-tetramethylpyrrocoll (IIb)

A slow stream of phosgene was passed into an ether solution of 3-acetyl-2,4-dimethylpyrrole (500 mg) during 30 min at 20°. The 4-acetyl-3,5-dimethylpyrrole-2-carbonyl chloride which crystallized out (670 mg) was taken up in dry benzene (100 ml), and added to a suspension of 3-acetyl-2,4-dimethylpyrrole (460 mg) in dry benzene (20 ml). The mixture was heated under reflux for 30 min the solvent then removed under red press, and the residual dark red gum triturated with MeOH. An insoluble colourless crystalline solid was obtained, which on recrystallization from MeOH gave the *pyrrocoll* (230 mg, 20%) as needles, m.p. 215°. (Found: C, 66·1; H, 5·3; N, 8·5. $C_{18}H_{18}N_2O_4$ requires: C, 66·2; H, 5·6; N, 8·6%.)

This pyrrocoll was also obtained by treatment of 4-acetyl-3,5-dimethylpyrrole-2-carbonyl chloride in pyridine with 3-acetyl-2,4-dimethylpyrrole in pyridine following the procedure described for the analogous pyrrocoll (IIa). ν_{max}(CO) in nujol mull: 1720, 1680 cm^{-1}.

5,5'-Dibenzyloxycarbonyl-3,3'-diethyl-4,4'-dimethylpyrrocoll

In the preparation of 5-benzyloxycarbonyl-2,4-dimethylpyrrole-2-carboxylic acid by treatment of the corresponding 2-methylpyrrole with sulphuryl chloride followed by alkali [cf.[8]] an alkali insoluble gummy by-product was obtained. This material was extracted into ether, and chromatographed on neutral alumina to give a light brown oily product which slowly crystallized on keeping. After recrystallization from benzene–light petroleum (b.p. 60–80°) the *pyrrocoll* (9%) was obtained as colourless needles, m.p. 140°. (Found: C, 71·5; H, 5·7; N, 5·4. $C_{32}H_{30}N_2O_6$ requires: C, 71·4; H, 5·6; N, 5·2%.) ν_{max} (CO) in nujol: 1730, 1700 cm^{-1}.

4-Ethoxycarbonyl-4'-ethyl-3,3',5,5'-tetramethylpyrroketone (Ic)

(i) EtMgBr (prepared from Mg (2·0 g) and EtBr (1·25 g)) in dry ether (50 ml) was treated with 3-ethoxycarbonyl-2,4-dimethylpyrrole (2·0 g) in dry ether (10 ml) at 20°. When the addition was complete the mixture was warmed briefly to complete reaction, and then decanted from unreacted Mg.

Meanwhile cryptopyrrole (1·51 g) in dry ether (25 ml) was treated with a slow stream of phosgene for 30 min. After removal of solvent *in vacuo* 4-ethyl-3,5-dimethylpyrrole-2-carbonyl chloride was obtained as a crystalline solid. The latter was taken up in a fresh portion of dry ether (25 ml), cooled to 0°, and added slowly (30 min) to the well stirred solution of the foregoing pyrryl Grignard reagent. The mixture was stirred for a further hour, and then the brown complex was decomposed by addition of ice and NH_4Cl. The ether layer was separated, and washed with water, when a solid separated out at the interface. On recrystallization from MeOH this solid gave the *pyrroketone* (0·80 g, 21%) as prisms, m.p. 236°. (Found: C, 67·7; H, 7·5; N, 9·1. $C_{16}H_{24}N_2O_3$ requires: C, 68·1; H, 7·6; N, 8·7%.) ν_{max} (CO) in nujol mull: 1678, 1555 cm^{-1}.

(ii) In another experiment similar to (i) the pyrryl Grignard reagent was added slowly to the acyl chloride in benzene. After working up as above the benzene layer was separated, dried ($MgSO_4$) and evaporated to dryness. The residual gum was triturated with benzene, and the resulting solid crystallized from MeOH to give the pyrroketone (29%) m.p. 236°.

(iii) Cryptopyrrole (1·0 g) in dry ether (25 ml) was added slowly (30 min) with stirring to a solution of EtMgBr in dry ether (25 ml) (prepared from EtBr (900 mg) and excess Mg (2·0 g)). Benzene (100 ml) was then added, the ether removed by distillation, and the solution decanted from unreacted Mg. $CdCl_2$ (750 mg) was added to the well stirred solution and the mixture heated on the steam bath for 1 hr (i.e. until a drop of the solution gave a negative Gilman test). The dipyrryl cadmium derivative thus prepared was added to 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carbonyl chloride (prepared from 1·35 g of the corresponding pyrrole and phosgene) in dry benzene (50 ml) and the mixture heated under reflux for 2 hr with stirring. The resulting brown solution was decomposed by treatment with dil H_2SO_4, and the organic layer separated, dried ($MgSO_4$) and evaporated to dryness. The residual solid, after crystallization from MeOH, gave the pyrroketone as prisms (760 mg, 30%) m.p. 236°.

Benzyl 3,4'-diethyl-4,3',5'-trimethylpyrroketone-5-carboxylate (Va)

5-Benzyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carbonyl chloride (prepared from 2·0 g of the corresponding 2-carboxylic acid) in dry benzene (50 ml) was treated with the dipyrryl cadium prepared from cryptopyrrole (0·85 g) as in the foregoing preparation of Ic (method (iii)). The red gummy

product was isolated in the same manner and triturated with methanol to give a colourless solid which was recrystallized from benzene–light petroleum (b.p. 60–80°) to give the *pyrroketone* (0·84 g, 32%) as colourless prisms, m.p. 184°. (Found: C, 73·4; H, 7·2; N, 7·2. $C_{34}H_{38}N_2O_3$ requires: C, 73·4; H, 7·2; N, 7·1%.) ν_{max} (CO) in chloroform: 1690, 1580 cm^{-1} λ_{max} (ε_{max}): 348 mμ (21,200) in CH_2Cl_2; 422 mμ (32,200) in CH_2Cl_2 containing 2% trifluoroacetic acid. NMR spectrum* ($CDCl_3$): CH_3CH_2—, 8·98*t*, 7·65*q*, 8·93*t*, 7·35*q*; CH_3—, 8·08, 7·80, 7·69; $C_6H_5CH_2O$—, 2·65, 4·73; N*H*—, 0·83, 0·54. Mass spectrum† (MS9—direct inlet): 393 (28), 392 (85), 377 (21), 363 (5), 283 (10), 270 (20), 269 (95), 256 (10), 255 (15), 241(14), 240 (15), 226 (10), 178 (11), 162 (9), 160 (11), 150 (14), 134 (10), 123 (18), 122 (11), 21 (6), 108 (15), 91 (100). Metastable peaks 363 (392 → 377), 336 (392 → 363), 216 (269 → 241).

Pyrroketones from Amides and Phosphoryl Chloride

In the following experiments, spectroscopic sampling was extensively employed to follow the course and extent of reaction. The samples were most conveniently obtained by use of a graduated hypodermic syringe inserted through a serum cap in a side neck of the reaction flask (as most of the reactions were carried out in an atmosphere of N_2). Best yields were obtained by use of scrupulously dried solvents, especially for dilution of the samples removed for spectroscopic estimation (as the amide–phosphoryl chloride complexes are rapidly decomposed by traces of moisture).

Benzyl 3,4-*diethyl*-3',4,5'-*trimethylpyrroketone*-5-*carboxylate* (Va)

(i) Compound IIIa (10·0 g) in dry ethylene chloride (120 ml) (λ_{max} 282 mμ, ε_{max} 21,000) was heated under reflux with $POCl_3$ (3 ml, 1 mole) until spectroscopic analysis of successive samples showed that the new peak which developed at 374 mμ had reached a maximum (ca. 15,000), and the extinction at 282 mμ had fallen to a minimum value. The solution was cooled to room temp, the flask flushed with N_2, and cryptopyrrole (4·0 g) in dry ethylene chloride (20 ml) added. The resultant solution was then stirred at 25°, until spectroscopic analysis showed that a new peak developing at 402 mμ had reached a maximum (ca. 1 hr, ε_{max} 7,900). (Heating the solution under reflux at this stage did not result in any significant increase in the extinction at 402 mμ). Sodium acetate trihydrate (60 g) in water (100 ml) was then added, and the mixture heated under reflux with vigorous stirring for 2 hr. After cooling the organic layer was separated, and the aqueous layer extracted with $CHCl_3$ (50 ml). The combined organic layers were washed with 10% Na_2CO_3aq, then with water, dried ($MgSO_4$) and evaporated to dryness. The residual dark brown oil crystallized on trituration with MeOH, and was recrystallized from $CHCl_3$–light petroleum (b.p. 40–60°) to give the required pyrroketone (6·6 g, 53%), m.p. 184°. This was identical (mixed m.p., IR, UV, NMR) with the sample prepared by the Grignard reactions above.

(ii) *With Dr. G. S. Sach.* Benzyl 5-dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylate (10 g) was dissolved in warm $POCl_3$ (15 ml), and spectroscopic analysis showed that the amide had been converted into the complex (λ_{max} 374 mμ, ε_{max} ~15,000). Excess $POCl_3$ was removed by evaporation under red press with ethylene dibromide (10 ml) added as a "chaser", and the residual oily complex was taken up in CH_2Cl_2 (15 ml). After treatment with cryptopyrrole (4·35 g) in CH_2Cl_2 (15 ml), and work-up as in (i) above, the pyrroketone (9·7 g, 80%) was obtained as pale yellow prisms, m.p. 182°.

(iii) In preliminary experiments the pyrrole-2-pyrrolidide analogous to IIIa was coupled with cryptopyrrole and gave the same pyrroketone (Va) in 36% yield by a method essentially similar to (i). The corresponding pyrrole-2-piperidide gave only a red viscous oil under the same conditions, which could not be crystallized.

(Ia) *and* (Ic)

These two pyrroketones were also prepared in the course of preliminary experiments on the Vilsmeier-Haack method by coupling 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-dimethylamide with ethyl 2,4-dimethylpyrrole-3-carboxylate and cryptopyrrole respectively. The methods used were essentially the same as those described in method (i) for Ia above, and the yields were 28%,

* In this and subsequent NMR spectra the peaks are singlets unless otherwise specified, i.e. *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet. The positions are given in τ-values.

† Intensities of the fragment ions are given in brackets relative to the most intense peak (base peak) as 100%. Only the more intense ions have been recorded.

and 21% respectively. These yields could almost certainly be improved since at the time these preparations were carried out the spectroscopic methods for following the reactions had not been fully developed.

4-Ethyl-4'-(2"-methoxycarbonylethyl)-3,5,3',5'-tetramethylpyrroketone (Vc)

4-Ethyl-3,5-dimethylpyrrole-2-dimethylamide (485 mg) was dissolved in warm $POCl_3$ (5 ml) to give the complex (λ_{max} 380 mμ, ε_{max} 27,000). Excess $POCl_3$ was removed by distillation under red press with ethylene bromide (10 ml) as a chaser. The orange oily complex was taken up in CH_2Cl_2 (30 ml) and the solution heated under reflux in a slow stream of N_2 during the addition (10 min) of 3-(2'-methoxycarbonylethyl)-2,4-dimethylpyrrole (prepared by thermal decarboxylation of the corresponding 5-carboxylic acid (663 mg)) in CH_2Cl_2 (20 ml). Heating was continued for 1½ hr until spectroscopic analysis showed that the new peak developing at 408 mμ had reached its maximum value (ε_{max} 18,000). The solvent was removed *in vacuo* and the residual oil hydrolysed by heating under reflux with 10% Na_2CO_3aq (50 ml) for 1 hr with vigorous stirring. The product was extracted with $CHCl_3$, and the extracts dried ($MgSO_4$) and evaporated to dryness. After chromatography on alumina (Brockmann grade 3) in benzene an orange oil was obtained which solidified on trituration with light petroleum (b.p. 40–60°) to give an amorphous solid (320 mg, 39%) m.p. 104°. Difficulty was experienced in attempts to recrystallize this compound for analysis but spectroscopic evidence clearly supports the assigned structure. ν_{max} (CO); mull, 1570, 1740 cm^{-1}. λ_{max} 355 mμ, ε_{max} 15,000 (CH_2Cl·CH_2Cl). λ_{max} 440 mμ, ε_{max} 28,000 (CH_2Cl·CH_2Cl + HCl). NMR spectrum ($CDCl_3$): CH_3CH_2— 8·95*t*, ca. 7·4; CH_3—, 7·88 (2), 7·80 (2); —CH_2CH_2—, ca. 7·5*m*, ca. 7·4*m*; CH_2O, 6·35; NH, 0·80, 0·70 τ.

4,4'-Diethyl-3,3',5,5'-tetramethylpyrroketone (Vb)

(i) *With Mr. K. M. Smith.* 4-Ethyl-3,5-dimethylpyrrole-2-dimethylamide (8·0 g) was converted into its $POCl_3$-complex (λ_{max} 380 mμ; ε_{max} 24,000) by the second method described in the preparation of Va, and taken up in CH_2Cl_2 (20 ml). Cryptopyrrole (5·6 g) was then added and the mixture heated under reflux for 1½ hr. The brown solution (λ_{max} 408 mμ; ε_{max} 18,000) formed, was stirred vigorously with 10% Na_2CO_3aq (100 ml) and heated under reflux for 2 hr. The required pyrroketone, which precipitated from the solution as a yellow crystalline solid, was filtered off, and the organic layer separated. The aqueous layer was extracted with more CH_2Cl_2 (50 ml) and the combined extracts washed with water, dried ($MgSO_4$) and concentrated to small bulk. The yellow solid which crystallized out was combined with the first crop, and the total product recrystallized from CH_2Cl_2 to give the pyrroketone (10·1 g, 89%) as pale yellow needles, m.p. 205–207°. (Lit.[27] m.p. 207°.) ν_{max} (CO); $CHCl_3$, 1575; mull, 1575 cm^{-1} λ_{max} 288, 357 mμ. ε_{max} 11,700, 25,000 (CH_2Cl_2); λ_{max} 440 mμ; ε_{max} 55,700 (CH_2Cl_2 containing 2% CF_3CO_2H). NMR ($CDCl_3$): CH_3CH_2, 8·93*t* (2), 7·61*q* (2); CH_3, 7·87 (2), 7·78 (2); NH, 1·17 (2) τ.

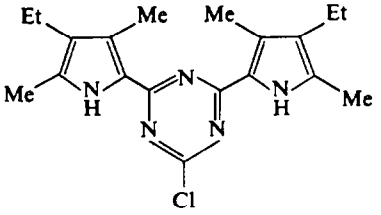
(ii) In preliminary experiments, using essentially the same but more dilute conditions than in (i), the hydrolysis was carried out with boiling 15% AcONaaq (instead of Na_2CO_3aq). The product (extracted with CH_2Cl_2) was a dark brown oil which was dissolved in a little hot MeOH. On cooling the pyrroketone (9%) crystallized as pale yellow needles, m.p. 205–207°. Evaporation of the filtrate gave a dark brown gum which was taken up in the minimum volume of hot light petroleum (b.p. 40–60°). On cooling, and scratching, an orange yellow crystalline solid separated which was shown by its spectral characteristics to be 4,4'-diethyl-mesodimethylamino-3,3',4,4'-tetramethylpyrromethene (23%). ν_{max} (C=N); $CHCl_3$. 1575; mull, 1585 cm^{-1} (cf. cryptopyrromethene, ν_{max} (C=C); $CHCl_3$, 1615; mull, 1605 cm^{-1}). λ_{max} 408 mμ; ε_{max} 19,000 (in both CH_2Cl_2 and 10% CF_3CO_2H—CH_2CO_2H). NMR spectrum ($CDCl_3$): CH_3CH_2, 8·99*t* (2), 7·78*q* (2); CH_3, 8·37 (2), 7·74 (2); CH_3—N, 6·43 (2); NH, not observed. Mass spectrum (MS9—direct inlet): 299 (M^+) (16), 284 (14), 255 (4), 241 (16), 212 (6), 163 (26), 123 (39), 122 (10), 109 (10), 108 (100). Metastable peaks: 270 (299 → 284), 186·5 (241 → 212). Attempts to purify this compound for analysis were unsuccessful, but hydrolysis with Na_2CO_3aq gave the pyrroketone (85%), m.p. 207°.

In preliminary experiments on the activation of pyrrole amides by reagents other than $POCl_3$, the use of *p*-toluenesulphonyl chloride, PCl_5 and cyanuryl chloride[26] were investigated. No crystalline product was obtained by use of *p*-toluenesulphonyl chloride in the attempted preparation of Ic, but

[26] H. Gold, *Angew. Chem.* **24**, 956 (1960).

[27] H. Fischer and H. Orth, *Liebigs Ann.* **489**, 73 (1931).

Va was obtained in 21% yield by the use of PCl_5. In an attempt to prepare Va using cyanuryl chloride (following a method similar to that described for Va (i)) a yellow crystalline product was obtained. On recrystallization from MeOH it formed yellow needles, m.p. 186°, and was shown to be identical with the free base of the *adduct* formed directly from cryptopyrrole (2 moles) with cyanuryl chloride (1 mole), i.e.



(Found: C, 63·2; H, 6·4; N, 18·8. $C_{19}H_{24}ClN_5$ requires: C, 63·7; H, 6·7; N, 19·5%.)

Reductions with Diborane

Diborane reductions were carried out using an external generator similar to the one described by Brown and Subba Rao.[18] The generator consisted of a 50 ml 2-necked flask equipped with a pressure equilibrated dropping funnel fitted with a N_2 inlet, an outlet for diborane and a magnetic stirrer. The diborane outlet was connected by a short length of Tygen tubing to a sintered glass bubbler that fitted into the reaction vessel through a ground glass joint (B29). The outlet from the reaction flask was connected to a wash bottle containing acetone to absorb any diborane that escaped from the reaction solution. The reaction flask was a cylindrical glass vessel fitted at its upper end with the B29 ground glass joint, and with a short side-arm just above the level that 25 ml liquid would occupy. The side-arm was sealed with serum cap.

Method. The system was flushed with N_2 and a solution of BF_3-etherate (3·2 ml) in diglyme (10 ml) placed in the generator and a solution of $NaBH_4$ (0·38 g) in diglyme placed in the dropping funnel. The compound to be reduced was then placed in the reaction vessel in tetrahydrofuran (25 ml) solution. The system was flushed again with N_2, and a very slow stream of N_2 allowed to continue flowing through. The $NaBH_4$ solution was then added dropwise over 15 min to the magnetically stirred solution of BF_3, and the diborane generated passed over into the reaction vessel through the sintered glass bubbler. After the addition was complete residual diborane was driven into the reaction vessel by a slightly faster stream of N_2.

Samples for spectroscopic analysis were withdrawn through the serum cap with a hypodermic syringe, and diluted with EtOH (to decompose excess diborane), to the required concentration (50 μmoles/litre) for a 1 cm cell.

For reactions in which a solution of diborane in tetrahydrofuran was added to a solution of the compound to be reduced a modified reaction vessel was used. This consisted of a tube 20 cm × 1 cm, fitted as before with a sintered glass bubbler through a B29 ground glass joint, and with a tap (Teflon key) fitted to the bottom. The tap was connected by a B19 ground glass joint to a 100 ml flask, and between the tap and the joint was a pressure equilibrating side-arm connected by Tygon tubing to the outlet from the vessel containing the bubbler. The solution of diborane in tetrahydrofuran could thus be added to the solution of the compound to be reduced while the whole system was kept under N_2.

In all the reactions described below the quantities of reagents used for generating the diborane were the same. The BF_3-etherate was distilled immediately before use. The diglyme was distilled from LAH under red. press., and the tetrahydrofuran dried over Na-wire and distilled from LAH directly into the reaction vessel.

Reduction of benzyl 3,4'-diethyl-4,3',5'-trimethylpyrroketone-5-carboxylate (Va)

The pyrroketone (300 mg) in dry tetrahydrofuran (25 ml) was reduced with diborane as described above. Samples for spectroscopic analysis showed the gradual reduction of the pyrroketone (λ_{max} 348 mμ, ε_{max} 21,000) to the corresponding pyrromethane (λ_{max} 286 mμ, ε_{max} 17,000). At no stage was more than a trace of the corresponding pyrromethene (λ_{max} 409 mμ, ε_{max} 32,000) or its borane complex (λ_{max} 435 mμ) observed in the samples. (A faint yellow colour due to the pyrromethene was usually observed in the solution immediately after beginning the reduction, but this rapidly faded.)

The reduction of the pyrroketone was complete in about 40 min, and MeOH (5 ml) was then added to decompose excess diborane. When the vigorous effervescence had ceased the solvent was removed under red. press. and the residual oil heated under reflux for 5 min with MeOH (25 ml) to decompose borane complexes. The MeOH was evaporated and the residue extracted with light petroleum (b.p. 40–60°), insoluble material being removed by filtration. After concentration of the petroleum extracts by distillation, a pale orange oil was obtained which crystallized slowly, and was recrystallized from light petroleum (b.p. 40–60°) to give the benzyl 3,4'-diethyl-4,3',5'-trimethylpyrromethane-5-carboxylate (230 mg, 79%) as needles, m.p. 122°.

Reduction of benzyl 3,4'-diethyl-4,3',5'-triethylpyrromethene-5-carboxylate

The pyrromethene (376 mg) in dry tetrahydrofuran (25 ml) was reduced by diborane by the method outlined above. Spectroscopic analysis showed the initial conversion of the pyrromethene into its borane complex (λ_{max} 435 mμ) and reduction was complete in about 40 min. The reaction mixture was worked up as in the foregoing experiment and gave the corresponding pyrromethane (240 mg, 64%) as needles, m.p. 122–123°.

Reduction of benzyl 4-ethyl-5-formyl-3-methylpyrrole-2-carboxylate (XIIa)

(i) The formylpyrrole[2] (271 mg) in tetrahydrofuran (25 ml) was reduced with diborane. After 1·5 hr the reaction mixture was poured into water (250 ml), the suspension made alkaline with 10% Na_2CO_3aq, and extracted with ether (2 × 100 ml). The combined ethereal layers were washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The pink solid residue was sublimed at 100°/1 mm to give benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (40 mg, 16%) m.p. (and mixed m.p. with an authentic sample) 104°.

(ii) Diborane was passed into dry tetrahydrofuran (25 ml) over 15 min and the solution immediately added to the 5-formylpyrrole (300 mg) in dry tetrahydrofuran (20 ml) under N_2. After shaking to mix the solution thoroughly the mixture was allowed to stand for 5 min and then excess diborane was decomposed by cautious addition of water (10 ml). The tetrahydrofuran was removed under red. press., CH_2Cl_2 and 10% Na_2CO_3aq added, and the organic layer separated washed with water and dried ($MgSO_4$). The solvent was evaporated under red. press. to give an oil which solidified on scratching. The latter was crystallized from light petroleum (b.p. 60–80°) to give *benzyl 4-ethyl-5-hydroxymethyl-3-methylpyrrole-2-carboxylate* (290 mg, 93%) as needles, m.p. 103°. (Found: C, 70·1; H, 6·9; N, 4·9. $C_{16}H_{19}NO_3$ requires: C, 70·3; H, 7·0; N, 5·1%.) λ_{max} (EtOH), 280 mμ, ε_{max} 19,800.

Reduction of 5-benzyloxycarbonyl-3-ethyl-4-methyl-4-methylpyrrole-2-carboxylic acid (XIId)

The pyrrole carboxylic acid (575 mg) in dry tetrahydrofuran (25 ml) was reduced with diborane. After 1·5 hr the solvent was removed under red. press., and the residual oil dissolved in glacial AcOH (5 ml) and water (25 ml). The solid which precipitated was extracted with CH_2Cl_2, and the latter washed with 10% Na_2CO_3aq, then with water and dried ($MgSO_4$). After evaporation of the CH_2Cl_2 the residual gelatinous solid was extracted with light petroleum (b.p. 60–80°) and insoluble material filtered off. The extracts were evaporated to dryness and the colourless oil obtained, crystallized on trituration with light petroleum (b.p. 40–60°). After recrystallization from the same solvent benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (180 mg, 35%) was obtained as needles, m.p. 100°, raised to 103° by sublimation at 100°/1 mm.

Reduction of benzyl-5-dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylate (XIIe)

(i) The dimethylamidopyrrole (300 mg) in dry tetrahydrofuran (25 ml) was shaken gently whilst being treated with diborane and the solution was then kept for 2 hr. The reaction mixture was worked up in essentially the same manner as for XIId above, and after evaporation of the CH_2Cl_2 extracts the residual orange oil was crystallized from light petroleum (b.p. 60–80°) to give *benzyl 5-dimethylaminomethyl-4-ethyl-3-methylpyrrole-2-carboxylate borane complex* (120 mg, 40%) as needles, m.p. 165°, raised to 172° on recrystallization from benzene–light petroleum (b.p. 40–60°). (Found: C, 69·0; H, 8·8; N, 8·8. $C_{18}H_{27}BN_2O_2$ requires: C, 68·8; H, 8·7; N, 8·9%.) This complex was identified by the characteristic B—H stretching bands in the IR spectrum and by comparison with an authentic sample prepared from the corresponding free amine (see below).

The mother liquors from the crystallization of the borane complex were evaporated to give an oil which was dissolved in a little hot light petroleum (b.p. 40–60°). On cooling a solid separated, which

after recrystallization from light petroleum (b.p. 40–60°) gave benzyl 4-ethyl-5-hydroxymethyl-3-methylpyrrole-2-carboxylate (60 mg, 20%) as needles m.p. 100°.

After removal of solvent from the mother liquors of the hydroxymethylpyrrole a gum was obtained which solidified on trituration with light petroleum (b.p. 40–60°). The solid was recrystallized from the same solvent to give benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (65 mg, 23%) as needles m.p. 100°.

The identities of the latter two products were confirmed by mixed m.p. and spectral comparisons with authentic material.

(ii) In another experiment the dimethylamidopyrrole was treated (under N_2) with a solution of diborane (i.e. the second method of reduction described above) and the mixture kept for 2 hr with occasional shaking. After working up as before the corresponding 5-dimethylaminopyrrole borane complex, the 5-hydroxymethylpyrrole and the 5-methylpyrrole were obtained in 20%, 52% and 8% yields respectively.

Preparation of benzyl 5-dimethylaminomethyl-4-ethyl-3-methylpyrrole-2-carboxylate borane complex (XIIf)

Benzyl 5-dimethylaminomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·0 g) in dry tetrahydrofuran (40 ml) was treated with diborane [generated from BF_3-etherate (4·8 ml) in diglyme (15 ml) and $NaBH_4$ (0·57 g) in diglyme (15 ml)] over 15 min. After being kept for a further 10 min under N_2 the solvent and excess diborane were removed under red. press., and the residual solid crystallized from benzene–light petroleum (b.p. 40–60°) to give the borane complex (1·0 g, 96%) as needles m.p. 172°. ν_{max} (B—H) ($CHCl_3$): 2360, 2320, 2260 cm^{-1}.

This complex was unaffected by treatment with dry HCl in dry benzene (30 min), or by heating under reflux in triethylamine (1 hr), being recovered essentially unchanged in over 90% yield. However the complex (100 mg) was decomposed by heating in pyridine (2 ml) at 100° for 2 hr. After cooling, the pyridine solution was poured into water (200 ml) to give an oily suspension which slowly solidified (2 hr). The solid was recrystallized from light petroleum (b.p. 40–60°) to give the 5-dimethylaminomethylpyrrole free base (90 mg, 94%) as colourless needles, m.p. and mixed m.p. with an authentic sample, 74°.

Derivatives of Va

3,4′-*Diethyl*-3′,4,5′-*trimethylpyrroketone*-2-*carboxylic acid* (Vd).

The pyrroketone (Va; 1·50 g) in tetrahydrofuran (100 ml) and triethylamine (0·1 ml) was hydrogenated over 10% Pd–C (150 mg) at 25° and 1 atm. Hydrogenolysis was complete in 15 min and after removal of catalyst and solvent the *pyrroketone carboxylic acid* (1·15 g, 100%) was obtained as tiny needles, m.p. 212° (with dec) after recrystallization from benzene for analysis. (Found: C, 67·8; H, 7·6; N, 9·0. $C_{17}H_{23}N_3O_3$ requires: C, 67·5; H, 7·3; N, 9·3%.) This acid did not give a positive reaction with Ehrlich's reagent, even on heating.

3,4′-*Diethyl*-5-*iodo*-3′,4,5′-*trimethylpyrroketone*

The foregoing carboxylic acid (2·17 g) was dissolved in MeOH (130 ml) and water (80 ml) and $NaHCO_3$ (1·84 g) added. The latter was dissolved by warming and I_2 (1·84 g) in MeOH (75 ml) was added slowly with stirring. The colour of the I_2 was immediately discharged on addition and the solution was kept for 2 hr at 25° before pouring into water (1 l.). The solid product precipitated was taken up in ether and chromatographed in ether on neutral alumina. A pale yellow band was eluted and after evaporation of solvent the residual gum crystallized on trituration with light petroleum (b.p. 60–80°). On recrystallization from light petroleum (b.p. 60–80°) the *iodopyrroketone* (1·20 g, 43%) was obtained as microprisms, m.p. 136°. (Found: C, 49·9; H, 5·5; N, 7·6. $C_{16}H_{21}INO_3$ requires: C, 50·0; H, 5·5; N, 7·3%.)

3,4′-*Diethyl*-3′,4,5′-*trimethylpyrroketone* (Ve)

The foregoing iodopyrroketone (500 mg) in EtOH (50 ml) was hydrogenated in a glass pressure bottle at 2 atm and 25° over 10% Pd–C (100 mg) and sodium acetate trihydrate (500 mg). After shaking overnight the catalyst was filtered off and the solution poured into water (200 ml). The yellow

solid precipitated was collected and recrystallized from light petroleum (b.p. 60–80°) to give the required *pyrroketone* (Ve; 270 mg, 80%) as prisms, m.p. 166°. (Found: C, 74·2; H, 8·5; N, 10·9. $C_{16}H_{22}N_2O$ requires: C, 74·5; H, 8·5; N, 10·9%.) With Ehrlich's reagent this compound gave only a yellow colour due to protonation of the carbonyl group, but even on heating no purple colour was observed. NMR spectrum ($CDCl_3$): CH_3CH_2, 8·96*t*, 8·92*t*, 7·63*q*, 7·36*q*; CH_3, 7·98 (2), 7·82; —*H*, 3·42*d*; N–H, 1·2, 1·5 (broad).

Bromination of pyrroketone (Va)

The pyrroketone (1·0 g) in dry tetrahydrofuran (50 ml) and dry ether (200 ml) was stirred and treated dropwise (during 10 min) with Br_2 (0·14 ml, 1 equiv) in dry ether (30 ml). Reaction was complete after a further 30 min (negative starch-iodide test) during which time the solution became very dark. The solvent was removed under red. press. to give a dark brown oil which could not be induced to crystallize. This oil was then taken up in pyridine but on addition of ether (in an attempt to isolate the pyridinium salt of the required 5′-bromomethylpyrroketone) only a brown gum was obtained. The latter was boiled with a little hot EtOH for 5 min and diluted with water. On cooling a brown solid separated and was recrystallized from aqueous EtOH (charcoal) to give *benzyl 5′-ethoxymethyl-3,4′-diethyl-3′,4-dimethylpyrroketone-5-carboxylate* (0·20 g; 18%) as needles, m.p. 140°. (Found: C, 71·5; H, 7·2; N, 6·4. $C_{26}H_{32}N_2O_4$ requires: C, 71·5; H, 7·4; N, 6·4%.) NMR spectrum ($CDCl_3$): CH_3CH_2, 8·93*t*, 8·92*t*, 8·82*t*, 7·59*q*, 7·35*q*, 6·51*q*; CH_3, 7·99, 7·68; —CH_2O—, 5·58; $C_6H_5CH_2O$—, 2·63, 4·72; N*H*—, 0·9 (2) (broad).

Benzyl 5′-chloromethyl-3,4′-diethyl-4,3′-dimethylpyrroketone-5-carboxylate (XVa)

(i) The pyrroketone (Va; 2·00 g) in dry tetrahydrofuran (80 ml) and dry ether (120 ml) at 3° was stirred during the addition (10 min) of t-butyl hypochlorite (0·61 ml, 1 equiv) in dry ether (30 ml). Reaction was complete immediately after the addition (negative starch-iodide test) and the solvent was removed by evaporation under red. press. The residual light brown oil crystallized on trituration with dry ether and was recrystallized from ether–light petroleum (b.p. 40–60°) to give the required *chloromethylpyrroketone* (1·8 g, 82%) as needles, m.p. 116–117°. (Found: C, 67·8; H, 6·4; N, 6·3. $C_{24}H_{27}ClN_2O_3$ requires: C, 67·5; H, 6·4; N, 6·6%.) NMR spectrum ($CDCl_3$): CH_3CH_2, 8·92*t*, 8·91*t*, 7·57*q*, 7·36*t*; CH_3, 8·04, 7·60; —CH_2Cl, 5·45; $C_6H_5CH_2$—, 2·67, 4·75; N*H*—, 0·9, 0·45.

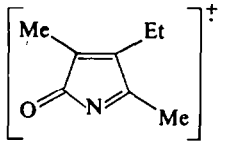
(ii) In a similar preparation to (i) the solution was cooled to −5° during addition of the t-butyl hypochlorite. However 15 min later a starch-iodide test was still positive. The cooling bath was therefore removed but by the time the temp had risen to 3° all the hypochlorite had reacted. The chloromethylpyrroketone was isolated as above in 78% yield.

(iii) In another similar preparation dry $CHCl_3$ was used as solvent and the chloromethylpyrroketone (55%), isolated as in (i) above, as needles m.p. 113–114° (mixed m.p. 114–115°).

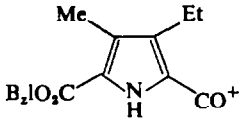
Benzyl 4-ethyl-5-(4′-ethyl-3′,5′-dimethylpyrrolyl-2′-oxycarbonyl)-3-methylpyrrol-2-carboxylate (XVI)

The pyrroketone (Va; 2·0 g) in $CHCl_3$ (containing 1% EtOH as stabiliser; 100 ml) at −6° was stirred and treated slowly (20 min) with t-butyl hypochlorite (0·61 ml; 1 equiv). Within 1–2 min of the completion of the addition a negative starch-iodide test was obtained, and the solvent was removed by distillation under red. press. The residual orange oil (which crystallized on trituration with a little light petroleum) was extracted with boiling light petroleum (b.p. 60–80°; 50 ml). The insoluble material was shown to be unreacted Va (0·4 g; 20%) and the filtrate was cooled to 0°. The crystalline solid which separated was recrystallized from light petroleum (b.p. 40–60°) to give the *pyrrolyloxycarbonylpyrrole* (XVI; 0·50 g; 24%) as plates, m.p. 125°. (Found: C, 70·6; H, 7·0; N, 6·9. $C_{34}H_{38}N_2O_4$ requires: C, 70·6; H, 6·9; N, 6·9%.) ν_{max} (CO); $CHCl_3$, 1650, 1665, 1710; mull, 1648, 1666, 1700, 1715, 1722 cm^{-1} λ_{max} 238, 303 mμ, ε_{max} 19,400, 20,000 (CH_2Cl_2). NMR spectrum ($CDCl_3$) CH_3CH_2—, 9·15*t*, 7·91*q*, 8·96*t*, 7·31*q*; CH_3—, 8·50, 8·33, 7·78; $C_6H_5CH_2$—, 2·68, 4·82; N*H*, 1·69, —0·05. Mass spectrum (MS9—direct inlet): 408 (M^+) (5), 270 (34), 139 (18), 137 (41), 136 (21), 124 (12), 122 (25), 110 (23), 108 (23), 91 (100). The differences between this spectrum and that of Va clearly confirm the structure assigned, particularly (i) the molecular ion which shows that the mol. wt. is 16 greater than the parent ketone, (ii) the virtual absence of the peak *m/e* 269 in this spectrum

(whereas it is 95% of the base peak in the spectrum of the parent ketone), and (iii) the relatively intense peak at *m/e* 137, which may be assigned the structure



and thus shows the position of insertion of the oxygen atom in the Baeyer-Villiger type oxidation. The peak *m/e* 270 may be assigned the structure



(see Part X)[28]

Benzyl 5'-formyl-3,4'-diethyl-4,3'-dimethylpyrroketone-5-carboxylate (XVd)

(i) The pyrroketone (Va; 1·10 g) and a catalytic amount of dibenzoyl peroxide in dry tetrahydrofuran (40 ml) and ether (200 ml) was cooled to 0° during the slow addition (1 hr) of sulphuryl chloride (0·52 ml, 2·2 equiv) from a micropipette. The solution was then stirred for a further 2 hr at 0°, and kept overnight at 25°, before removing the solvent at 25° under red. press. on a rotary evaporator. The residual oil was taken up in benzene (200 ml) and the solution saturated with dry dimethylamine, and poured into water (200 ml). The mixture was stirred and heated under reflux on the steam bath for 2 hr, and the organic layer was then separated and washed with dil HClaq followed by water. After removal of the solvent the residual dark brown gum was taken up in hot MeOH (20 ml) and a few drops of water added. The solid, which separated on cooling, was recrystallized from aqueous MeOH to give the *formylpyrroketone* (0·61 g; 54%) as needles, m.p. 170°. (Found: C, 70·9; H, 6·5; N, 7·2. $C_{24}H_{26}N_2O_4$ requires: C, 70·9; H, 6·5; N, 6·9%.) ν_{max} (CO); $CHCl_3$, 1627, 1645 *sh*, 1680; mull, 1623, 1640, 1695 cm^{-1}. λ_{max} (ε_{max}): 350 (24,300) (CH_2Cl_2), 370 (23,800) CCH_2Cl_2 + 2%CF_3CO_2H).

The 2,4-*dinitrophenylhydrazone*, prepared in MeOH, was purified by chromatography on alumina in benzene solution and crystallized from benzene as red needles m.p. 219°. (Found: C, 61·3; H, 5·2. $C_{30}H_{28}N_6O_7$ requires: C, 61·6; H, 4·8%.)

(ii) The chloromethylpyrroketone (XVa; 1·80 g) in dry ether (200 ml) and dry tetrahydrofuran (10 ml) was cooled to 3° during the addition (during 10 min) of t-butylhypochlorite (0·51 ml; 1 equiv) in dry ether (10 ml). Immediately after the addition no hypochlorite could be detected in the solution on testing with starch-iodide paper. The solvent was removed by evaporation under red. press. to give a pale brown oil which crystallized on trituration with light petroleum. On recrystallization from dry ether–light petroleum (b.p. 40–60°) the XVc (1·75 g; 90%) was obtained as buff microprisms, m.p. 142–143°. NMR spectrum ($CDCl_3$): CH_3CH_2—, 8·91*t*, 8·91*t*, 7·53*q*, 7·33*q*; CH_3, 8·00, 7·68; —$CHCl_2$ 3·22; $C_6H_5CH_2$—, 2·64, 4·72; N*H*, 0·77, 0·64.

This dichloromethylpyrroketone was hydrolysed as in (i) above with dimethylamine etc., and the formylpyrroketone (1·3 g; 75% overall yield) obtained as needles m.p. and mixed m.p. with the product in (i), 170°. NMR spectrum ($CDCl_3$): CH_3CH_2—, 8·80*t* (2), 7·31*q*, 7·22*q*; CH_3—, 7·73, 7·66; $C_6H_5CH_2$—, 2·72, 5·09; —*CH*O, 1·00; N*H*, −0·9, −1·0.

3,4'-Diethyl-5'-formyl-4,3'-dimethylpyrroketone-5-carboxylic acid

The pyrroketone (XVd; 110 mg) in dry AcOEt was hydrogenated over 4% Pd–$BaSO_4$ for 14 hr at 25° and 1 atm. After removal of catalyst and solvent the solid residue was crystallized from benzene–MeOH to give the *pyrroketone-carboxylic acid* (80 mg; 95%) as prisms, m.p. 220° (dec). (Found: C, 64·7; H, 6·4; N, 8·4. $C_{17}H_{20}N_2O_4$ requires: C, 64·5; H, 6·4; N, 8·9%.)

[28] A. H. Jackson, G. W. Kenner, H. Budzikiewicz, C. Djerassi and J. M. Wilson, *Tetrahedron* in press.

Tripyrrolic Compounds

Benzyl 2,4,6-*triethyl*-1,3,5,6′-*tetramethyl-a-oxo-tripyrrene-b*-1′-*carboxylate hydrobromide*

A suspension of the formylpyrroketone (XVd; 1·50 g) in EtOH (5 ml) and cryptopyrrole (500 mg) was treated with conc HBr (1 ml). The mixture was warmed gently to dissolve the solid, and on cooling a crystalline solid separated out from the deep red solution. On recrystallization from benzene the *oxotripyrrene hydrobromide* (0·92 g; 34%) formed red prisms (with a green reflex) m.p. 195°. (Found: C, 67·8; H, 6·9; N, 6·3; Br, 12·2. $C_{32}H_{38}BrN_3O_3$ requires: C, 68·0; H, 6·7; N, 6·3; Br, 11·9%.) λ_{max} 498 mμ (MeOH).

Benzyl 2,4,6-*triethyl-a-hydroxy*-1,3,5,6′-*tetramethyltripyrradiene dihydriodide* (XVII)

In a similar preparation to the foregoing, but using purified HI instead of HBr, the *tripyrradiene dihydriodide* (1·03 g, 31%) was obtained as red prisms, m.p. 182°. (Found: C, 50·4; H, 4·9; N, 4·9; 0, 6·1; I, 33·4 (potentiometric). $C_{32}H_{39}I_2N_3O_3$ requires: C, 50·3; H, 5·1; N, 5·5; 0, 6·3; I, 33·3%.) λ_{max} 364, 498 mμ, ε_{max} 16,000, 32,400 (EtOH).

Benzyl 2,4,6-*triethyl*-1,3,5,6′-*tetramethyltripyrrane*-1′-*carboxylate* (XVIII)

The foregoing *tripyrradiene dihydriodide* (177 mg) in MeOH (100 ml) was treated with a large excess of KBH_4 (ca. 2·5 g) in water (20 ml). After warming for a short while the solution became colourless and was poured into water and was extracted with $CHCl_3$. After washing with water, and drying ($MgSO_4$) the $CHCl_3$ was evaporated under red. press. (N_2 leak) and gave an almost colourless residue (51 mg) m.p. 120°. This material was very unstable, and could not be recrystallized without decomposition. The UV spectrum (λ_{max} 287 mμ) was consistent with the tripyrrane structure (XVIII), and this was confirmed by mixed m.p. and spectral comparisons with an authentic sample prepared in earlier work.[1]

Benzyl 2,4,6-*triethyl*-1,3,5,6′-*tetramethyl-b-oxotripyrrane*-1′-*carboxylate* (XIV)

With Dr. D. Warburton. A solution of the acid (Vd; 1·10 g) and MeOLi (0·14 g) in redistilled dry formamide (100 ml) was combined with a solution of benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·20 g) in dry pyridine (0·9 ml) and the mixture was heated at 100° for 17 hr under N_2. After cooling and dilution with water (1 l.) the product was extracted into AcOEt (4 × 250 ml). The combined extracts were dried (Na_2SO_4), evaporated to dryness under red. press. (N_2 leak) at 25–30°, and the residual oil triturated with EtOH at 0°. The dark brown solid obtained was crystallized from EtOH, followed by AcOEt, and gave the oxotripyrrane (0·39 g; 21%) as pale yellow needles, m.p. 203°. (Found: C, 75·0; H, 7·7; N, 8·2. $C_{32}H_{39}N_3O_3$ requires: C, 74·8; H, 7·7; N, 8·2%.)

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