Pyrroles and Related Compounds. Part XXII.[1] Syntheses of Pyrromethanes and a Tripyrrane [2]

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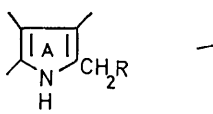
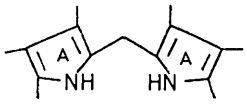
Treatment of 2-acetoxymethylpyrroles with 2-unsubstituted pyrroles in either methanol or acetic acid containing a catalytic quantity (<0·1 equiv.) of toluene-*p*-sulphonic acid hydrate, affords high yields of the corresponding pyrromethanes. The reaction in methanol is modified to give an acceptable yield of the tripyrrane (15), a member of a class of compound of current biosynthetic interest.

HIGH yields of symmetrically substituted pyrromethanes (2) have been obtained either by heating 2-bromomethylpyrroles (1a) in alcoholic solvents,[3] or, more recently, by heating the corresponding 2-acetoxymethylpyrroles (1b) in acetic acid,[4] or in methanol containing hydrochloric acid.[5] However, unsymmetrically substituted pyrromethanes (4) are considerably more useful as intermediates for the synthesis of porphyrins of biological significance;[6] they are also much less amenable to synthesis.

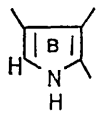


(1)

a; R = Br c; R = H
b; R = OAc d; R = OMe



(2)



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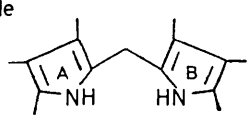
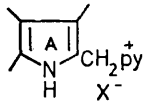


(4)

Since 1960, the method of choice for the preparation of unsymmetrical pyrromethanes (4) has been the heating of 2-halogenomethylpyrroles [*e.g.* (1a)] with 2-unsubstituted pyrroles (3) under reflux in acetic acid containing sodium acetate;[7] 2-halogenomethylpyrroles are rapidly converted[2,8,9] into the corresponding 2-acetoxymethylpyrroles (1b) under these conditions. In view of the ease of preparation of the latter from 2-methylpyrroles (1c) with lead tetra-acetate, and also their stability, the 2-acetoxymethylpyrroles (1b) are usually preferred to the more unstable 2-halogenomethylpyrroles [*e.g.* (1a)] as starting materials. Though applicable to the synthesis of a large variety of diversely substituted pyrromethanes (4), MacDonald's method[7] does not often afford yields of pyrromethanes greater than 50%; moreover, the work-up invariably requires careful column chromatography of the crude products.

Clezy and his co-workers[4] have recently reported a modification of the acetic acid method[7] which involves heating of the reaction mixture at 90° (instead of 140°) and in the absence of sodium acetate.† The yields of pyrromethanes obtained were in the region 60—70%, which reflects the milder conditions of the reaction, since chromatography was usually unnecessary in order to obtain a pure crystalline product.

An alternative route to pyrromethanes was discovered by us;[10] condensation of a halogenomethylpyrrole pyridinium salt (5) with a lithium pyrrolecarboxylate (6) in solvents such as formamide or methanol–water afforded good yields of unsymmetrically substituted pyrromethanes (4). However, the versatility of this method is limited by the need to avoid very strongly electron-withdrawing substituents in ring B.



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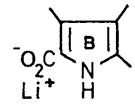


(6)

We now report two useful modifications of MacDonald's route[7] to unsymmetrically substituted pyrromethanes. The first of these arose out of the need to synthesise the pyrromethane (9) in connection with our studies on the synthesis of protoporphyrin-IX and its deuteriated derivatives; the 2-chloroethyl substituents in (9) were intended[11] to become the vinyl substituents in rings A and B of protoporphyrin-IX, through elimination of hydrogen chloride at the porphyrin stage.[12] Accordingly, we attempted the preparation of (9) by heating the pyrroles (7) and (8) in acetic acid. The only stable

† We have independently shown that the sodium acetate could be omitted without any adverse effect, since syntheses of pyrromethanes from pyrroles with 2-chloroethyl substituents afforded by-products containing 2-acetoxyethyl side-chains when the medium contained sodium acetate. Omission of the acetate eliminated these by-products.

[1] Part XXI, G. W. Kenner, S. W. McCombie, and K. M. Smith, *Annalen*, in the press.

[2] Preliminary publication, A. M. d'A. Rocha Gonsalves, G. W. Kenner, and K. M. Smith, *Tetrahedron Letters*, 1972, 2203.

[3] *E.g.* H. Fischer and H. Orth, 'Die Chemie des Pyrrols,' vol. I, Akademische Verlag, Leipzig, 1934, p. 333.

[4] P. S. Clezy and A. J. Liepa, *Austral. J. Chem.*, 1970, **23**, 2443.

[5] A. F. Mironov, T. R. Ovsepyan, R. P. Evstigneeva, and N. A. Preobrazenskii, *Zhur. obshchei Khim.*, 1965, **35**, 324.

[6] K. M. Smith, *Quart. Rev.*, 1971, **25**, 31.

[7] E. J. Tarlton, S. F. MacDonald, and E. Baltazzi, *J. Amer. Chem. Soc.*, 1960, **82**, 4389.

[8] R. Fletcher, Research Fellowship Report, Liverpool, 1967.

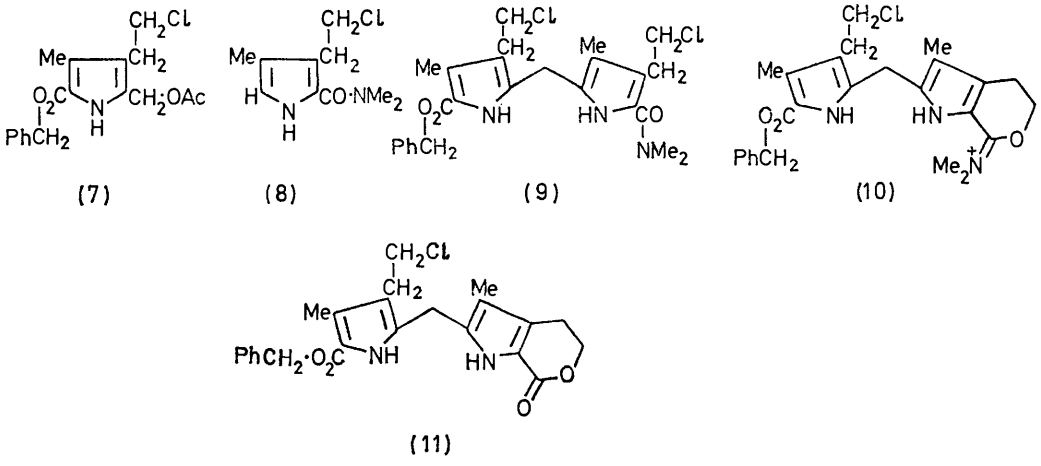
[9] J. M. Osgerby, J. Pluscec, Y. C. Kim, F. Boyer, N. Stojanac, H. D. Mah, and S. F. MacDonald, *Canad. J. Chem.*, 1972, **50**, 2652.

[10] (*a*) A. Hayes, G. W. Kenner, and N. R. Williams, *J. Chem. Soc.*, 1958, 3779; (*b*) A. H. Jackson, G. W. Kenner, and D. Warburton, *ibid.*, 1965, 1328.

[11] G. W. Kenner and K. M. Smith, *Ann. New York Acad. Sci.*, in the press.

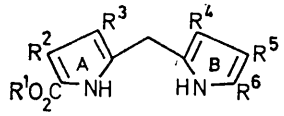
[12] *Cf.* R. P. Carr, A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1971, 487.

product isolated from a series of reactions, at various temperatures was the lactone (11),* the formation of which could be rationalised in terms of attack of the nucleophilic oxygen atom of the required compound (9) upon the chloroethyl side-chain, followed by hydrolysis of the intermediate (10). Hence, it appeared that the pyrromethane (9) was being produced, but that it was unstable under the reaction conditions. We therefore examined other approaches to pyrromethanes, and found that treatment of the pyrroles (7) and (8) in methanol containing a catalytic quantity (<0·1 equiv.) of toluene-*p*-sulphonic acid hydrate, at 35° during about 4 h, afforded an 85% yield of the required pyrromethane (9).† This general procedure has been applied to a representative series of synthetically useful pyrromethanes, as shown in Table (A). In all cases where a direct comparison with other synthetic routes is possible, improved



(7) (8) (9) (10) (11)

Pyrromethanes prepared by toluene-*p*-sulphonic acid catalysed condensations



Substituents †								
R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	Lit. yield (%)	Ref.
(A) Methanol procedure								
$PhCH_2$	Me	P^{Me}	Et	Me	CO_2CH_2Ph	93	*	
$PhCH_2$	Me	CH_2CH_2Cl	Me	Et	$CO{\cdot}NMe_2$	90	*	
$PhCH_2$	Me	CH_2CH_2Cl	Me	CH_2CH_2Cl	$CO{\cdot}NMe_2$	85	*	
$PhCH_2$	Me	Et	Me	Et	$CO{\cdot}NMe_2$	89	86	*a*
$PhCH_2$	Me	P^{Me}	Me	Et	$CO{\cdot}NMe_2$	93	69	*a*
$PhCH_2$	Me	P^{Me}	P^{Me}	Me	CO_2Bu^t	85	47·5	*b*
$PhCH_2$	Me	P^{Me}	P^{Me}	Me	CO_2CH_2Ph	92	65	*c*
$PhCH_2$	P^{Me}	Me	P^{Me}	Me	CO_2Bu^t	75		*d*
$PhCH_2$	Me	P^{Me}	Me	CH_2CH_2Cl	CO_2Bu^t	85		*e*
$PhCH_2$	Me	P^{Me}	Me	COMe	Me	91	70	*f*
(B) Acetic acid procedure								
$PhCH_2$	Me	CH_2CH_2OAc	Me	Et	$CO{\cdot}NMe_2$	92	*	
$PhCH_2$	Me	CH_2CH_2Cl	Me	P^{Me}	CO_2Bu^t	79	*	
$PhCH_2$	Me	CH_2CH_2OAc	Me	P^{Me}	CO_2Bu^t	84	*	
Bu^t	Me	P^{Me}	Me	P^{Me}	CO_2CH_2Ph	75		*d*
$PhCH_2$	Me	P^{Me}	Me	P^{Me}	$CO{\cdot}NMe_2$	81	62	*a*
$PhCH_2$	Me	CH_2CH_2OAc	Me	CH_2CH_2OAc	$CO{\cdot}NMe_2$	78	49	*b*, *d*
$PhCH_2$	Me	CH_2CH_2OAc	Me	P^{Me}	$CO{\cdot}NMe_2$	88		*g*

* New compound. † In all cases, ring A in the product pyrromethane is derived from the appropriate 2-acetoxymethylpyrrole (1b).

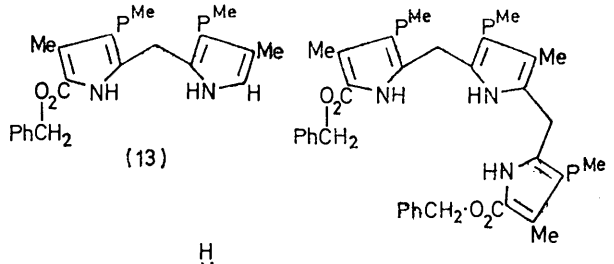
[a] A. H. Jackson, G. W. Kenner, G. McGillivray, and K. M. Smith, *J. Chem. Soc.* (*C*), 1968, 294; [b] R. P. Carr, A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1971, 487; [c] A. W. Johnson, I. T. Kay, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 1959, 3416; [d] J. A. S. Cavaleiro, G. W. Kenner, and K. M. Smith, following paper; [e] J. A. S. Cavaleiro, G. W. Kenner, and K. M. Smith, *J.C.S. Chem. Comm.*, 1973, 183; [f] P. S. Clezy and A. J. Liepa, *Austral. J. Chem.*, 1970, **23**, 2443; [g] A. H. Jackson, G. W. Kenner, and K. M. Smith, unpublished results.

* A compound to which the structure (10) could be assigned was isolated; however, it was not completely characterised because of its ready decomposition into the pyrromethane lactone (11).

† This pyrromethane was efficiently converted into the lactone (11) by heating under reflux in acetic acid, thereby confirming the initial hypothesis that (11) was obtained from (9).

yields were obtained. Moreover, t-butyl ester protecting groups were also stable under the reaction conditions. Isolation of the products was conveniently achieved by dilution of the reaction mixture with water, followed by collection of the crystalline pyrromethane, which did not normally need further purification. (Neutralisation of the toluene-*p*-sulphonic acid with sodium acetate at the end of the reaction was found to be useful in avoiding excessive darkening of the reaction mixture during crystallisation of the product.)

No pyrromethanes were produced when the 2-acetoxymethylpyrroles and 2-unsubstituted pyrroles were heated in methanol in the absence of the acid catalyst; neither was there any evidence of the production of symmetrical pyrromethanes (due to self-condensation of the 2-acetoxymethylpyrrole) in the presence of the catalyst. The latter observation is presumably a consequence of two connected factors: (i) 2-unsubstituted pyrroles are invariably more soluble in methanol than the 2-acetoxymethylpyrroles, which are usually used in suspension and



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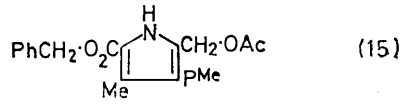


(14)

(15)

P^{Me} = $CH_2 \cdot CH_2 \cdot CO_2Me$

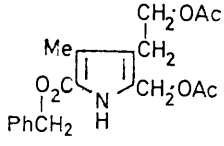
therefore are never in excess; (ii) 2-unsubstituted pyrroles are more potent nucleophiles than are 2-acetoxymethylpyrroles.

We were impressed by the mildness of the methanol–toluene-*p*-sulphonic acid procedure and decided to attempt extension of the method to tripyrrane synthesis. These compounds had earlier been of interest as possible intermediates in porphyrin synthesis and we had successfully prepared some tripyrranes,[10b] but the pyridinium salt–lithium carboxylate method was not sufficiently versatile and non-linear condensation products were occasionally obtained. More recently, Clezy [4] has attempted the synthesis of tripyrranes using similar condensation methods with morpholino- and piperidino-derivatives; though some tripyrranes were prepared, a generally useful synthesis was not developed.

Treatment of the 5-unsubstituted pyrromethane (13) with the 2-acetoxymethylpyrrole (14) in methanol containing toluene-*p*-sulphonic acid gave a 35% yield of the tripyrrane (15) upon cooling the reaction mixture. T.l.c. of the mother liquors showed evidence of further quantities of (15) but rapid darkening of the mixture prevented its isolation in pure form. The tripyrrane (15) was obtained colourless directly from the reaction mixture, but, even in the crystalline state, it darkened slowly at room temperature. However, the tripyrrane was completely characterised and there are no obvious limitations to the substituent arrangements which can be obtained. The n.m.r. spectrum confirmed that the tripyrrane (15) was isomerically pure, showing that the reaction conditions were sufficiently mild as to impede random condensations and redistributions.

Tripyrranes are of particular importance in several current investigations. It has been established [13] that pyrromethanes are the immediate biosynthetic precursors of the porphyrins (and presumably corrins) after porphobilinogen; the most logical substances after the pyrromethanes in the natural pathway are tripyrranes (produced by elongation of the former with porphobilinogen), and so these are of great current interest. Indeed, MacDonald [9] has already published details of his approach to a tripyrrane of presumed biological significance (*via* borohydride reduction of a tripyrrene), and results of radiochemical feeding experiments are awaited with interest.

Our second modification of MacDonald's pyrromethane synthesis arose from attempted syntheses of 2-acetoxyethyl-substituted pyrromethanes [*e.g.* (18)] by the methanol–toluene-*p*-sulphonic acid route outlined above. Not surprisingly, these conditions, when applied to the condensation of pyrroles (16) and (17), caused methanolysis of the product pyrromethane (18) (and presumably also of the starting materials) and the required compound was heavily contaminated with the by-product (19). The troublesome methanolysis was avoided by changing the solvent from methanol to acetic acid; thus, heating of the pyrroles (16) and (17) in acetic acid, at 35—40°



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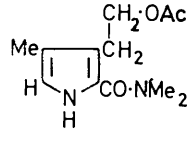

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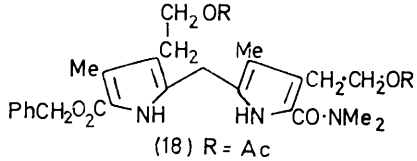


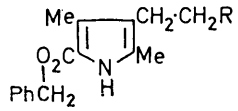
(18) R = Ac
(19) R = H

during 4 h, in the presence of a catalytic quantity of toluene-*p*-sulphonic acid, resulted in the isolation of a 78% yield of the pure pyrromethane (18). Other examples, which demonstrate the scope of this approach,

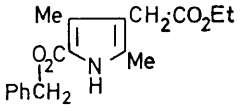
[13] *E.g.* L. Bogorad and J. Pluscec, *Biochemistry*, 1970, **9**, 4736; B. Frydman, S. Reil, A. Valasinas, R. B. Frydman, and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 2738; R. B. Frydman, A. Valasinas, H. Rapoport, and B. Frydman, *FEBS Letters*, 1972, **25**, 309; A. R. Battersby, in 'XXIIIrd International Congress of Pure and Applied Chemistry,' vol. 5, Butterworths, London, 1971, p. 1.

are presented in Table (B), with yield comparisons where possible.

This second modification has certain disadvantages. It is more difficult to follow the progress of the reaction by t.l.c., because the acetic acid, unless removed, affects the development of the plate. The work-up of the reaction mixture is also more complicated, requiring dilution

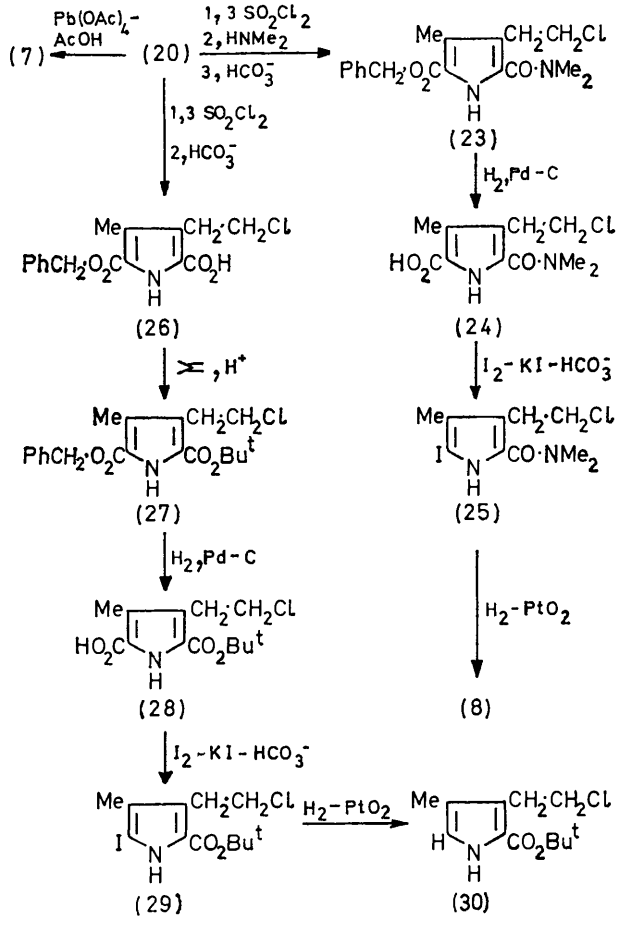


(20) R = Cl
(22) R = OH



(21)

with water and extraction of the product into methylene chloride. However, the acetic acid method is preferable in certain cases; for example, when functions susceptible to methanolysis are present, and also when the product

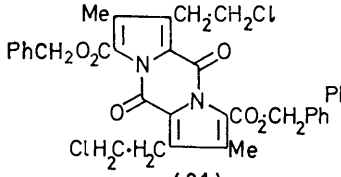


SCHEME

pyrromethane is non-crystalline.* In such cases, an aqueous work-up is required anyway, and small quantities of 2-methoxymethylpyrroles (1d), by-products from the methanol route † which are difficult to remove from the required pyrromethanes, can be avoided by using the acetic acid approach.

The (2-chloroethyl)pyrroles used for the preparation of many of the pyrromethanes described herein were all obtained by standard methods (Experimental section) from the parent pyrrole (20) as shown in the Scheme. Compound (20) was in turn prepared in high overall yield from the ethoxycarbonylmethylpyrrole (21) by reduction with diborane to the (2-hydroxyethyl)pyrrole [12] (22), followed by treatment with thionyl chloride and pyridine.

Two by-products were isolated from the reaction to prepare the pyrrolecarboxylic acid (26); the first of these was the highly insoluble pyrrocoll (31) and we have established that, in general, these compounds predominate over the required carboxylic acids, if the intermediate trichloromethylpyrroles are hydrolysed in concentrated solution. The second by-product was the formylpyrrole (32), no doubt obtained by hydrolysis of incompletely chlorinated material. In an attempt to eliminate pyrrocoll formation, a rapid hydrolysis of the trichloromethyl intermediate was performed, with aqueous sodium hydrogen carbonate solution, on a boiling water-bath during 90 min. Unfortunately, the product isolated from this reaction was the (2-hydroxyethyl)-



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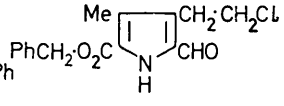

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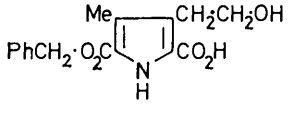

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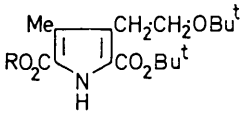

(34) R = PhCH$_2$
(35) R = H

pyrrolecarboxylic acid (33) which was not characterised, but was transformed into the fully characterised t-butyl ether (35) *via* the oily mixed ester (34), following established procedures.

EXPERIMENTAL

M.p.s were measured on a hot-stage apparatus. Unless otherwise stated, neutral alumina (Merck; Brockmann Grade III) was used for all chromatographic separations. Reactions were followed by t.l.c. as described in earlier parts

* We have often found (*e.g.* ref. 14) t-butyl pyrromethane-5-carboxylates or di-t-butyl pyrromethane-5,5′-dicarboxylates to be low-melting solids or uncrystallisable oils.

† These are not, strictly speaking, by-products, since they appear to react with 2-unsubstituted pyrroles to give pyrromethanes. However, they seem to do so at a lower rate than the 2-acetoxymethylpyrroles from which they are produced.

[14] A. M. d'A. Rocha Gonsalves, G. W. Kenner, and K. M. Smith, *Chem. Comm.*, 1971, 1304.

of this Series. Thin-layer plates of pyrromethane reaction mixtures were developed in the usual way, by exposure to bromine vapour, thereby producing a bright red pyrromethane spot from the colourless pyrromethane. N.m.r. spectra were measured in deuteriochloroform solution with tetramethylsilane as internal standard with a Varian HA-100 instrument.

Pyrroles

Benzyl 4-(2-Chloroethyl)-3,5-dimethylpyrrole-2-carboxylate (20).—Benzyl 4-(2-hydroxyethyl)-3,5-dimethylpyrrole-2-carboxylate (22) [13] (5·47 g) in methylene chloride (20 ml) and pyridine (1·6 ml) was heated at 50° during the rapid, but dropwise, addition of thionyl chloride (1·43 ml) to the stirred solution. Dry nitrogen was then passed through the solution at 50° during 1 h before the latter was diluted with methylene chloride and then washed with 2N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution, and then water. The organic phase was dried (Na_2SO_4) and evaporated to dryness, and then the residue was dissolved in benzene and filtered through a short column of alumina (100 g) (elution with benzene). Evaporation of the filtrate gave a solid, which was recrystallised from methylene chloride–n-hexane to give the *(2-chloroethyl)pyrrole* (5 g, 86%), m.p. 121—122° (Found: C, 65·7; H, 6·3; N, 4·55. $C_{16}H_{18}ClNO_2$ requires C, 65·9; H, 6·2; N, 4·8%), τ 1·10br (1H, NH), 2·65 (5H, m, Ph), 4·72 (2H, s, PhCH_2), 6·52 (2H, t) and 7·20 (2H, t) (ClCH_2·CH_2), and 7·73 and 7·81 (each 3H, s, Me).

Elution of the alumina column with methylene chloride afforded starting material (22) (0·5 g).

Benzyl 5-Acetoxymethyl-4-(2-chloroethyl)-3-methylpyrrole-2-carboxylate (7).—Lead tetra-acetate (4·6 g) was added in portions during 2 h to a stirred solution of the foregoing pyrrole (3·0 g) in acetic acid (175 ml) and acetic anhydride (4 ml). After stirring at room temperature during a further 20 h, water (250 ml) was added to complete precipitation. The precipitate was collected by filtration, washed with water, and then dried (3·56 g; 99%). The *acetoxymethylpyrrole*, recrystallised from methylene chloride–n-hexane, had m.p. 165—169° (decomp.) (Found: C, 62·0; H, 6·0; N, 3·95. $C_{18}H_{20}ClNO_4$ requires C, 61·8; H, 5·8; N, 4·0%), τ 0·72br (1H, NH), 2·61 (5H, m, Ph), 4·70 (2H, s, PhCH_2), 4·99 (2H, s, CH_2·O), 6·48 (2H, t) and 7·09 (2H, t) (ClCH_2·CH_2), 7·75 (3H, s, Me), and 7·98 (3H, s, COMe).

Benzyl 4-(2-Chloroethyl)-5-dimethylcarbamoyl-3-methylpyrrole-2-carboxylate (23).—Sulphuryl chloride (5·5 ml) was added dropwise during 1 h to a stirred solution of benzyl 4-(2-chloroethyl)-3,5-dimethylpyrrole-2-carboxylate (6·0 g) in dry ether (220 ml). A precipitate which formed initially dissolved with stirring, which was continued during 20 h before evaporation of the solution to give a viscous oil. Tetrahydrofuran (60 ml) was added and the solution was added dropwise, during 15 min, to a stirred aqueous 40% solution of dimethylamine (60 ml). After stirring for a further 15 min the solution was extracted with methylene chloride, which was washed with water and then evaporated to dryness. The residual oil was taken up in tetrahydrofuran (60 ml) and treated with saturated aqueous sodium hydrogen carbonate (60 ml); the mixture was stirred vigorously until the imine absorption at $\lambda_{max.}$ 307 nm had disappeared. After extraction with methylene chloride, the organic phase was dried (Na_2SO_4) and evaporated to dryness. The *dimethylcarbamoylpyrrole* (6·5 g, 80%) was obtained as hexagonal prisms (from methyl chloride–n-hexane), m.p. 99—100° (Found: C, 62·1; H, 6·2; N, 8·0. $C_{18}H_{21}ClN_2O_3$ requires C, 62·0; H, 6·1; N, 8·0%), τ 0·39br (1H, NH), 2·61 (5H, m, Ph), 4·71 (2H, s, PhCH_2), 6·42 (2H, t) and 7·06 (2H, t) (ClCH_2·CH_2), 7·00 (6H, s, NMe_2), and 7·70 (3H, s, Me).

4-(2-Chloroethyl)-5-(dimethylcarbamoyl)-3-methylpyrrole-2-carboxylic Acid (24).—A solution of the foregoing pyrrole (6·0 g) in tetrahydrofuran (100 ml) containing triethylamine (3 drops) as an accelerator, was hydrogenated at atmospheric pressure and room temperature over 10% palladised charcoal (0·6 g). When hydrogen uptake had ceased (2 h) filtration through Celite and evaporation *in vacuo* gave the *pyrrolecarboxylic acid* (4·36 g, 98%). Recrystallisation from methylene chloride–n-hexane gave colourless plates, m.p. 194—198° (with decarboxylation) (Found: C, 51·2; H, 5·8; N, 10·5. $C_{11}H_{15}ClN_2O_3$ requires C, 51·1; H, 5·8; N, 10·8%), [$(CD_3)_2SO$] τ −1·62br (1H, CO_2H), 6·41 (2H, t) and 7·22 (2H, t) (ClCH_2·CH_2), 7·14 (6H, s, NMe_2), and 7·81 (3H, s, Me).

4-(2-Chloroethyl)-5-(dimethylcarbamoyl)-2-iodo-3-methylpyrrole (25).—The foregoing pyrrolecarboxylic acid (2·38 g) in methanol (24 ml) at 65° was treated dropwise, during 5 min, with sodium hydrogen carbonate (1·9 g) in water (18 ml). Iodine (2·38 g) and potassium iodide (2·3 g) in methanol (12 ml) and water (6 ml) were then added dropwise during 10 min. After stirring during a further 10 min at 65°, water (100 ml) was added and the required pyrrole was collected by filtration as pale yellow needles (2·75 g, 86%). The *iodopyrrole*, recrystallised from methylene chloride–n-hexane, had m.p. 157—159° (Found: C, 35·1; H, 4·1; N, 7·9. $C_{10}H_{14}ClIN_2O$ requires C, 35·3; H, 4·1; N, 8·2%), τ 0·74br (1H, NH), 6·50 (2H, t) and 7·05 (2H, t) (ClCH_2·CH_2), 6·98 (6H, s, NMe_2), and 8·02 (3H, s, Me).

4-(2-Chloroethyl)-5-(dimethylcarbamoyl)-3-methylpyrrole (8).—The foregoing iodopyrrole (1·06 g) and sodium acetate trihydrate (1·2 g) were dissolved in methanol (20 ml) and hydrogenated at room temperature and atmospheric pressure over Adams platinum oxide (100 mg) for 5 h. Filtration through Celite and evaporation almost to dryness followed by dropwise addition of water resulted in crystallisation of the pyrrole as needles. The *2-unsubstituted pyrrole*, recrystallised from methylene chloride–n-hexane, had m.p. 131—132° (Found: C, 55·7; H, 6·8; N, 13·0. $C_{10}H_{15}ClN_2O$ requires C, 55·9; H, 7·0; N, 13·05%), τ 0·89br (1H, NH), 3·50 (1H, d, *J* 3 Hz, α-H), 6·44 (2H, t) and 7·05 (2H, t) (ClCH_2·CH_2), 7·00 (6H, s, NMe_2), and 8·00 (3H, s, Me).

2-Benzyloxycarbonyl-4-(2-chloroethyl)-3-methylpyrrole-5-carboxylic Acid (26).—With vigorous stirring, a solution of benzyl 4-(2-chloroethyl)-3,5-dimethylpyrrole-2-carboxylate (15·6 g) in dry ether (500 ml) was treated, dropwise during 1 h, with sulphuryl chloride (16·4 ml, *ca.* 3·8 equiv.). After stirring for a further 6 h, the solvent was evaporated off *in vacuo* to give a viscous oil which was taken up in dioxan (140 ml) and then treated with saturated aqueous sodium hydrogen carbonate (140 ml). The mixture was stirred at room temperature during 16 h, treated with more aqueous sodium hydrogen carbonate (140 ml), and then stirred briskly during a further 24 h. Ether (500 ml) was added along with sodium carbonate (10 g) and after extraction, the aqueous phase was collected. Re-extraction with more aqueous sodium carbonate was then carried out, and the ether phase was set aside. The combined aqueous layers were flushed with a stream of air during 30 min and then treated with sulphur dioxide gas (to pH 6). The precipitated white solid was collected, dried, and then recrystallised from

methylene chloride–n-hexane, to give the *pyrrolecarboxylic acid* (26) (5·2 g, 30%), m.p. 178—182° (Found: C, 59·85; H, 5·1; N, 4·3. $C_{16}H_{16}ClNO_4$ requires C, 59·7; H, 5·0; N, 4·35%), τ [$(CD_3)_2SO$] −2·95br (1H, NH), −1·76br (1H, CO_2H), 2·60 (5H, m, Ph), 4·72 (2H, s, $PhCH_2$), 6·33 (2H, t) and 6·88 (2H, t) ($ClCH_2{\cdot}CH_2$), and 7·76 (3H, s, Me).

A precipitate which had been present in the ether layer throughout the work-up was filtered off and dried in air. Recrystallisation from methylene chloride–n-hexane gave *dibenzyl 3,8-bis-(2-chloroethyl)-2,7-dimethyl-5,10-dioxo-5H,10H-dipyrrolo[1,2-a:1′,2′-d]pyrazine-1,6-dicarboxylate* (31) (3·5 g, 21%), m.p. 203—205° (Found: C, 63·1; H, 4·6; N, 4·6. $C_{32}H_{28}Cl_2N_2O_6$ requires C, 63·3; H, 4·65; N, 4·6%), τ 2·66 (10H, m, 2Ph), 4·68 (4H, s, $2CH_2Ph$), 6·34 (4H, t) and 6·79 (4H, t) ($2ClCH_2{\cdot}CH_2$), and 7·92 (6H, s, 2Me).

The ether layer was evaporated to dryness, and the residue was crystallised from methylene chloride–n-hexane to give the 2-formylpyrrole (32) (4·5 g, 28%), m.p. 110—111°, identical with the compound prepared by rational synthesis, and reported below.

In a trichlorination of the methylpyrrole (20) (5·8 g) with sulphuryl chloride (5·8 ml) the hydrolysis was carried out, as above with aqueous sodium hydrogen carbonate, but with heating on a boiling water-bath during 1·5 h. Work-up as described above, with aqueous sodium carbonate and sulphur dioxide, afforded the (2-hydroxyethyl)pyrrolecarboxylic acid (33) (3 g, 50%) after extraction of the aqueous solution (pH 6) with methylene chloride, evaporation, and crystallisation from methylene chloride–n-hexane. This compound was not characterised, but was treated with isobutene–sulphuric acid as described below for the synthesis of compound (27) to give the oily mixed ester (34) (65%) [τ 0·46br (1H, NH), 2·72 (5H, m, Ph), 4·78 (2H, s, $PhCH_2$), 6·64 (2H, t) and 7·13 (2H, t) ($O{\cdot}CH_2{\cdot}CH_2$), 7·73 (3H, s, Me), and 8·47 and 8·89 (each 9H, s, Bu^t)]. Catalytic hydrogenation in tetrahydrofuran over 10% palladised charcoal gave a 95% yield of the *pyrrolecarboxylic acid* (35), m.p. 140—142° (Found: C, 62·5; H, 8·3; N, 4·6. $C_{17}H_{27}NO_5$ requires C, 62·75; H, 8·4; N, 4·3%), τ −1·50br (1H, CO_2H), 0·45br (1H, NH), 6·56 (2H, t) and 7·05 (2H, t) ($O{\cdot}CH_2{\cdot}CH_2$), 7·65 (3H, s, Me), and 8·39 and 8·82 (each 9H, s, Bu^t).

Benzyl 4-(2-Chloroethyl)-5-formyl-3-methylpyrrole-2-carboxylate (32).—Sulphuryl chloride (4·6 ml, *ca.* 2·05 equiv.) was added dropwise during 1 h to a stirred solution of benzyl 4-(2-chloroethyl)-3,5-dimethylpyrrole-2-carboxylate (8·13 g) in ether (350 ml). An initially formed precipitate had disappeared by the time all the sulphuryl chloride had been added. After stirring at room temperature during a further 27 h the solvent was evaporated off at room temperature under vacuum. The oily residue was taken up in tetrahydrofuran (250 ml) and sodium hydrogen carbonate (12 g) in water (250 ml) was added. The mixture was stirred briskly during 21 h before being diluted with ether and washed with water; then the organic phase was dried (Na_2SO_4) and evaporated to dryness. Crystallisation from methylene chloride–n-hexane afforded the *formylpyrrole* (7·5 g, 88%) identical with the by-product from the foregoing reaction; m.p. 110—111° (Found: C, 62·7; H, 5·3; N, 4·5. $C_{16}H_{16}ClNO_3$ requires C, 62·85; H, 5·3; N, 4·6%), τ 0·19 (1H, s, CHO), 0·35br (1H, NH), 2·60 (5H, s, Ph), 4·69 (2H, s, $PhCH_2$), 6·39 (2H, t) and 6·85 (2H, t) ($ClCH_2{\cdot}CH_2$), and 7·70 (3H, s, Me).

Benzyl 4-(2-Chloroethyl)-3-methyl-5-t-butoxycarbonylpyrrole-2-carboxylate (27).—An ice-cold suspension of 2-benzyloxycarbonyl-4-(2-chloroethyl)-3-methylpyrrole-5-carboxylic acid (4·8 g) in chloroform (100 ml) was treated with isobutene (100 ml) and concentrated sulphuric acid (0·8 ml). The mixture was then stirred in the flask, sealed with a stopper secured with rubber bands, at room temperature, during 16 h. A large quantity of pyrrole acid was seen still to be in suspension, and therefore chloroform (250 ml) was added and the mixture was stirred until clear (48 h). The solution was neutralised with sodium hydrogen carbonate and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residual oil was chromatographed with petroleum (b.p. 60—80°)–benzene mixtures as eluant. Evaporation of the eluates and crystallisation from methylene chloride–n-hexane gave the *pyrrole mixed ester* (5·3 g, 94%), m.p. 59·5—60·5° (Found: C, 63·5; H, 6·4; N, 3·8. $C_{20}H_{24}ClNO_4$ requires C, 63·6; H, 6·4; N, 3·7%), τ 0·53br (1H, NH), 2·63 (5H, m, Ph), 4·69 (2H, s, $PhCH_2$), 6·42 (2H, t) and 6·89 (2H, t) ($ClCH_2{\cdot}CH_2$), 7·70 (3H, s, Me), and 8·42 (9H, s, Bu^t).

4-(2-Chloroethyl)-3-methyl-5-t-butoxycarbonylpyrrole-2-carboxylic Acid (28).—The foregoing pyrrole (4·5 g) in tetrahydrofuran (200 ml) containing triethylamine (4 drops) as an accelerator, was hydrogenated at room temperature and atmospheric pressure over 10% palladised charcoal (0·5 g) until uptake of hydrogen had ceased. Filtration through Celite, evaporation, and crystallisation from methylene chloride–n-hexane gave the *pyrrolecarboxylic acid* (3·4 g, 99%), m.p. 192—194° (Found: C, 54·2; H, 6·2; N, 4·75. $C_{13}H_{18}ClNO_4$ requires C, 54·3; H, 6·3; N, 4·9%), τ 0·39br and 1·5br (each 1H, CO_2H and NH), 6·38 (2H, t) and 6·84 (2H, t) ($ClCH_2{\cdot}CH_2$), 7·66 (3H, t, Me), and 8·39 (9H, s, Bu^t).

t-Butyl 4-(2-Chloroethyl)-2-iodo-3-methylpyrrole-5-carboxylate (29).—Sodium hydrogen carbonate (2·2 g) in water (55 ml) was added at 55° to the foregoing pyrrole (3·0 g) in methanol (80 ml). Iodine (2·95 g) and potassium iodide (3·9 g) in methanol (50 ml) and water (15 ml) were then added dropwise during 30 min while the temperature was maintained at 55°. After stirring for a further 40 min at this temperature, methylene chloride (100 ml) was added, and the organic layer was washed with dilute aqueous sodium thiosulphate and then dried (Na_2SO_4). The solvent was evaporated off *in vacuo* and the residue was crystallised from methylene chloride–n-hexane to give the *iodopyrrole* (3·33 g, 86%), m.p. 136—137° (Found: C, 39·1; H, 4·8; N, 3·5. $C_{12}H_{17}ClINO_2$ requires C, 39·0; H, 4·6; N, 3·8%), τ 0·90br (1H, NH), 6·47 (2H, t) and 6·90 (2H, t) ($ClCH_2{\cdot}CH_2$), 8·05 (3H, s, Me), and 8·46 (9H, s, Bu^t).

t-Butyl 4-(2-Chloroethyl)-3-methylpyrrole-5-carboxylate (30).—The foregoing iodopyrrole (1·97 g) in methanol (50 ml) containing sodium acetate trihydrate (2 g) and Adams platinum oxide (25 mg) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen had ceased (8 h). After filtration through Celite and evaporation almost to dryness, methylene chloride was added, and the solution was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was filtered through a short column of alumina, with petroleum (b.p. 60—80°) and then with benzene as eluant. Evaporation of the eluates gave a white crystalline solid (1·29 g, 99%), which was crystallised from methylene chloride–n-hexane to give the *2-unsubstituted pyrrole*, m.p. 97—98° (Found: C, 58·9; H, 7·2; N, 5·7. $C_{12}H_{18}ClNO_2$ requires C, 59·1; H, 7·4; N, 5·75%), τ 0·75br (1H, NH), 3·39 (1H, d, J 3 Hz, α-H), 6·41 (2H, t) and 6·89 (2H, t) ($ClCH_2{\cdot}CH_2$), 7·97 (3H, s, Me), and 8·44 (9H, s, Bu^t).

Pyrromethanes

Attempted Synthesis of Benzyl 3,4′-Bis-(2-chloroethyl)-5′-dimethylcarbamoyl)-3′,4-dimethylpyrromethane-5-carboxylate by MacDonald's Method.[7]—Benzyl 2-acetoxymethyl-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylate (0·68 g) and 4-(2-chloroethyl)-5-(dimethylcarbamoyl)-3-methylpyrrole (0·42 g) were dissolved in warm acetic acid (17 ml) and the solution was then heated at 120—130° during 1 h before being poured into cold water (500 ml). After extraction with methylene chloride, the organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and then evaporated to dryness. The oily residue was taken up in ether; addition of petroleum (b.p 60—80°) afforded pale yellow crystals (0·49 g, 49%) of the pyrromethane imine salt (10), m.p. 137—138°. A satisfactory elemental analysis of this compound was not obtained on account of its ready hydrolysis during recrystallisation; τ 2·69 (5H, m, Ph), 4·79 (2H, s, PhCH_2), 5·65 (2H, t, O·CH_2), 6·52 (2H, t, ClCH_2), 7·12 and 7·25 (each 2H, t, CH_2·CH_2X), 6·13 (2H, t, CH_2), 6·77br (6H, s, $\overset{+}{N}Me_2$), and 7·71 and 8·05 (each 3H, s, Me), *m/e* 468 (65%), 432 (100), and 417 (57); *m** 403 (432 ⟶ 417) and 399 (468 ⟶ 432).

The mother liquors from the preceding crystallisation were evaporated to dryness and chromatographed on alumina [elution with benzene through to benzene–ethyl acetate (65 : 35)]. Evaporation of the latter eluates and crystallisation of the residue from ether–light petroleum (b.p. 60—80°) gave 2-[5-*benzyloxycarbonyl*-3-(2-*chloroethyl*)-4-*methylpyrrol*-2-*ylmethyl*]-4,5-*dihydro*-3-*methylpyrano*[3,4-b]-*pyrrol*-7(1H)-*one* (11) (0·11 g, 13%), m.p. 179—181° (Found: C, 65·2; H, 5·7; N, 6·2. $C_{24}H_{25}ClN_2O_4$ requires C, 65·4; H, 5·7; N, 6·35%), τ −0·60br (1H, NH), 0·15br (1H, NH), 2·65 (5H, m, Ph), 4·70 (2H, s, PhCH_2), 5·49 (2H, t, O·CH_2), 6·54 (2H, t, ClCH_2), 7·00 and 7·22 (each 2H, t, CH_2·CH_2X), 6·04 (2H, s, CH_2), and 7·72 and 8·00 (each 3H, s, Me), *m/e* 440 (100%) and 404 (30).

(A) *Methanol–Toluene*-p-*sulphonic Acid Procedure.*—*Dibenzyl 3′-ethyl*-3-(2-*methoxycarbonylethyl*)-4,4′-*dimethylpyrromethane*-5,5′-*dicarboxylate*. A suspension of benzyl 5-acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (0·373 g) and benzyl 4-ethyl-3-methylpyrrole-2-carboxylate (0·243 g) in methanol (5 ml) was treated with toluene-*p*-sulphonic acid hydrate (10 mg) and heated with stirring under nitrogen at 40° during 5 h. The solution was diluted with water (0·5 ml) and the *pyrromethane* (0·520 g, 93%) was isolated by filtration. It was recrystallised from methylene chloride–n-hexane and had m.p. 89—90° (Found: C, 70·9; H, 6·6; N, 4·9. $C_{33}N_{36}N_2O_6$ requires C, 71·2; H, 6·5; N, 5·0%), τ 0·66br and 1·05br (each 1H, NH), 2·74 (10H, s, 2Ph), 4·80 (4H, s, 2PhCH_2), 6·14 (2H, s, CH_2), 6·44 (3H, s, OMe), 7·29 (2H, t) and 7·4—7·7 (4H, m) (CH_2·CH_2 and CH_2·CH_3), 7·72 and 7·75 (each 3H, s, Me), and 8·93 (3H, t, CH_2·CH_3).

The following new compounds were prepared in an analogous way.

Benzyl 3-(2-*chloroethyl*)-5-(*dimethylcarbamoyl*)-4′-*ethyl*-3′,4-*dimethylpyrromethane*-5-*carboxylate*. This was prepared (90%) from benzyl 2-acetoxymethyl-3-(2-chloroethyl)-4-methylpyrrole-2-carboxylate and 5-(dimethylcarbamoyl)-4-ethyl-3-methylpyrrole, m.p. 158—159° (from methylene chloride–n-hexane) (Found: C, 66·5; H, 6·9; N, 8·9. $C_{26}H_{32}ClN_3O_3$ requires C, 66·4; H. 6·9; N, 8·9%), τ 0·12br and 0·18br (each 1H, NH), 2·69 (5H, m, Ph), 4·76 (2H, s, PhCH_2), 6·21 (2H, s, CH_2), 6·66 and 7·15 (each 2H, t) (ClCH_2·CH_2), 7·00 (6H, s, NMe_2), 7·62 (2H, q) and 8·89 (3H, t) (CH_2·CH_3), and 7·73 and 8·00 (each 3H, s, Me).

Benzyl 3,4′-*bis*-(2-*chloroethyl*)-5-(*dimethylcarbamoyl*)-3′,4-*dimethylpyrromethane*-5-*carboxylate* (9). This compound, prepared (85%) from benzyl 2-acetoxymethyl-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylate and 4-(2-chloroethyl)-5-(dimethylcarbamoyl)-3-methylpyrrole, crystallised from methylene chloride–n-hexane with m.p. 137—138° (Found: C, 61·7; H, 6·2; N, 8·25. $C_{26}H_{31}Cl_2N_3O_3$ requires C, 61·9; H, 6·2; N, 8·3%), τ −0·15br and 0·50br (each 1H, NH), 2·65 (5H, s, Ph), 4·73 (2H, s, PhCH_2), 6·21 (2H, s, CH_2), 6·46 (2H, t), 6·63 (2H, t), and 6·9—7·3 (4H, m) (2ClCH_2·CH_2), 6·99 (6H, s, NMe_2), and 7·71 and 7·99 (each 3H, s, Me).

This compound was also prepared (86%) from the same two pyrroles in equal amounts of methanol and methylene chloride containing toluene-*p*-sulphonic acid hydrate at 40° during 12 h.

(B) *Acetic Acid–Toluene*-p-*sulphonic Acid Procedure.*—*Benzyl* 3-(2-*acetoxyethyl*)-5′-(*dimethylcarbamoyl*)-4′-*ethyl*-3′,4-*dimethylpyrromethane*-5-*carboxylate*. A solution of benzyl 3-(2-acetoxyethyl)-2-acetoxymethyl-4-methylpyrrole-5-carboxylate (372 mg) and 5-(dimethylcarbamoyl)-4-ethyl-3-methylpyrrole (190 mg) in acetic acid (5 ml) was treated with toluene-*p*-sulphonic acid hydrate (11 mg) and then heated at 40—42° during 3 h with stirring under nitrogen. Methylene chloride was then added and the solution was washed with aqueous sodium acetate, aqueous sodium hydrogen carbonate, and finally water. The organic phase was dried (Na_2SO_4) and evaporated to dryness and the residue was crystallised from ether–n-hexane to give the *pyrromethane* (453 mg, 92%), m.p. 162—164° (Found: C, 68·05; H, 7·25; N, 8·4. $C_{28}H_{35}N_3O_5$ requires C, 68·1; H, 7·15; N, 8·5%), τ 0·14br (2H, 2NH), 2·71 (5H, s, Ph), 4·78 (2H, s, PhCH_2), 6·03 (2H, t, CH_2O), 6·26 (2H, s, CH_2), 7·03 (6H, s, NMe_2), 7·2—7·8 (4H, m, CH_2·CH_2·O and CH_2·CH_3), 7·74, 8·01, and 8·03 (each 3H, s; 2Me and COMe), and 8·92 (3H, t, CH_2·CH_3).

The following new compounds were prepared in an analogous way.

Benzyl 3-(2-*chloroethyl*)-4′-(2-*methoxycarbonylethyl*)-3′,4-*dimethyl*-5-*t*-*butoxycarbonylpyrromethane*-5-*carboxylate*. Prepared (79%) from benzyl 2-acetoxymethyl-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylate and t-butyl 4-(2-methoxycarbonylethyl)-3-methylpyrrole-5-carboxylate, the *pyrromethane* had m.p. 134—136° (from methylene chloride–n-hexane) (Found: C, 64·4; H, 6·7; N, 4·9. $C_{30}H_{37}ClN_2O_6$ requires C, 64·7; H, 6·7; N, 5·0%), τ 0·30br and 0·85br (each 1H, NH), 2·74 (5H, s, Ph), 4·79 (2H, s, PhCH_2), 6·19 (2H, s, CH_2), 6·39 (3H, s, OMe), 6·67 (2H, t, ClCH_2), 6·9—7·7 (6H, m, CH_2·CH_2·CO and CH_2·CH_2Cl), 7·76 and 8·04 (each 3H, s, Me), and 8·52 (9H, s, Bu^t).

Benzyl 3-(2-*acetoxyethyl*)-4′-(2-*methoxycarbonylethyl*)-3′,4-*dimethyl*-5-*t*-*butoxycarbonylpyrromethane*-5-*carboxylate*. Prepared (84%) from benzyl 3-(2-acetoxyethyl)-2-acetoxymethyl-4-methylpyrrole-5-carboxylate and t-butyl 4-(2-methoxycarbonylethyl)-3-methylpyrrole-5-carboxylate, the *pyrromethane* had m.p. 158—159° (from methylene chloride–n-hexane) (Found: C, 65·5, 65·5, 65·4; H, 7·1, 6·8, 7·0; N, 4·5, 4·8, 4·7. $C_{32}H_{40}N_2O_8$,0·5H_2O requires C, 65·2; H, 7·0; N, 4·75%), τ 0·88br and 1·09br (each 1H, NH), 2·69 (5H, s, Ph), 4·77 (2H, s, PhCH_2), 6·00 (2H, t, CH_2·O), 6·18 (2H, s, CH_2), 6·37 (3H, s, OMe), 7·0—7·7 (6H, m, CH_2·CH_2·O and CH_2·CH_2·CO), 7·73, 8·01, and 8·05 (each 3H, s, 2 Me and COMe), and 8·49 (9H, s, Bu^t).

Tripyrrane

Dibenzyl 2,3,5-Tris-(2-methoxycarbonylethyl)-1,4,6-trimethyltripyrrane-1′,6′-dicarboxylate (15).—Benzyl 3,3′-bis-(2-methoxycarbonylethyl)-4,4′-dimethyl-5-t-butoxycarbonylpyrromethane–5-carboxylate [12] (0·290 g) was dissolved in trifluoroacetic acid (4 ml) and set aside at room temperature during 30 min while a slow stream of nitrogen was passed through it. The solvent was evaporated off and the residual oil was dissolved in methylene chloride which was then washed with saturated aqueous sodium hydrogen carbonate and dried (Na_2SO_4). The solvent was evaporated off to leave an oil, which was treated with benzyl 2-acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-5-carboxylate (0·186 g) and toluene-*p*-sulphonic acid hydrate (9 mg) in methanol (4 ml). The solution was warmed at 35° with stirring during 5 h before being cooled and neutralised with a few crystals of sodium acetate trihydrate. The *tripyrrane* was filtered off (0·140 g, 35%) (t.l.c. showed further quantities to be present in the mother liquors). A sample recrystallised from ether–n-hexane had m.p. 97—99° (Found: C, 68·3; H, 6·6; N, 5·4. $C_{45}H_{51}N_3O_{10}$ requires C, 68·1; H, 6·5; N, 5·3%), τ −0·59br, −0·28br, and 1·25br (each 1H, NH), 2·76 and 2·90 (each 5H, m, Ph), 5·38 and 5·42 (each 2H, s, $PhCH_2$), 6·39 and 6·48 (each 2H, s, CH_2), 6·41 and 6·43 (3H, s and 6H, s; 3OMe), 7·1—7·7 (12H, m, $3CH_2{\cdot}CH_2$), and 7·75, 7·81, and 7·98 (each 3H, s, Me), *m/e* 793 (100%), 762 (5), 720 (2), 706 (23), 702 (46), and 685 (10), *m** 628 (793 ⟶ 706) and 621 (793 ⟶ 702).

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