Mechanism of Heterocyclic Ring Expansions. Part III.[1] Reaction of Pyrroles with Dichlorocarbene

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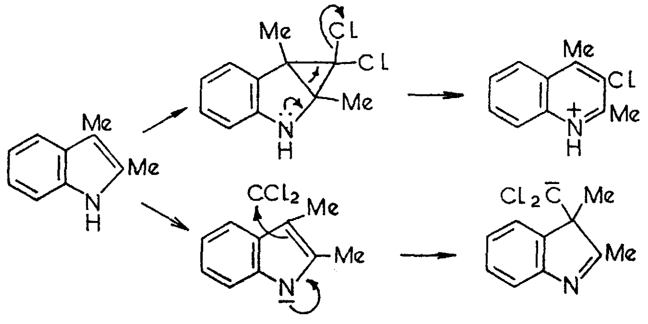
2,5-Dimethyl-, 2,3,4,5-tetramethyl-, and 3,4-dimethyl-2,5-diphenyl-1*H*-pyrrole react with dichlorocarbene in basic solution to give 2-dichloromethyl-2*H*-pyrrole and 3-chloropyridines in low yield. However, in neutral aprotic solution high yields of 3-chloropyridines are formed in a synthetically useful reaction; 2*H*-pyrroles are not formed.

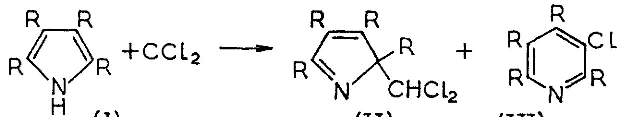
These results support earlier mechanistic proposals.

THE REACTION of 1*H*-indoles with dichlorocarbene gives 3*H*-indoles and quinolines. A reinvestigation[2] of this reaction, particularly with 2,3-dimethyl-1*H*-indole, showed that the 3*H*-indoles were not converted into the quinolines and hence were not intermediates in the ring expansion, as previously claimed.[3] A reaction scheme was proposed[2] in which the two products were formed by different routes, as shown, for example, in the Scheme.



SCHEME

In similar reactions with di- and tetra-methyl-1*H*-pyrroles (I) analogous products were formed and it was again claimed[4] that the 2*H*-pyrroles (II) could be converted into the pyridines (III) in the reactions. Our failure to convert 3*H*-indoles into quinolines obviously cast doubt on this. We have now found, however, that the 3*H*-pyrroles are convertible into pyridines, but that the pyridines formed are not the chloropyridines formed in the carbene reaction nor products derived from them (see Part V). First, however, we studied the reaction of dichlorocarbene with 2,5-dimethyl-, 2,3,4,5-tetramethyl-, and 3,4-dimethyl-2,5-diphenyl-1*H*-pyrrole.



(I) (II) (III)

Dichlorocarbene was generated in two ways: in basic conditions from chloroform and ethanolic sodium ethoxide, and in neutral conditions by thermolysis of sodium trichloroacetate in 1,2-dimethoxyethane. All the carbene reactions were run in anhydrous conditions under nitrogen (since the pyrroles were very readily oxidised); in the sodium trichloroacetate reactions it was important to dissolve the salt by careful warming first, otherwise tars were formed at its surface. Striking differences were found in the amounts of products formed in the two sets of conditions (see Table).

TABLE

Pyrrole	Conditions	2*H*-Pyrrole (II) (%)	Pyridine (III) (%)	1*H*-Pyrrole (I) recovered (%)
2,5-Me$_2$	Basic	6	9	38
	Neutral	0	70	25
2,3,4,5-Me$_4$	Basic	12	5	10
	Neutral	0	55	0
3,4-Me$_2$,2,5-Ph$_2$	Basic	8	1	90
	Neutral	0	90	0

In basic conditions the pyrrole and its conjugate base compete with the excess of ethoxide ions and solvent molecules for dichlorocarbene and much of the carbene will be lost by solvolysis—hence the low yield of both products. In the neutral aprotic conditions however these by-product pathways are eliminated, or much reduced, and an increase in yield should result. Indeed the amounts of pyridines (III) formed were greatly increased, approaching a quantitative yield with dimethyldiphenyl-1*H*-pyrrole and, after allowing for recovered starting material, with dimethyl-1*H*-pyrrole; the lower yield with tetramethyl-1*H*-pyrrole is ascribed to its greater sensitivity to oxidation.

The complete absence of 2*H*-pyrroles in the neutral conditions supports the proposal[2] that ring-expanded products arise from initial cycloaddition of dichlorocarbene to neutral molecules, and that 2*H*-pyrroles arise from electrophilic attack by dichlorocarbene on the ambident pyrryl anion (*cf.* the Scheme).

The sodium trichloroacetate reaction provides a useful synthetic route to the substituted 3-chloropyridines; 1*H*-pyrrole itself gave only 7% of 3-chloropyridine, however.

The structures of the products, particularly the 2*H*-pyrroles which had been in doubt, were established spectroscopically (see Experimental section).

In a related study of the reaction of 2,5-dimethyl-1*H*-pyrrole with chloroform and potassium hydroxide in aqueous ethanol, Nicoletti and Forcellese have shown

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[1] Part II, C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 1964, 938.

[2] C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 1964, 928.

[3] G. Plancher and O. Carrasco, *Atti. Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1904, **13**, I, 575.

[4] G. Plancher and U. Ponti, *Atti. Accad. naz. Lincei, Rend. Classe, Sci. fis. mat. nat.*, 1909, **18**, II, 469.

that the relative amount of 2*H*-pyrrole formed increases with increase of water in the medium.[5]

EXPERIMENTAL

For general directions, see Part I.[2]

2,5-Dimethyl-1*H*-pyrrole [5] was distilled under nitrogen, b.p. 60°/12 mm., and stored in a sealed, dark-glass container under nitrogen at 0°. 2,3,4,5-Tetramethyl-1*H*-pyrrole was prepared by the same method from ammonium carbonate (0·2 mole) and 3,4-dimethylhexane-2,5-dione (0·1 mole) to give golden plates (90%), m.p. 108° (lit.,[6] m.p. 110°), which darkened rapidly on exposure to air and light; it was dried *in vacuo* over phosphorous pentoxide and used immediately without further purification. Vacuum sublimation followed by crystallisation from light petroleum (b.p. 40—60°) gave plates, m.p. 110°.

3,4-*Dimethyl*-2,5-*diphenyl*-1H-*pyrrole*.—2,3-Dimethyl-1,4-diphenylbutane-1,4-dione was prepared (*cf*. ref. 7) by heating propiophenone (100 g.) with lead dioxide (120 g.) in dry benzene (200 ml.) under reflux for 24 hr. The mixture was cooled, filtered, and separated from the water formed. The benzene solution was dried and evaporated to give a viscous yellow oil (90 g.). Chromatography of this on basic alumina (in several portions) gave diketone (36·2 g.), m.p. 66° [from light petroleum (40—60°)] (lit.,[7] m.p. 67°); dioxime, m.p. 245° (lit.,[7] m.p. 245°). The diketone (13·3 g.) in ethanol was saturated with ammonia and heated in an autoclave at 150° for 10 hr. The mixture was evaporated to dryness to give a brown solid which crystallised from ethanol as almost colourless needles of 3,4-*dimethyl*-2,5-*diphenyl*-1H-*pyrrole* (11·4 g., 92%), m.p. 136° (Found: C, 87·5; H, 7·1; N, 5·3. $C_{18}H_{17}N$ requires C, 87·5; H, 6·9; N, 5·7%), $\lambda_{max.}$ 208 (log ε 4·11), 321 mμ (4·34); $\nu_{max.}$ 3415 (N–H), 1605 (pyrrole ring C=C), 1589, 1499 (phenyl ring C=C), 1293, 1272 (C–N), 766, 702, 697 cm.$^{-1}$ (monosubstituted phenyl); n.m.r. (CCl_4) τ 7·75 (3H, methyls), 2·42 (10H, phenyls), 2·0 (1H, broad band, N–H). The pyrrole was dried *in vacuo* over phosphorus pentoxide before use.

2,5-*Dimethyl*-1H-*pyrrole and Dichlorocarbene*.—(a) *Basic conditions*. Sodium (11·5 g., 0·5 mole) was dissolved in absolute ethanol (200 ml.) in a flask fitted with a reflux condenser and mechanical stirrer, and flushed with nitrogen. The 1*H*-pyrrole (19 g., 0·2 mole) was added and the mixture was heated to 55° on a water-bath. Chloroform (40 ml.) in ethanol (40 ml.) was added dropwise during 1 hr. and the mixture was stirred at 55° for a further 18 hr. The sodium chloride was filtered off and volatile materials were removed under nitrogen at 40°/15 mm. The residue was treated with ice-cold 10% hydrochloric acid (200 ml.) and was then thoroughly extracted with ether, with minimum exposure to the air. The acidic solution was basified with concentrated aqueous potassium hydroxide whereupon a brown ether-insoluble solid was precipitated. This solid was collected and dried to give an orange sternutatory powder (4·5 g.). The alkaline filtrate was thoroughly extracted with ether and the aqueous layer was discarded.

The nonbasic fraction, a red oil (7 g.), was largely unchanged 2,5-dimethyl-1*H*-pyrrole (g.l.c., i.r.) and the pure 1*H*-pyrrole (37%) was recovered by distillation. The orange solid could not be crystallised, but on sublimation at 120°/1 mm. a portion (0·5 g.) gave 2,5-dimethyl-1*H*-pyrrole-3-carbaldehyde (22 mg., 0·8%), m.p. 143° (lit.,[4] m.p. 144°) $\nu_{max.}$ 3320, 3190 (NH), 1635 (C=O), 1602 (C=C), 1370 (C–N), 840 (aldehyde C–H), 807 cm.$^{-1}$ (ring C–H); n.m.r. ($CDCl_3$) τ 7·70 (3H, 5-Me), 7·40 (3H, 2-Me), 3·64 (1H, m, 4-H), 1—0 (1H, very broad, N–H), –0·02 (1H, aldehyde H).

The basic fraction, a dark brown oil (9·7 g.), contained three compounds (g.l.c.) separated by chromatography on neutral alumina. (i) 3-Chloro-2,6-dimethylpyridine (2·60 g., 9·2%) b.p. 71°/12 mm., [picrate, m.p. 153° (lit.,[4] m.p. 150—151°] $\lambda_{max.}$ 274 mμ (log ε 3·61); $\nu_{max.}$ 1576, 1450, 1140, 1053, 1026, 829, 725, 715 cm.$^{-1}$; n.m.r. (CCl_4) τ 7·62 (3H, 6-Me), 7·52 (3H, 2-Me), 3·25 (2H, d, *J* 7·8 c./sec., 5-H), 2·66 (2H, d, *J* 7·8 c./sec., 4-H).

(ii) 2,5-Dimethyl-1*H*-pyrrole (0·13 g.) (i.r. and g.l.c. retention times).

(iii) 2-Dichloromethyl-2,5-dimethyl-2*H*-pyrrole (2·18 g., 6·3%), a pale yellow oil, b.p. 90°/12 mm., [picrate, m.p. 144°, (lit.,[4] m.p. 144°)] $\lambda_{max.}$ 2·30 mμ (log ε 3·23) (2H-pyrrole absorption); $\nu_{max.}$ 2990, 2940 (methyl C–H), 1622, 1532 (C=N and C=C), 1450, 1435, 1385 (methyl C–H), 1349 (C–N), 783, 769, 754, 738 cm.$^{-1}$ (C–H and C–Cl of dichloromethyl); n.m.r. (CCl_4) τ 8·53 (3H, 2-Me), 7·81 (3H, 5-Me), 3·99 (1H, $CHCl_2$), 3·57 (1H, d, *J* 5·4 c./sec.) and 2·67 (1H, d, *J* 5·4 c./sec.) (3- and 4-H). The existence of two adjacent olefinic protons confirms the 2*H*-pyrrole structure.

(b) *Neutral conditions*. 2,5-Dimethyl-1*H*-pyrrole (19 g., 0·2 mole) and sodium trichloroacetate (110 g., 0·6 mole) were heated under reflux in 1,2-dimethoxyethane (250 ml.) for 24 hr. under nitrogen. The solution was filtered, the volatile material was removed, and the dark, oily residue was worked up as in the previous experiment. Two fractions were obtained. The nonbasic fraction (4·85 g., 25%) was unchanged 2,5-dimethyl-1*H*-pyrrole (g.l.c., i.r.). The basic fraction (21·2 g.) was largely 3-chloro-2,6-dimethylpyridine with a trace of starting pyrrole (g.l.c.); fractional distillation gave pure chloropyridine (20 g., 70%). No 2*H*-pyrrole or 2,3-dimethyl-1*H*-pyrrole-3-carbaldehyde could be detected (g.l.c., t.l.c.).

2,3,4,5-*Tetramethyl*-1H-*pyrrole and Dichlorocarbene*.—(a) *Basic conditions*. The pyrrole (12·3 g., 0·1 mole) was added to a solution of sodium (5·75 g., 0·25 mole) in absolute ethanol (100 ml.) and treated with chloroform (20 ml.) in ethanol (20 ml.) under nitrogen at 55° for 18 hr. as above. The solution was filtered, evaporated, and extracted as before to give two fractions.

The nonbasic, dark oil (1·45 g.) was largely starting pyrrole (t.l.c.); chromatography on basic alumina gave tetramethyl-1*H*-pyrrole (1·21 g., 9·8%), m.p. 107—108°, as the only product.

The basic fraction (10·2 g.) contained three compounds (t.l.c.), separated by chromatography on neutral alumina: (i) tetramethyl-1*H*-pyrrole (0·45 g., 0·4%), m.p. 107—108°. (ii) 3-Chloro-2,4,5,6-tetramethylpyridine (0·89 g., 5·3%), needles, m.p. 41—42° (after sublimation at 50°/1 mm.) (lit.,[8] m.p. 39—40°), forming a picrate, m.p. 154°, (lit.,[9] m.p. 150—152°) $\lambda_{max.}$ 221 (log ε 3·67), 274 mμ (3·59); $\nu_{max.}$ 1576, 1556 (ring C=C and C=N), 1450, 1417 (methyl C–H), 1177, 1007, 977, 777, 732 (pyridine ring vibrations), 725 cm.$^{-1}$; n.m.r. (CCl_4) τ 7·80 (3H, 5-Me), 7·68 (3H, 4-Me), 7·55 (3H, 6-Me), 7·43 (3H, 2-Me). (iii) 2-Dichloromethyl-2,3,4,5-tetra-

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methyl-2*H*-pyrrole (2·38 g., 11·6%), prisms from light petroleum (b.p. 40—60°), m.p. 85° (lit.,[9] m.p. 86—87°), forming a picrate, orange prisms, m.p. 189°, (lit.,[9] m.p. 189°) $\lambda_{max.}$ 284 mμ (log ε 3·34) (2*H*-pyrrole absorption); $\nu_{max.}$ 1661, 1573 (C=C and C=N), 1440, 1383 (methyl C–H), 1330 (C–N), 1270, 1259, 1198, 1119, 1100, 1077, 920, 804, 765, 732, 692 cm.$^{-1}$; n.m.r. (CCl_4) τ 8·61 (3H, 2-Me), 8·29 (3H, q, *J* 1·2 c./sec., 4-Me), 8·19 (3H, q, *J* 1·2 c./sec., 3-Me), 7·81 (3H, 5-Me), 4·14 (1H, $CHCl_2$).

(b) *Neutral conditions.* 2,3,4,5-Tetramethyl-1*H*-pyrrole (11·1 g., 0·09 mole) and sodium trichloroacetate (50 g., 0·27 mole) were heated under nitrogen in refluxing 1,2-dimethoxyethane (100 ml.) for 24 hr. The solution was filtered, evaporated, and extracted as before to give two fractions. The nonbasic fraction (7·15 g.) consisted of polymeric tarry materials and was not investigated further. The basic fraction (8·40 g.) consisted of one compound (t.l.c.) and chromatography on neutral alumina gave pure 3-chloro-2,4,5,6-tetramethylpyridine (8·21 g., 55%), m.p. 40°. 2-Dichloromethyl-2,3,4,5-tetramethyl-2*H*-pyrrole could not be detected (t.l.c.).

3,4-*Dimethyl*-2,5-*diphenyl*-1H-*pyrrole and Dichlorocarbene.*—(a) *Basic conditions.* The pyrrole (10 g., 0·04 mole) was added to a solution of sodium (2·3 g., 0·1 mole) in absolute ethanol (100 ml.) and the mixture was treated with chloroform (10 ml.) in ethanol (10 ml.) as before. The solution was filtered, extracted, and evaporated to give two fractions. The nonbasic solid (8·98 g.) was largely starting material (t.l.c.) and crystallization from ethanol gave 3,4-dimethyl-2,5-diphenyl-1*H*-pyrrole (8·9 g., 89%), m.p. 136°.

The basic fraction, a brown solid (1·1 g.), contained two compounds (t.l.c.). Crystallisation from light petroleum (b.p. 40—60°)–ether gave 2-*dichloromethyl*-3,4-*dimethyl*-2,5-*diphenyl*-2H-*pyrrole* (0·9 g., 6·8%) as needles, m.p. 127° (Found: C, 69·0; H, 5·2; N, 4·1. $C_{19}H_{17}Cl_2N$ requires C, 69·1; H, 5·2; N, 4·2%) $\lambda_{max.}$ 209 (log ε 4·15), 248 mμ (3·98); $\nu_{max.}$ 1654, 1545 (2*H*-pyrrole C=C and C=N), 1604, 1500 (Ar C=C), 1450 (methyl C–H), 1351 (C–N), 1229, 1162, 1055, 1027 (Ar C–H), 792, 752, 655 (C–H and C–Cl of $CHCl_2$), 778, 714, 704 cm.$^{-1}$ (monosubstituted benzene); n.m.r. ($CDCl_3$) τ 7·99 (3H, m, 3-Me), 7·93 (3H, m, 4-Me), 3·40 (1H, $CHCl_2$), 2·1—2·7 (Ar). The mother liquor from the recrystallisation was chromatographed on basic alumina to give the following: (i) 3-*Chloro*-4,5-*dimethyl*-2,6-*diphenylpyridine* (0·1 g., 0·9%), m.p. 148° (from ethanol) (Found: C, 77·4; H, 5·4; N, 4·6. $C_{19}H_{16}ClN$ requires C, 77·7; H, 5·5; N, 4·8%) [*picrate*, m.p. 155° (from ethanol) (Found: C, 57·5; H, 3·7; N, 10·8. $C_{25}H_{19}ClN_4O_7$ requires C, 57·4; H, 3·6; N, 10·7%)] $\lambda_{max.}$ 214 (log ε 4·29), 232 (4·20), 287 mμ (3·82) (pyridine conjugated with phenyl rings); $\nu_{max.}$ 1553, 1450, 1371 (methyl C–H), 1400, 1146, 1077, 1040 (Ar C–H), 1026, 901, 793, 775, 764 (pyridine ring vibrations), 769, 710, 704 (monosubstituted benzene), 674 cm.$^{-1}$; n.m.r. (CCl_4) τ 7·68 (3H, 5-Me), 7·50 (3H, 4-Me), *ca.* 2·5 (10H, Ar). (ii) 2-Dichloromethyl-3,4-dimethyl-2,5-diphenyl-2*H*-pyrrole (0·1 g., 0·8%) (i.r., t.l.c.).

(b) *Neutral conditions.* 3,4-Dimethyl-2,5-diphenyl-1*H*-pyrrole (2·5 g., 0·01 mole) and sodium trichloroacetate (5·6 g., 0·03 mole) were heated in refluxing 1,2-dimethoxyethane (50 ml.) under nitrogen for 24 hr. The solution was filtered, evaporated, and extracted as before to give a basic fraction only, a brown solid (3·2 g.) consisting mainly of one compound (t.l.c.). Crystallisation from ethanol gave 3-chloro-4,5-dimethyl-2,6-diphenylpyridine (2·7 g., 90%), m.p. 148°. No 2*H*-pyrrole could be detected in this reaction (t.l.c.).

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