374. *Pyrroles and Related Compounds. Part IV.*[1] *Mass Spectrometry in Structural and Stereochemical Problems. Part XXX.*[2] *Mass Spectra of Monocyclic Derivatives of Pyrrole.*

By H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson.

Mass spectra of 53 pyrroles (Table 1) are recorded (Table 2). The general characteristics of fragmentation are discussed in detail; the capacity of the pyrrole nucleus to bear a positive charge and detachment of hydrogen from the heterocyclic nitrogen atom have profound influences. The principal modes of fragmentation for carboxylic esters are shown in Table 3. In suitably disubstituted pyrroles double cleavage to ions like (*j*), (*k*), and (*n*) is important.

Mass spectrometry has been very valuable in structural work with many natural products,[3] and doubtless it will become equally important in the porphyrin field, where the quantities of available material are often minute and analytical difficulties are troublesome. Indeed mass spectra of two metal complexes of porphyrins have already been recorded.[4] We have therefore engaged in a joint programme of synthesis (at Liverpool) and mass spectrometry (at Stanford). This Paper is concerned solely with monocyclic derivatives of pyrrole, which were studied to provide a background for interpreting fragmentations of compounds containing two or more pyrrole rings. The data are likely to be useful in connection with bile pigments, natural products such as prodigiosin,[5] and intermediates in porphyrin syntheses, even if the macrocyclic porphyrins themselves should behave

[1] Part III, *J.*, preceding paper.
[2] Part XXIX, Kjaer, Ohashi, Wilson, and Djerassi, *Acta Chem. Scand.*, 1963, **17**, 2143.
[3] Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill, New York, 1962; Djerassi, *Pure Appl. Chem.*, 1963, **6**, no. 4, and references cited therein.
[4] Hood, Carlson, and O'Neal in "Encyclopaedia of Spectroscopy," ed. Clark, Reinhold, New York, 1960, Vol. I, p. 616; Mead and Wilde, *Chem. and Ind.*, 1961, 1315.
[5] Wasserman, McKeon, Smith, and Forgione, *J. Amer. Chem. Soc.*, 1960, **82**, 506; Rapoport and Holden, *ibid.*, 1962, **84**, 635.

TABLE 1.

Pyrroles investigated.

Compound Number	Substituents at positions 1	2	3	4	5
I	H	H	H	H	H
II	Me	H	H	H	H
III	H	Me	H	H	H
IV	H	Me	Me	H	H
V	H	Me	H	Me	H
VI	H	Me	H	H	Me
VII	H	H	Me	Me	H
VIII	H	Me	Me	Me	H
IX	H	H	Me	Et	H
X	H	Me	Et	Me	H
XI	Me	Me	H	H	Et
XII	Me	Me	H	H	Vinyl
XIII	H	CHO	H	H	H
XIV	H	Me	Et	Me	CHO
XV	H	COMe	H	H	H
XVI	H	Me	COMe	Me	H
XVII	H	Me	COMe	Me	Me
XVIII	H	CO_2H	H	H	H
XIX	H	CO_2Me	H	H	H
XX	H	CO_2Et	H	H	H
XXI	Me	CO_2Et	H	H	H
XXII	H	CO_2Et	Me	H	H
XXIII	H	CO_2Et	H	H	Me
XXIV	H	CO_2Et	Me	H	Me
XXV	H	CO_2Et	H	Me	Me
XXVI	H	$CO_2 \cdot CH_2 \cdot Ph$	H	Me	Me
XXVII	H	CO_2Et	H	Me	Et
XXVIII	H	CO_2Me	Me	Et	Me
XXIX	H	CO_2Et	Me	Et	Me
XXX	H	$CO_2 \cdot CH_2 \cdot Ph$	Me	Et	Me
XXXI	H	CO_2Et	Et	Me	Me
XXXII	H	CO_2Me	Me	$CH_2 \cdot CH_2 \cdot CO_2Me$	Me
XXXIII	H	Me	CO_2Me	Me	H
XXXIV	H	Me	CO_2Et	Me	H
XXXV	H	Me	CO_2Et	Me	Me
XXXVI	H	CO_2H	CO_2Et	H	H
XXXVII	H	CO_2Me	Me	CO_2Me	Me
XXXVIII	H	CO_2Et	Me	CO_2Et	Me
XXXIX	H	CO_2H	Et	Me	CO_2Et
XL	H	CO_2Me	Et	Me	CO_2Me
XLI	H	CO_2Et	Et	Me	CO_2Et
XLII	H	CO_2Et	Me	CHO	Me
XLIII	H	CO_2Et	Me	Et	CHO
XLIV	H	Me	CO_2Et	Me	CHO
XLV	H	CO_2H	COMe	Me	Me
XLVI	H	CO_2Et	COMe	Me	Me
XLVII	H	CO_2Me	Me	COMe	Me
XLVIII	H	CO_2Et	Me	COMe	Me
XLIX	H	H	CO_2Et	OMe	H
L	H	CO_2Et	OH	CO_2Et	H
LI	H	CO_2Et	OMe	CO_2Et	H
LII	Me	CO_2Et	OMe	CO_2Et	H
LIII	H	CO_2Et	H	CO_2Et	OMe

differently. We have found that porphyrins themselves can be handled mass-spectrometrically by a device [6] for direct insertion of the samples, and these results will be reported in due course.

Mass spectra of pyrrole and of four simple homologues have been reported,[7] and we now add seven more examples. In the case of pyrrole itself, the molecular ion is the base peak, but there is extensive cleavage of the nucleus. Re-examination of part of

[6] Lynch, Wilson, Budzikiewicz, and Djerassi, *Experientia*, 1963, **19**, 211.
[7] American Petroleum Institute, Research Project 44, Data Sheets 1532, 1347, 1418, 1536, 1719.

the spectrum with the MS9 double-focusing spectrometer * has yielded the following information. The most abundant fragment (*m/e* 39) is $C_3H_3^+$, doubtless the cyclopropenyl ion, accompanied by less than 1% of C_2HN^+. Next in intensity, the peak at *m/e* 41 is solely due to $C_2H_3N^+$, resulting from loss of acetylene. A third peak (*m/e* 40), only slightly weaker than its neighbours, comprises two fragments, $C_3H_4^+$ and $C_2H_2N^+$ (ratio 4·5 : 1). The former corresponds to loss of HCN and it is thus formally, and perhaps structurally, similar to the fragment having *m/e* 41. Similarly the minor component is probably the aza-analogue of the cyclopropenyl ion. This example demonstrates the necessity of highly resolved spectra for understanding the processes of ring cleavage. Until we can make such measurements, we are concentrating on peaks at higher mass numbers, summarised in Table 2.

TABLE 2.

Principal peaks in mass spectra of pyrroles.

Peaks are listed in descending order of *m/e* ratio with intensities, expressed as percentage of the strongest (base) peak, in parentheses. Peaks below 5% have been omitted. In general, peaks below *m/e* 100 have been omitted unless they are especially prominent, except for compounds (I—XIII), (XV), (XVIII—XX) for which the list is comprehensive.

I: 68(5), 67(100), 66(8), 41(63), 40(54), 39(68), 38(25), 34(17).

II: 82(6), 81(100), 80(80), 78(6), 55(19), 54(15), 53(33), 52(8), 51(10), 50(9), 42(34), 41(7), 40(9), 39(39), 38(12), 37(7).

III: 81(60), 80(100), 53(22), 52(9), 51(8), 50(7), 41(6), 40(6), 39(9), 38(5).

IV: 97(5), 96(67), 95(100), 94(12), 81(24), 68(9), 54(12), 53(6), 52(7), 43(9), 42(10).

V: 95(61), 94(100), 93(5), 80(19), 67(7), 65(5), 53(7), 42(6), 41(13), 40(5), 39(19), 38(5).

VI: 95(58), 94(100), 93(9), 80(18), 53(8), 52(8), 51(9), 50(6), 42(15), 41(8), 39(8).

VII: 95(63), 94(100), 93(7), 80(30), 67(15), 66(5), 65(8), 53(10), 52(8), 51(7), 41(24), 40(8), 39(33).

VIII: 109(59), 108(100), 107(9), 106(6), 94(49), 93(10), 79(13), 77(10), 67(13), 66(5), 65(9), 42(13), 41(22), 40(6), 39(27), 38(5).

IX: 109(42), 108(8), 95(7), 94(100), 80(6), 67(12), 65(5), 53(6), 52(5), 51(5), 41(11), 39(12).

X: 123(34), 122(7), 109(8), 108(100), 107(8), 106(7).

XI: 123(28), 95(7), 94(100), 93(5), 52(6), 41(9), 40(6), 38(7).

XII: 122(7), 121(73), 120(39), 106(9), 95(7), 94(100), 93(9), 92(5), 80(7), 79(13), 78(7), 77(14), 67(5), 66(6), 65(9), 63(5), 54(5), 53(17), 52(11), 51(14), 50(6), 42(50), 41(17), 40(5), 39(31), 38(5).

XIII: 96(8), 95(100), 94(68), 67(5), 66(49), 41(10), 40(14), 39(40), 38(17), 37(10).

XIV: 151(34), 150(6), 137(9), 136(100).

XV: 110(6), 109(80), 95(7), 94(100), 67(5), 66(50), 53(7), 43(13), 41(5), 40(10), 39(35), 38(12), 37(6).

XVI: 138(5), 137(49), 123(8), 122(100), 94(7).

XVII: 152(5), 151(76), 150(7), 137(10), 136(100), 108(18), 107(7).

XVIII: 112(7), 111(100), 94(32), 93(98), 67(29), 66(34), 65(48), 64(9), 55(5), 45(9), 44(22).

XVIII, after treatment with D_2O: 114(6), 113(40), 112(24), 95(23), 94(18), 93(87), 70(5), 69(17), 68(17), 67(60), 66(33), 65(100), 64(15), 57(5), 56(8), 55(12), 53(12), 46(20), 45(5).

XIX: 126(5), 125(72), 95(8), 94(100), 93(36), 67(7), 66(38), 65(12), 64(5).

XX: 139(27), 111(20), 95(15), 94(100), 93(90), 67(19), 66(43), 65(20), 64(5), 40(11), 39(44), 38(15), 37(5).

XXI: 153(43), 125(14), 124(7), 109(10), 108(100), 107(5), 106(12), 81(26), 80(24), 79(10), 78(7), 77(7).

XXII: 154(10), 153(82), 125(20), 124(66), 109(14), 108(100), 107(88), 106(50), 81(20), 80(43), 79(49), 78(18).

XXIII: 154(8), 153(73), 125(16), 109(13), 108(97), 107(100), 106(12), 81(21), 80(35), 79(45), 78(13).

XXIV: 168(11), 167(96), 139(11), 138(28), 123(10), 122(82), 121(100), 120(39), 95(22), 94(28), 93(32), 92(17).

XXV: 168(10), 167(84), 152(9), 123(10), 122(85), 121(100), 120(25), 95(17), 94(28), 93(53), 92(15), 91(5).

XXVI: 230(16), 229(100), 184(7), 123(6), 122(45), 121(7), 108(17), 107(12), 95(16), 94(12), 93(9), 92(36), 91(410).

XXVII: 182(10), 181(81), 167(10), 166(100), 153(5), 138(48), 137(7), 136(52), 135(8), 134(18), 121(10), 120(98), 109(8), 108(25), 107(51), 106(18).

* Mr. M. Barber (A.E.I. Instrumentation Division) kindly did this work.

TABLE 2. (*Continued.*)

XXVIII: 181(31), 167(5), 166(38), 150(51), 149(7), 148(10), 135(10), 134(100), 120(5), 108(5), 107(6), 106(13).

XXIX: 196(5), 195(43), 181(5), 180(31), 166(5), 152(5), 150(21), 149(10), 148(12), 135(10), 134(100), 107(5), 106(9).

XXX: 258(19), 257(100), 243(8), 242(45), 166(23), 150(33), 149(7), 148(14), 136(5), 134(26), 123(32), 122(5), 108(12), 107(11), 106(7), 92(27), 91(330), 65(32).

XXXI: 196(15), 195(87), 180(22), 167(10), 166(58), 152(15), 151(6), 150(50), 149(50), 148(100), 136(10), 135(9), 134(92), 123(17), 122(32), 121(21), 120(32), 118(6), 108(18), 107(32), 106(50), 105(7), 104(11).

XXXII: 239(32), 211(9), 208(13), 180(12), 167(11), 166(100), 165(5), 164(5), 147(18), 146(10), 135(14), 134(100), 133(12), 120(11), 119(7), 118(5), 107(5), 106(15), 105(9), 104(13).

XXXIII: 154(7), 153(74), 152(5), 138(34), 123(7), 122(100), 121(38), 120(18), 94(21), 93(44), 92(5).

XXXIV: 168(8), 167(76), 139(11), 138(100), 123(9), 122(98), 121(31), 120(15), 94(18), 93(30).

XXXV: 182(9), 181(68), 153(11), 152(100), 137(5), 136(48), 135(13), 134(10), 108(11), 107(20).

XXXVI: 184(4), 183(27), 155(13), 139(25), 138(56), 137(9), 124(5), 121(8), 120(75), 111(29), 95(12), 94(100), 93(47).

XXXVII: 212(13), 211(93), 196(12), 181(7), 180(63), 179(49), 178(14), 164(28), 152(8), 151(18), 150(5), 149(11), 148(100), 147(49), 136(8), 122(7), 121(8), 120(18), 119(20).

XXXVIII: 240(14), 239(100), 211(11), 210(44), 195(9), 194(63), 193(33), 183(5), 182(34), 167(13), 166(31), 165(25), 164(64), 149(15), 148(86), 147(30).

XXXIX: 226(10), 225(77), 211(6), 210(50), 197(7), 196(44), 192(6), 182(9), 181(15), 180(15), 179(12), 178(57), 166(13), 165(11), 164(100), 163(8), 162(36), 161(10), 160(26), 153(6), 152(11), 151(26), 146(28), 138(6), 136(15), 135(12), 134(30), 133(26), 132(5), 121(5), 120(40), 119(5), 108(10), 107(9), 106(18), 105(15), 104(12).

XL: 226(9), 225(72), 211(10), 210(82), 194(17), 193(7), 192(12), 179(10), 178(100), 166(8), 165(15), 163(5), 162(46), 161(10), 160(43), 150(8), 148(11), 146(9), 134(20), 133(24), 132(5), 107(5), 106(14), 105(14), 104(13).

XLI: 254(11), 253(71), 238(26), 225(14), 224(100), 210(7), 209(5), 208(28), 207(9), 206(21), 196(8), 192(28), 180(11), 179(20), 178(79), 165(5), 164(51), 163(9), 162(68), 161(14), 160(74), 148(6), 146(10), 136(5), 135(12), 134(29), 133(28), 132(6), 120(5), 119(6), 108(5), 107(13), 106(24), 105(19), 104(18).

XLII: 196(13), 195(90), 166(7), 151(5), 150(48), 149(100), 148(78), 123(12), 122(21), 121(78), 120(9).

XLIII: 210(8), 209(63), 194(6), 180(15), 164(20), 163(8), 162(35), 148(40), 136(12), 135(100), 134(13), 120(6), 108(7), 107(5), 106(12).

XLIV: 196(11), 195(90), 167(17), 166(90), 151(12), 150(100), 149(31), 148(26), 138(6), 123(27), 122(15), 121(31), 120(8)

XLV: 181(60), 166(50), 163(50), 149(50), 148(200), 137(44), 136(5), 122(8), 121(100).

XLVI: 209(73), 195(5), 194(44), 166(34), 164(21), 163(28), 162(14), 149(6), 148(64), 136(6), 135(29), 134(10), 122(22), 121(13), 120(27), 108(9), 107(44), 106(19).

XLVII: 196(5), 195(36), 180(25), 165(5), 164(10), 162(6), 149(10), 148(100).

XLVII, after treatment with D_2O: 196(23), 195(10), 181(20), 180(8), 165(6), 162(5), 149(8), 148(100).

XLVIII: 209(32), 194(23), 164(13), 163(6), 162(9), 149(10), 148(100), 43(34).

XLIX: 169(59), 126(14), 125(8), 124(100), 123(7), 122(37), 110(16), 109(35), 94(17).

L: 227(42), 209(5), 183(5), 182(30), 181(100), 155(7), 153(15), 140(7), 137(15), 136(39), 135(100), 127(7), 124(8), 110(5), 109(18), 108(6), 107(5).

LI: 242(9), 241(69), 197(33), 196(14), 195(32), 169(10), 168(9), 167(35), 166(47), 152(10), 151(9), 150(100), 149(6), 148(20), 139(12), 138(25), 136(20), 135(17), 123(11), 122(18), 121(25), 120(10), 110(13), 109(6), 108(5), 53(95).

LII: 256(14), 255(100), 240(7), 212(5), 211(6), 210(55), 209(6), 208(23), 194(14), 183(28), 182(22), 181(9), 180(68), 168(13), 166(8), 155(5), 153(5), 152(40), 150(22), 140(5), 138(10), 137(6), 136(30), 124(13), 123(16), 122(6), 109(5), 108(11).

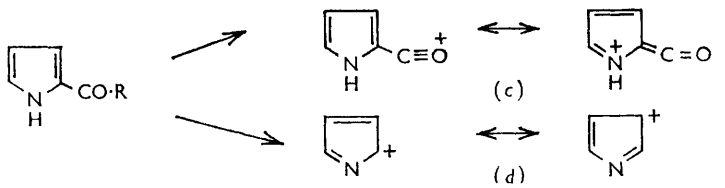
LIII: 256(15), 255(100), 241(10), 240(74), 227(5), 212(29), 211(7), 210(57), 208(11), 196(5), 195(10), 184(31), 183(9), 182(25), 180(5), 168(15), 167(16), 156(24), 150(9), 141(7), 140(6), 139(5), 138(16) 137(5), 127(17), 113(9), 112(8), 111(7).

The spectrum of 1-methylpyrrole differs notably from that of pyrrole in two respects. Instead of the large peak (*m/e* 28), corresponding to $HC{\equiv}\overset{+}{N}H$, there is a peak (*m/e* 42), doubtless from $HC{\equiv}\overset{+}{N}Me$, and there is a very strong M — 1 peak. The latter is probably due to the pyridinium cation, because this ring expansion should be at least as easy as

that from toluene to tropylium cation, which has been elegantly demonstrated by isotopic experiments,[8] but the hypothesis needs confirmation. Alternatively, the fragment might be merely the unrearranged azafulvene cation. The M — 1 peak becomes the base peak in the spectra of *C*-methylated pyrroles (III—VIII), and this could also be accounted to ring expansion. However, there is a significant difference from the behaviour of analogous benzenes.[9] Xylenes exhibit much greater loss of a methyl group than of a hydrogen atom, whereas in the pyrrole series the M — 15 peak, although significant, is only a fraction of the M — 1 peak. Thus, although methyl is perhaps lost from the molecular ion with ring expansion, the main peak may well correspond to an unrearranged ion, (*a*) or (*b*).* The exceptional reactivity of halogenomethyl-, acetoxymethyl-, and similarly substituted pyrroles expresses the marked tendency to form such ions in solution. Throughout the following discussion, the fragments formed by fission of a bond at one remove from the pyrrole ring will be assumed to have the form (*a*) or (*b*), rather than that of a rearranged pyridinium ion. The spectra of the four isomeric di-*C*-methylpyrroles (IV—VII) are very similar, but insertion of an ethyl group (*e.g.*, in X) makes a profound change. The M — 15 peak is now the base peak and there is little

further fragmentation. These results are also ascribed to formation of stable ions of type (*a*) or (*b*), and, in general, the more complex pyrroles are spared major breakdown by initial cleavage of substituents yielding a series of relatively stable ions. Similar observations have been made with alkylindoles.[10] Two 1-methylpyrroles (XI, XII) are remarkable in losing a 2-ethyl or 2-vinyl group in the major cleavage.

Acylpyrroles display a marked tendency to form acylium ions, *e.g.*, (*c*). Thus 2-formylpyrrole (XIII), like benzaldehyde, gives a strong M — 1 peak; the only other abundant fragments are at *m/e* 66 [loss of the formyl group, ion (*d*)] and *m/e* 39 (cyclopropenyl ion, cf. case of pyrrole). Likewise 2-acetylpyrrole (XV) shows M — 15 (*c*) as the base peak and the remainder of the spectrum is identical with that of 2-formylpyrrole, with the addition of $CH_3{\cdot}CO^+$ (*m/e* 43). In this instance the ion (*d*) could arise either directly by loss of $CH_3{\cdot}CO$ or *via* ion (*c*). The spectrum of 3-acetyl-2,4,5-trimethylpyrrole (XVII) shows a metastable peak at 86·5 corresponding to this loss of carbon monoxide (Calc. 85·8 for *m/e* 136→108), and therefore in all probability the two-step process accounts for at least part of the peak at *m/e* 66 from the simple ketone (XV). In comparison with



2-acetylpyrrole, the 3-acetylpyrroles (XVI, XVII) give relatively small peaks due to loss of the acetyl group, and this difference may be rationalised by assuming that the ejection of the 2-substituent is facilitated by a 1,2-shift of hydrogen, such as is often observed in rearrangements of carbonium ions,[11] yielding ion (*d*). It should be noted

* Italicised letters denote fragments, and paths of fragmentation are classified with small arabic numerals.

[8] Rylander, Meyerson, and Grubb, *J. Amer. Chem. Soc.*, 1957, **79**, 842.
[9] Ref. 7, Sheets 177—180.
[10] Beynon and Williams, *Appl. Spectroscopy*, 1959, **13**, 101.
[11] Cf. Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, pp. 474 ff.

that ion (*d*) (*m/e* 66) is a minor contributor to the spectrum of pyrrole itself, and hence the path through the acylium ion (*c*) by expulsion of carbon monoxide is probably especially favourable. In contrast to all the above-mentioned formyl- and acetylpyrroles, 3-ethyl-5-formyl-2,4-dimethylpyrrole (XIV) shows only small M — 1 and M — 29 peaks; the base peak is at M — 15 and evidently cleavage of the 3-ethyl substituent to an ion of type (*b*) takes precedence and inhibits further fragmentation.

Amongst derivatives of pyrrole the nuclear carboxylic esters occupy a special place, because they are the products of Knorr syntheses from β-oxo-esters and also frequently intermediates in syntheses of polypyrroles. We have consequently devoted special attention to these compounds. Benzenoid carboxylic esters have been carefully studied by mass spectrometry,[12,13] and the principal general modes of cleavage are equivalent to paths (1), (3), (6) (Table 3) and, given an *o*-methyl group, path (4). While pyrroles behave similarly, they also fragment in additional, theoretically interesting ways. Thus the spectrum (Fig. 1) of ethyl pyrrole-2-carboxylate (XX) is like that of ethyl benzoate

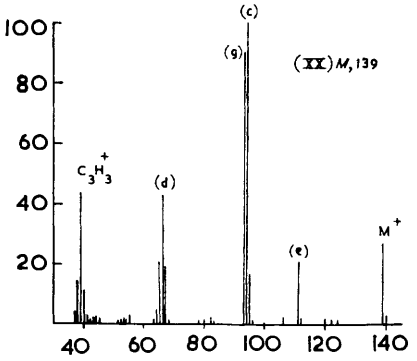


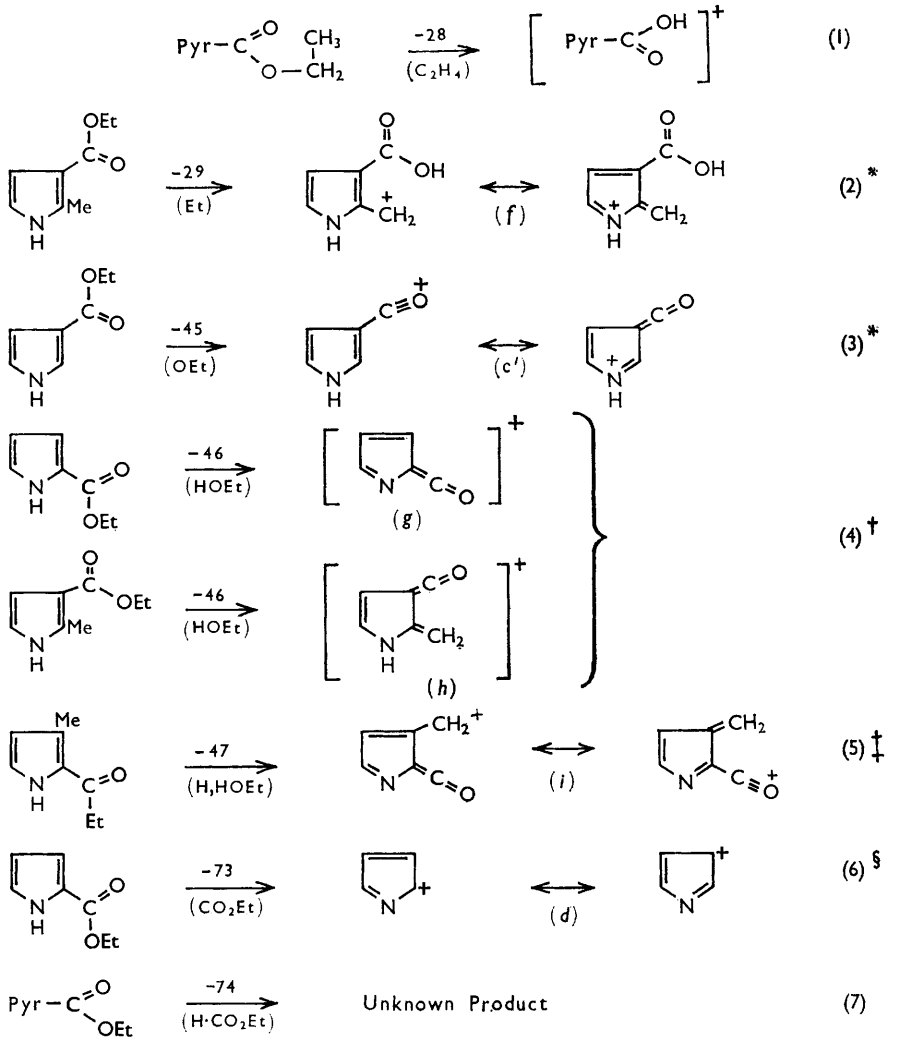
FIG. 1. Mass spectrum of ethyl pyrrole-2-carboxylate (XX), $C_7H_9NO_2$.

with the addition of peaks corresponding to cleavages (4) and (7) (*m/e* 93 and 65). Cleavage (4) is obviously due to the N–H group and indeed it is lacking in the spectrum, which otherwise is similar, of the *N*-methyl derivative (XXI). Cleavage (7) deserves more comment. It is particularly strong (*m/e* 65) in the spectrum of pyrrole-2-carboxylic acid (XVIII) and it is not shifted by deuteration of the two active hydrogen atoms; it must therefore involve loss of the hydrogen from nitrogen as well as the carboxyl group. The product could be formulated as the ion of cyclopropenyl cyanide, but this is purely speculative and it must be realised that cleavage (7) is also prominent in spectra of pyrrole-3-carboxylates. The differences between the spectrum of the acid (XVIII) and that of its deuterated derivative also confirm the interpretations of cleavages (3), (4), and (6). Thus the peak at *m/e* 93 (M — 18) is retained in the spectrum of the deuterated compound because both active hydrogen atoms are eliminated, while a new peak at *m/e* 95 mainly replaces that at *m/e* 94 (M — 17) in the spectrum of undeuterated acid (XVIII). The product of cleavage (6) at *m/e* 66 appears at *m/e* 67 in the spectrum of the deuterated compound, confirming the loss of one active hydrogen atom. Methyl pyrrole-2-carboxylate (XIX) behaves like the ethyl ester with the expected omission of the peak (*m/e* 111) due to cleavage (1). The spectra of benzyl esters (XXVI, XXX) are, not surprisingly, dominated by the peak at *m/e* 91 (tropylium ion). Location of the ester group at the 2- or 3-position does not have a profound influence on the spectra, but two differences are noteworthy. Cleavage (2) is more pronounced with the 3-esters (XXXIV, XXXV) than with comparable 2-esters (XXII, XXIV). A methyl ester (XXXIII) produces a corresponding M — 15 fragment, but this is missing from the spectrum of methyl

[12] McLafferty and Gohlke, *Analyt. Chem.*, 1959, **31**, 2076.
[13] Emery, *Analyt. Chem.*, 1960, **32**, 1495.

TABLE 3.

Principal cleavages of pyrrole-carboxylic ethyl esters. [These schemes, except for (1), apply to other esters with appropriate adjustments of changes in mass. Pyr denotes a pyrrole nucleus].



* Also in pyrrole-2-carboxylates.
† Hydrogen may be detached from another neighbour.
‡ Probably a two-step process, *e.g.*, (2) followed by (4) (elimination of water).
§ Also in pyrrole-3-carboxylates, and the migration of hydrogen from nitrogen is not certain although likely. At least partly, a two-step process, *viz.* loss of carbon monoxide after (3).

o-toluate; [12] the extra resonance stabilisation of ion (*f*), due to its immonium character, is probably responsible for this difference between the pyrrole and benzene series. Secondly, cleavage (4) plays a greater role with the 2-esters, actually being the base peak in examples (XXIII, XXIV, XXV), and hence we formulate it with detachment of hydrogen from nitrogen, rather than from neighbouring methyl, leading to ion (*g*), rather than an isomer like (*h*). Once again, comparison of methyl 2,4-dimethylpyrrole-3-carboxylate (XXXIII) and methyl *o*-toluate [12] is instructive. In both cases the base peak is at M — 31 (3), but

the peaks at M — 32 (4) and M — 59 (6) are stronger in the toluate spectrum. Immonium resonance does not especially stabilise ion (*h*), and formation *via* (6) of the stabilised ion (*d*) involves a 1,3-shift of hydrogen. As with the acetylpyrroles already discussed, cleavage (6) is more important with pyrrole-2-carboxylates than with 3-esters.

The distribution of methyl groups around the nucleus of a pyrrolecarboxylate does not affect the spectra greatly, except that cleavages (2) and (5) depend on the presence of an alkyl group next to the ester.* For example, the spectrum of ethyl 5-methylpyrrole-2-carboxylate (XXIII) is very similar to that of the 3-methyl isomer (XXII) with omission of peaks at *m/e* 124 and 106. The latter spectrum (Fig. 2) can be interpreted as follows: *m/e* 153, M^+; 125, (*e*), (1); 124, isomer of (*f*), (2); 108, homologue of (*c*), (3); 107, homologue of (*g*), (4); 106, (*i*), (5); 80, homologue of (*d*), (6); 79, unknown, (7). Cleavage (5) ostensibly involves simultaneous detachment of hydrogen from nitrogen and from the methyl group on the other flank of the carboxylate residue. In fact, it is more likely that cleavage (5) is a combination of (2) followed by (4), water being eliminated in

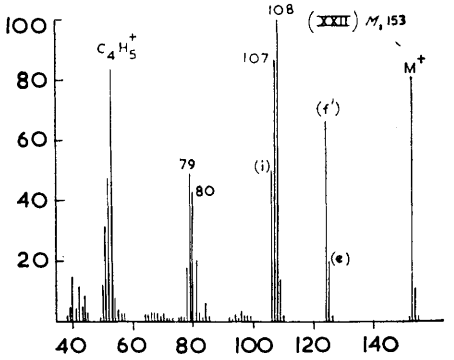
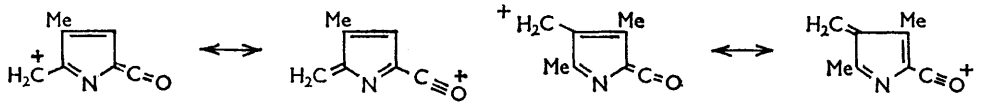


FIG. 2. Mass spectrum of ethyl 3-methylpyrrole-2-carboxylate (XXII), $C_8H_{11}NO_2$.

the second stage instead of ethanol. Some supporting evidence from metastable peaks in more complex esters (XL, XLI) is presented below.

An ethyl substituent in the pyrrole nucleus of an ester fundamentally changes the pattern of fragmentation. In many cases, the most probable first step is loss of a methyl radical from the *C*-ethyl group. Thus the base peak in the spectrum of ethyl 5-ethyl-4-methylpyrrole-2-carboxylate (XXVII) (M^+, 181) is at *m/e* 166, and this ion of type (*a*) is the precursor of other fragments. A metastable peak at *m/e* 86·7 signifies the transition (calc. for 166→120, 86·8) to ion (*j*) by path (4), and the peak at *m/e* 120 is almost as strong as the base peak (*m/e* 166). With ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (XXIX) the analogous ion (*k*) easily outweighs the M — 15 precursor, and as a rule fragments are more efficiently stabilised by ionic resonance between the 2- and 4-positions than between 2,5 or 2,3. A second metastable peak at 115·7 corresponds to cleavage (1) of the M — 15 fragment (calc. for 166→138, 114·8). When the ethyl group is next to the ester residue, as in the isomeric ethyl 3-ethyl-4,5-dimethylpyrrole-2-carboxylate (XXXI), the picture is quite different; cleavage (2), leading to a peak at *m/e* 166, is prominent and cleavage (5),



i.e., (2) followed by (4), supplies the base peak at *m/e* 148. These steps are analogous to the fragmentations of the diesters (XL, XLI), discussed below and illustrated by structures

* Presumably cleavage (4) would also be lacking from the spectra of unsubstituted pyrrole-3-carboxylates and their 5-alkyl derivatives, but we do not have any examples in Table 1.

(*x*) and (*y*). The two principal fragments (*m/e* 148, 134) are stabilised by 2,3-ionic resonance, and the population of smaller fragments is relatively much greater than in the case of the isomeric ester (XXIX) which gives the main fragment (*m/e* 134) stabilised by 2,4-ionic resonance.

In considering multiple fragmentation, it should be noted that an even-electron species, for example the foreging M — 15 fragments or the products of cleavages (2), (3), (5), or (6), will only lose even-electron fragments thus preserving its own status. On the other hand the odd-electron product of cleavage (1) or (4) can lose either odd- or even-electron fragments.

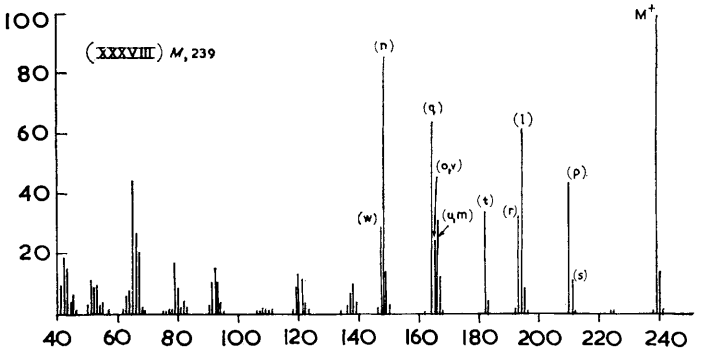


FIG. 3. Mass spectrum of diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate (XXXVIII), $C_{12}H_{17}NO_4$.

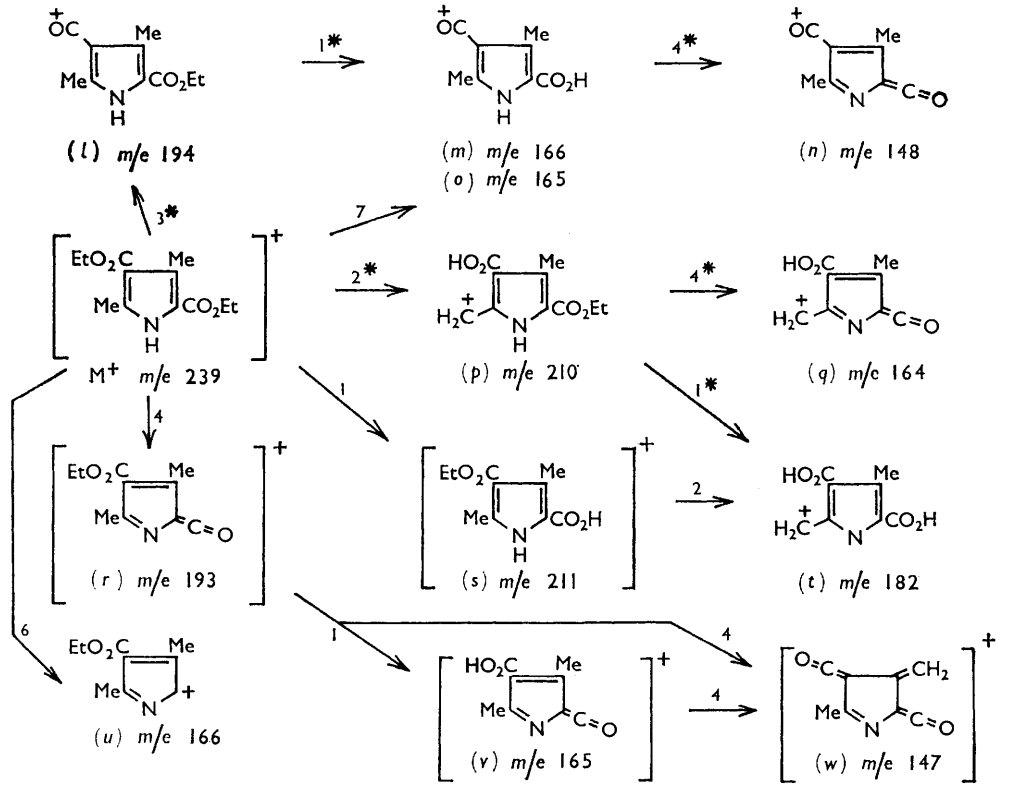
The propionate residue behaves like an ethyl group in suffering easy cleavage. Thus the peak at *m/e* 166 in the spectrum of the ester (XXXII) shares the status of base peak with that at *m/e* 134 corresponding to ion (*k*) derived by secondary cleavage (4) (metastable peak at 108·6, calc. for 166→134, 108·2).

With the aid of the foregoing consideration of monocarboxylates, it is possible to understand the major fragmentations of esters of pyrroledicarboxylic acids. Thus the spectrum of dimethyl 3,5-dimethylpyrrole-2,4-dicarboxylate (XXXVII) can be interpreted as follows: *m/e* 211, M^+; 196, (2); 180, (3); 179, (4); 178, (5); 164, (4) on 196; 152 (6); 151 (7); 148, (*n*), (4) on 180; 147, (4) on 179. The corresponding diethyl ester (XXXVIII) undergoes more complex fragmentation, because cleavage (1), an even-electron change, is now available to the molecular ion and to all the fragments still containing an ethoxy-group. Nevertheless, it is possible to assign structures to all the principal fragments above *m/e* 140 (Fig. 3) as shown in the flow sheet,* where an asterisk indicates that a postulated cleavage is confirmed by an appropriate metastable peak. The transitions 210→182 and 239→194 would give coincident metastable peaks and therefore, although both are marked, only one peak may actually be present.

The flow sheet gives only one positional isomer of each ion, although in many instances two or more isomers are conceivable and may well contribute to a single peak in the spectrum. To some extent this simplification of the diagram is arbitrary, but, as already explained, cleavage (4) is more likely to break the 2-carboxylate group with participation of the neighbouring N–H group, cleavage (6) is also easier with 2-carboxylates, and cleavage (2) is more characteristic of 3-carboxylates (but the choice of neighbouring methyl group is purely arbitrary). Cleavage (3) is approximately equally noticeable in the spectra of simple pyrrole-2- and -3-carboxylates, but it is considerably more important

* [*Note added July 29th*, 1963.] Through the courtesy of A.E.I. Ltd., the spectrum of the diester (XXXVIII) has been re-examined in the MS9 spectrometer. This has confirmed our assignment of two species to each of the peaks at *m/e* 165, 166. They are composed, respectively, of 73% of *m/e* 165·092 (calc. for $C_8H_7NO_3$: *v*, 165·095) and 27% of *m/e* 165·128 (calc. for $C_9H_{11}NO_2$: *o*, 165·132), and 69% of *m/e* 166·1027 (calc. for $C_8H_8NO_3$: *m*, 166·1035) and 31% of *m/e* 166·1397 (calc. for $C_9H_{12}NO_2$: *u*, 166·1399).

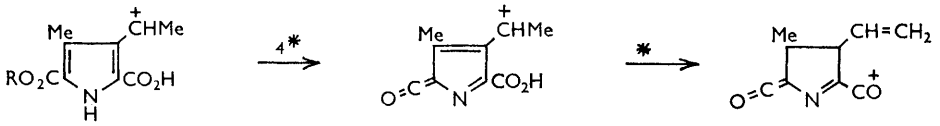
in the case of ethyl 5-formyl-2,4-dimethylpyrrole-3-carboxylate (XLIV) than when the ester and aldehyde residues are transposed in compound (XLII). This comparison is directly relevant and moreover the selective hydrolysis (by strong sulphuric acid [14]) of the 4(equivalent to 3)-ester group in the diester (XXXVIII) must proceed through the ion (*l*), which therefore probably accounts for most of the peak at *m/e* 194.



Perhaps the most interesting fragment is the resonant oxonium ion (*n*) which is almost as abundant as the molecular ion (the base peak) and actually outweighs it in the spectrum of the dimethyl ester (XXXVII). Formation of such ions, which are essentially like (*j*) and (*k*), is characteristic of pyrroles, as distinct from benzenoid compounds, because it involves the N–H group. Even in the spectrum of ethyl 2-carboxypyrrole-3-carboxylate (XXXVI), the corresponding ion, *m/e* 120, is the second most abundant, although simple decarboxylation plays a considerable role. There are also substantial peaks at *m/e* 162 in the spectra of the diethyl ester (XLI), dimethyl ester (XL), and 5-monoethyl ester (XXXIX) of 3-ethyl-4-methylpyrrole-2,5-dicarboxylic acid. The base peak in the spectrum of the diethyl ester (XLI) corresponds to M — 29 (*m/e* 224). That this is due to cleavage (2) and not to loss of the 3-ethyl group is shown by the complete lack of a peak at *m/e* 196 in the spectrum of the dimethyl ester (XL) and a corresponding reinforcement of the M — 15 peak, which is partly due to fission of the 3-ethyl group giving an ion of type (*b*). Cleavage (2) could involve either ester residue but its exceptional intensity [cleavage (2) is more characteristic of 3-carboxylates] suggests that an ion (*x*) is produced because the ethyl group yields a stabilised carbonium ion. This hypothesis, which agrees with the previous interpretation of the spectrum of a simpler ester (XXXI), is confirmed by the reduced relative intensity of the M — 29 peak in the spectrum of the monoester

[14] Fischer and Walach, *Ber.*, 1925, **58**, 2820.

(XXXIX); this fragment must be produced by elimination of ethyl with the aid of the 4-methyl group. Metastable peaks in the spectrum of the diethyl ester demonstrate transitions from *m/e* 224 to 206, 196, and 178. The first transition corresponds to loss of water by cleavage (4) and, combined with the previous step, it makes up cleavage (5) of the



(*x*) *m/e* 224 (R = Et) 210 (R = Me) (*y*) *m/e* 178 (*z*) *m/e* 160

parent ion; an analogous two-stage process (225→210→192) is indicated by a metastable peak at 176·2 (calc. 175·6) in the spectrum of the dimethyl ester (XL). This also shows the transition, 210→178 [cleavage (4)], to ion (*y*), but naturally the transition 224→196 [cleavage (1)] in the ethyl ester has no analogy in the methyl case. Both esters produce a metastable peak (144·0, 144·3), corresponding to the step 178→160 (calc. 143·8). Almost certainly the product is the ion (*z*), one of the characteristic pyrrole derivatives discussed above.

In the main the behaviour of acylpyrrolecarboxylic esters follows the patterns already discussed, but a few points deserve comment. The acetylium ion (*m/e* 43) gives the base peak in the spectrum of ethyl 3-acetyl-4,5-dimethylpyrrole-2-carboxylate (XLVI), whereas ion (*n*) (*m/e* 148) takes this place in the spectra of the isomeric 4-acetyl-2-ester (XLVIII) and the methyl ester (XLVII). The general intensity of ions below 148 is very much less in these esters than in the former case (XLVI), an example of the greater stability of 2,4-resonant ions (see above). Deuteration of the methyl ester (XLVII) confirmed that cleavage (4) removed hydrogen from nitrogen rather than from the 3-methyl group. Comparison of the isomeric formyl-esters, (XLII) and (XLIV), is instructive. Both show large M^+ peaks but cleavage (3) gives a stronger peak in the case of the 3-ester (XLIV), weaker in the case of the 2-ester (XLII) [cf. discussion above of choice made by the diesters (XXXVIII) and (XXXVII)]. As elsewhere, cleavage (4) is more marked with the 2-ester, cleavage (2) with the 3-ester. Neither of these aldehydes nor compound (XLIII) shows an appreciable M — 1 peak, and evidently this cleavage, which is characteristic of the simple aldehydes, is subordinate to fission of the ester residues.

Nuclear methoxy-groups suffer loss of methyl, but otherwise the spectra of compounds (XLIX—LIII) are like those of alkylpyrroles, except that certain cleavages are blocked. The ortho-effect described for *o*-ethoxybenzoic acid [15] was not observed.

Experimental

All mass spectra were measured with a Consolidated Electrodynamics Corp. mass spectrometer No. 21—103 C with an all-glass inlet system heated to 200°, while the isatron temperature was maintained at 270°. The ionising voltage was kept at 70 ev and the ionising current at 50 μA.

All the compounds are described by Fischer and Orth [16] except for compounds (XXV),[17] (XXVII),[17] (XXX),[18] those described below, and the following seven compounds; compounds (XI) and (XII) were supplied by Professor G. Fodor, and compounds (XLIX—LIII) by Professor H. Rapoport. The structures of all the compounds prepared in Liverpool were confirmed by n.m.r. spectra.[19]

[15] Spiteller, *Monatsh.*, 1962, **92**, 1147.
[16] Fischer and Orth, " Die Chemie des Pyrrols," Akademishe Verlag, Leipzig, 1934, Vol. I.
[17] Fischer and Fink, *Z. physiol. Chem.*, 1948, **283**, 152.
[18] Hayes, Kenner, and Williams, *J.*, 1958, 3779.
[19] Jackson and Kenner, to be published.

Ethyl 1-*Methylpyrrole*-2-*carboxylate* (XXI).—A slow stream of carbonyl chloride was passed into 1-methylpyrrole (1·0 g.) in dry ether (50 ml.) for 30 min. at 25°. Excess of carbonyl chloride was removed in a current of air, the ether removed by evaporation, and the residual oil distilled to afford *ethyl* 1-*methylpyrrole*-2-*carboxylate* (0·6 g., 31%) as an oil, b. p. 93—94°/16 mm. (Found: C, 62·9; H, 7·1; N, 9·3. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%).

Benzyl 4,5-*Dimethylpyrrole*-2-*carboxylate* (XXVI) (with Miss J. M. Judge).—Sodium nitrite (69 g.) in water (150 ml.) was slowly added at 0—5° with stirring to benzylacetoacetate (192 g.) in acetic acid (200 ml.). This solution and a mixture of zinc powder (210 g.) and sodium acetate (100 g.) were added slowly with stirring and cooling to the sodium salt of ethyl hydroxymethylenemethyl ketone (122 g.) in glacial acetic acid (300 ml.) at 65—75°. After 1 hr. at 100°, the solution was decanted into ice and water (12 l.). The oil, which separated, slowly solidified, and was filtered off, washed with water, and crystallised from aqueous methanol affording the required *pyrrole* (80 g., 40%) as needles, m. p. 112° (Found: C, 73·1; H, 6·6; N, 6·3. $C_{14}H_{15}NO_2$ requires C, 73·3; H, 6·6; N, 6·1%).

Methyl 4-*Ethyl*-3,5-*dimethylpyrrole*-2-*carboxylate* (XXVIII).—Methyl acetoacetate (69 g.) in glacial acetic acid (100 ml.) was nitrosated at 0—5° by the slow addition, with stirring, of sodium nitrite (42 g.) in water (70 ml.). Next day, the solution was run slowly into a solution, kept at 75—80°, of 3-ethylpentane-2,4-dione (77 g.) in glacial acetic acid (200 ml.), simultaneously with the portionwise addition of a mixture of zinc powder (78 g.) and anhydrous sodium acetate (78 g.). The mixture was finally heated at 100° for a further 45 min. and then poured into ice and water (3 l.). The precipitate was removed by filtration, washed with water, and crystallised from aqueous methanol to give *methyl* 4-*ethyl*-3,5-*dimethylpyrrole*-2-*carboxylate* (43 g., 40%) as needles, m. p. 110—112°, raised to 115° by recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 66·5; H, 8·1; N, 8·0. $C_{10}H_{15}NO_2$ requires C, 66·3; H, 8·3; N, 7·7%).

Methyl 2,4-*Dimethylpyrrole*-3-*carboxylate* (XXXIII).—Methyl 5-carboxy-2,4-dimethylpyrrole-3-carboxylate (1·0 g.) was heated under reflux with ethanolamine (0·7 g.) for 1 hr. The hot mixture was then poured on to ice (30 g.), and the precipitate filtered off, washed with water, and crystallised from methanol, giving *methyl* 2,4-*dimethylpyrrole*-3-*carboxylate* (0·5 g., 64%) as needles, m. p. 98—100°, raised to 102—104° on recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 62·9; H, 7·3; N, 9·2. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%).

Dimethyl 3-*Ethyl*-4-*methylpyrrole*-2,5-*dicarboxylate* (XL).—This was prepared by esterification of the corresponding dicarboxylic acid [16] (0·5 g.) with diazomethane. It was purified by chromatography in benzene on alumina, followed by sublimation at 70—80°/0·1 mm. to give the required *dimethyl ester* as pale cream needles, m. p. 96° (Found: C, 58·9; H, 6·9; N, 6·3. $C_{11}H_{15}NO_4$ requires C, 58·65; H, 6·7; N, 6·2%).

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University of Liverpool. [*Received, May 29th,* 1963.]