72. *The Halogenation of Methyl Pyrrole-2-carboxylate and of Some Related Pyrroles.*

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The heterolytic and homolytic chlorinations of methyl pyrrole-2-carboxylate have been studied, and in the former case comparison is made with heterolytic bromination. Ring chlorination with sulphuryl chloride in ether is shown to involve both heterolytic and homolytic mechanisms. Direct syntheses of methyl 4- and 5-chloro-, 4,5- and 3,5-dichloro-, 4- and 5-bromo-, and 4,5-dibromopyrrole-2-carboxylates are reported, together with an indirect synthesis of methyl 3,4-dichloropyrrole-2-carboxylate. The effect of the increased acidity of the imino-hydrogen on some chemical and spectroscopic properties of these halogenopyrroles is discussed.

THE chlorination of pyrrole systems is usually effected with sulphuryl chloride, where the use of sufficient reagent leads to substitution of all vacant ring positions,[1] and ultimately to chlorination of α-methyl groups.[1,2] Little is known of the selectivity of this reagent in cases where more than one ring position is vacant, whilst other chlorinating agents have received only passing use in pyrrole systems.[1] To provide information useful from both theoretical and synthetic standpoints on the direction of partial halogenation in pyrroles, we have studied the chlorination of methyl pyrrole-2-carboxylate (I) with both heterolytic and homolytic reagents. The previously reported heterolytic bromination of this ester with bromine in acetic acid is also studied in detail,* and some halogenations of related 2-carbonylpyrroles are clarified.

Structure Determination of the Halogenation Products.—The orientation of halogen functions in the reaction products was established primarily by nuclear magnetic resonance spectroscopy.† In pyrrole itself, H-2 and H-5 resonate at τ 3·40, H-3 and H-4 at τ 3·87, and the presence of a diamagnetically anisotropic carbonyl function in the 2-position would be expected, by analogy with other aromatic systems,[3] to deshield strongly the adjacent H-3 whilst only weakly deshielding H-5 and scarcely affecting H-4. In agreement, methyl pyrrole-2-carboxylate shows the unshifted H-4 resonance as a multiplet centred at τ 3·87, whilst the absorptions centred at τ 3·14 and 3·23 cannot, on chemical shift alone, be unequivocally assigned between H-3 and H-5. The introduction of chlorine or bromine substituents into pyrrole rings, as in other systems,[3,4] was found to cause only minor shifts in the resonance frequencies of the remaining hydrogens. Consequently, the presence of hydrogen at the 4-position of a 2-carbonyl-halogenopyrrole is readily recognised, but hydrogen in the 3-position cannot be distinguished by chemical shift alone from hydrogen in the 5-position.

Thus, of the various chlorination products, apart from the known methyl 3,4,5-trichloropyrrole-2-carboxylate [5] the structure of which was confirmed by n.m.r. spectroscopy, the most readily identified is methyl 3,5-dichloropyrrole-2-carboxylate, m. p. 165—167°, by virtue of its characteristic ring hydrogen resonance at τ 3·92. In the case of methyl

* Professor H. J. Anderson kindly informs us that his independent work at the Memorial University of Newfoundland leads to conclusions similar to our own concerning the nature and ratio of products formed in this bromination reaction.

† Spectra were recorded at 60 Mc./sec. for *ca.* 11% solution in carbon tetrachloride (except where otherwise stated), using tetramethylsilane as internal reference.

[1] Fischer-Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft M.B.H., Leipzig, 1934, Vol. I, p. 75, and references cited therein.

[2] Mathewson, *J. Org. Chem.*, 1963, **28**, 2153.

[3] Jackman, "Applications of N.m.r. Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 62.

[4] White, in "Physical Methods in Heterocyclic Chemistry," ed. Katritzky, Academic Press, London, 1963, Vol. II, p. 103.

[5] Mazzara and Borgo, *Gazzetta*, 1905, **35**, 104.

4,5-dichloropyrrole-2-carboxylate, m. p. 164—165·5°, the structure cannot be deduced solely from its resonance spectrum, in which the absorption at τ 3·24 could be due to a hydrogen in either the 3- or 5-position, but follows from its non-identity with authentic methyl 3,4-dichloropyrrole-2-carboxylate, m. p. 151·5—153°. This third dichloro-isomer was synthesised by two unequivocal routes described later in this Paper.

Of the three possible monochlorinated isomers of methyl pyrrole-2-carboxylate, only two were encountered in this work. The structure of methyl 4-chloropyrrole-2-carboxylate, m. p. 101·5—103°, is clearly defined by its n.m.r. spectrum, in which both ring protons appear in the same low field region at τ 3·08 and 3·23 and resonance at higher field characteristic of H-4 is absent. The second monochloro-isomer, m. p. 96·5—98·5°, is probably that reported earlier by Mazzara and Borgo,[5] m. p. 92—94°, who did not, however, establish the position of the chlorine substituent. This compound, giving ring proton resonances at τ 3·23 and 3·97, is clearly unsubstituted in the 4-position and was identified as methyl 5-chloropyrrole-2-carboxylate by further chlorination to a mixture of the 3,5- and the 4,5-dichloro-ester.

Of the bromination products, methyl 3,4,5-tribromopyrrole-2-carboxylate has been described previously [6] and its structure was confirmed by n.m.r. spectroscopy, whilst the dibromo-ester, m. p. 157—158°, is that reported by Rinkes.[7] By direct comparison with material synthesised by an unequivocal route, Rinkes showed that his compound was not methyl 3,4-dibromopyrrole-2-carboxylate, and suggested [7] on mechanistic grounds that it was probably the 4,5- rather than the 3,5-isomer. This 4,5-dibromo-structure is verified by the absence of the characteristic H-4 signal in its resonance spectrum, the ring proton appearing at τ 3·12 (in $CDCl_3$).

The two monobromo-esters, m. p.s 98·5—100·5° and 106·5—108°, obtained on treatment of the ester (I) with one mole of bromine, must be the 4- and the 5-isomer, since use of two moles of reagent under the same conditions gave the 4,5-dibromo-ester in very high yield. These monobromo-isomers were differentiated by their ring proton absorptions, the 4-bromo-ester, m. p. 98·5—100·5°, giving two signals of similar chemical shift at τ 3·08 and 3·18, the 5-bromo-ester, m. p. 106·5—108°, showing signals at τ 3·26 and 3·87.

Analysis of the Reaction Mixtures.—In general, crude reaction mixtures were separated as far as possible into their pure components by column chromatography, steam distillation, and crystallisation. The relatively small quantities of mixtures which remained were analysed qualitatively by infrared spectroscopy, and both qualitatively and quantitatively by n.m.r. spectroscopy. Such mixtures involving dichloro-esters were *N*-methylated (in almost quantitative yields) prior to n.m.r. analysis, in order to increase their solubility and hence increase the accuracy of integration of the spectra. Table 1 shows the yields of all products obtained from reactions of methyl pyrrole-2-carboxylate (I) with 1·0—1·1 and 2·0—2·2 moles of the halogenating reagents.

TABLE 1.

Percentage yields [a] of products from halogenation of methyl pyrrole-2-carboxylate (I).

	Reagent, 1·0—1·1 moles				Reagent, 2·0—2·2 moles			
Product [b]	Br_2	Cl_2	t-BuOCl	SO_2Cl_2	Br_2	Cl_2	t-BuOCl	SO_2Cl_2
Recovered (I)	0	35	0	0	0	0	0	0
4-Halogeno- (I)	56	23	0	40	0	8	0	0
5-Halogeno- (I)	23	20	80	44	0	5	0	0
4,5-Dihalogeno- (I)	16	20	0	4	88	71	0	50
3,5-Dihalogeno- (I)	0	0	20	4	0	0	82	37
3,4,5-Trihalogeno- (I)	1	1	0	2	8	2	17	4
Total material accounted for	96	99	100	94	96	86	99	91

[a] Maximum errors considered to be not greater than ±10% of the values quoted. [b] No 3-halogeno- or 3,4-dihalogeno- (I) was found.

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[6] Ciamician and Silber, *Ber.*, 1884, **17**, 1150; *Gazzetta*, 1885, **14**, 166.

[7] Rinkes, *Rec. Trav. chim.*, 1941, **60**, 303.

From the viewpoint of the synthetic utility of these reactions, careful chromatography permits the separation of the pure compounds in yields approaching those in Table 1, with the exception that the mixture of methyl 4,5- and 3,5-dichloropyrrole-2-carboxylates, produced by using 2 moles of sulphuryl chloride, is extremely difficult to resolve either before or after *N*-methylation.

Reaction of the Ester (I) *with Molecular Halogens.*—Reaction of the ester (I) at 60° for 15 minutes with one mole of bromine in acetic acid occurred with evident preference for attack at the 4-position, some 5-bromo- and 4,5-dibromo-ester also resulting. Chlorine in acetic acid at room temperature is a more reactive and correspondingly less selective reagent, one mole overnight giving approximately equal yields of the 4- and 5-monochloro-esters and of the 4,5-dichloro-ester even whilst considerable starting material remained unreacted. Increasing the proportion of halogen to two moles relative to the ester (I) gave high yields of the corresponding 4,5-dihalogeno-esters. Halogen attack at the 3-position finally occurs only when both the 4- and 5-positions are occupied, and use of three moles of bromine gives the 3,4,5-tribromo-ester in 93% yield. These directing effects are those expected for attack by electrophilic species, probably the corresponding molecular halogens,[8] on a pyrrole ring in which the presence of an electron-withdrawing group in the 2-position renders the 4- and 5-positions of comparable reactivity, which is considerably in excess of that of the 3-position. Similar directing effects operate in the nitration of such 2-substituted pyrroles.[9]

Reaction of the Ester (I) *with t-Butyl Hypochlorite.*—In contrast with the molecular halogens, with t-butyl hypochlorite in carbon tetrachloride solution (normally a source of free chlorine radicals [10]) the primary attack on the ester (I) occurred exclusively at the 5-position, followed by secondary, selective attack at the 3-position. Excellent yields of the 5-chloro- and 3,5-dichloro-esters are readily obtainable by this route. The same orientation resulted from use of t-butyl hypochlorite in a hydroxylic solvent, t-butyl alcohol, a combination which in some cases [10,11] is known to yield an electrophilic chlorinating species.

The directing influence of the 2-methoxycarbonyl group towards homolytic attack is explicable in terms of Wheland's atom localisation energy theory.[12] With halogen atoms of low reactivity and consequently high selectivity, preferential reaction at the 5- and then at the 3-position is controlled by the relative extent of delocalisation of the five remaining π electrons in the respective free-radical transition states (II) and (III). The area over which delocalisation can occur in the transition state (IV) leading to 4-halogenation is minimal, and consequently this position is the last to be attacked. The preference for halogenation in the 5-position is not due to association of the reagent with the imino-hydrogen, or to *N*-halogenation followed by rearrangement, since treatment of methyl 1-methylpyrrole-2-carboxylate with one mole of hypochlorite gave the corresponding 5-chloro-compound in 91% yield.

Reaction of the Ester (I) *with Sulphuryl Chloride.*—Mazzara and Borgo [5] described the treatment of methyl pyrrole-2-carboxylate (I) in ether at room temperature with one mole of sulphuryl chloride to yield an unidentified monochloro-ester. Careful re-investigation of this reaction showed the presence of the 4- and 5-chloro-esters (the Italians' product probably being the latter) in approximately equal yield, together with minor amounts of higher substitution products.

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[8] de la Mare and Ridd, "Aromatic Substitution," Butterworths Scientific Publications, London, 1959, p. 116, and references cited therein.

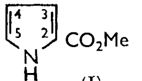
[9] (*a*) Rinkes, *Rec. Trav. chim.*, 1934, **53**, 1167; Anderson, *Canad. J. Chem.*, 1959, **37**, 2053; Fournari and Tirouflet, *Bull. Soc. chim. France*, 1963, 484; (*b*) Fournari, *ibid.*, 1963, 488.

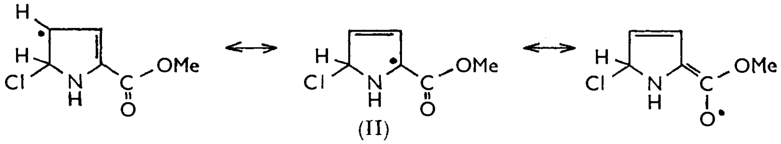
[10] Walling, "Free Radicals in Solution," Wiley and Sons, New York, 1957, p. 386; Anbar and Ginsburg, *Chem. Rev.*, 1954, **54**, 925, and references cited therein.

[11] Ref. 8, p. 107.

[12] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900; Williams, "Homolytic Aromatic Substitution," Pergamon Press, London, 1960, p. 18, and references cited therein.

With two moles of reagent, Mazzara and Borgo [5] obtained an apparently homogeneous, unidentified dichloro-ester, m. p. 132—134°, which in Beilstein's Handbuch [13] is described without justification as methyl 3,4-dichloropyrrole-2-carboxylate. Analysis of the products of this reaction by n.m.r. spectroscopy showed the absence of any 3,4-dichloro-ester, whilst methyl 3,5- and 4,5-dichloropyrrole-2-carboxylates were present in comparable amounts. Repetition of the Italians' isolation procedure [5] gave their product (34% yield), m. p. 132—134°, which was shown by n.m.r. spectroscopy, gas–liquid chromatography of the *N*-methylated material, and direct comparison with an authentic preparation, to contain equal parts of the 4,5- and 3,5-dichloro-esters, m. p.s 164—165·5° and 165—167,° respectively. The melting point behaviour of the binary system formed by these esters indicates that they form a 1 : 1 solid compound [14] with the congruent m. p. 132—134°, perhaps as the result of a particular packing in the crystal.


(I)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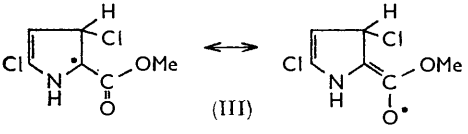
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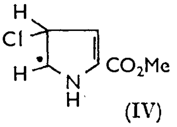
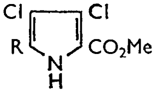

(IV)


(V: R = CHO)
(VI: R = CO$_2$H)
(VII: R = CCl$_3$)
(VIII: R = CO$_2$Me)

The chlorination products obtained with sulphuryl chloride in ether solution at room temperature, conditions under which this reagent is commonly used in pyrrole work, necessitate that substitution is occurring by both homolytic and electrophilic mechanisms. Thus, although chlorination of the ester (I) in the 5-position could result from either mechanism, attack at the 3-position after the 5-position has been filled is characteristic of chlorine radicals, while attack at the 4-position to afford 4-chloro- and 4,5-dichloro-esters is characteristic of electrophilic species. Electrophilic chlorination with sulphuryl chloride, frequently carried out in the presence of a halogen carrier, has previously [15] been considered to occur by dissociation of the reagent into molecular chlorine and sulphur dioxide. Under the present reaction conditions, however, this dissociation itself would probably be mainly homolytic in nature, and the production of both electrophilic molecular chlorine and free chlorine radicals would thus be dependent on radical chain reactions, initiated by light and by traces of peroxides [15] in the ether solvent. In agreement, the use of peroxide-free ether as solvent and 2,6-dimethylphenol as an antioxidant, under subdued lighting conditions, altered considerably the products formed in the reaction of the ester (I) with sulphuryl chloride. Two moles of reagent, under conditions otherwise similar to those used earlier, gave the 4- and 5-chloro-esters (21 and 42% yield, respectively), together with a small amount (6%) of methyl 3,4,5-trichloropyrrole-2-carboxylate. The absence of 3,5-dichlorinated material indicates that homolytic substitution is now inhibited, whilst the relatively selective attack at either the 4- or 5-position may result from sulphuryl

[13] Beilstein, " Handbuch der Organische Chemie," Springer, Berlin, 1935, Vol. XXII, p. 25.

[14] Cf. Glasstone, " Textbook of Physical Chemistry," MacMillan and Co. Ltd., London, 1955, p. 755.

[15] Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142; ref. 10, p. 380, and references cited therein.

chloride itself acting as a polarisable carrier[16] of electrophilic chlorine in the manner shown (ArH represents the nucleophilic pyrrole system):

Synthesis of Methyl 3,4-*Dichloropyrrole*-2-*carboxylate*.—Chlorination of methyl 5-formylpyrrole-2-carboxylate with two moles of sulphuryl chloride afforded, in 87% yield, the 3,4-dichloro-aldehyde (V), which was quantitatively oxidised to the acid (VI) by alkaline silver oxide.[17] In an alternative route, this acid (VI) was prepared in 45% overall yield from methyl 5-methylpyrrole-2-carboxylate, using improvements on Fischer and Elhardt's procedures (cf. ref. 18) in the chlorination with sulphuryl chloride to yield compound (VII) and in the subsequent hydrolysis of the trichloromethyl group. Pyrolysis of the acid (VI) caused only decomposition and sublimation of unchanged material, and decarboxylation to methyl 3,4-dichloropyrrole-2-carboxylate was best effected by heating in quinoline with copper powder. Some 3,4-dichloropyrrole was also produced on decarboxylation of the impure acid (VI) as prepared by the modified Fischer–Elhardt route, presumably because of the presence of some 3,4-dichloropyrrole-2,5-dicarboxylic acid resulting from over-hydrolysis of the methyl ester (VII).

An unsuccessful approach to the synthesis of the required acid (VI) followed the work of Colacicchi,[19] in which chlorination of 2,5-dimethylpyrrole with eight moles of sulphuryl chloride was followed by hydrolysis, affording low yields of 3,4-dichloropyrrole-2,5-dicarboxylic acid and the corresponding dialdehyde. However, the acidic fraction we thus obtained could not be purified as such, and treatment with diazomethane, although brief, caused extensive *N*-methylation (cf. Fournari,[9b] and other examples in the present work). Chromatography of esterified mixture afforded the desired dimethyl 3,4-dichloropyrrole-2,5-dicarboxylate (VIII) in low yield, together with the corresponding *N*-methyl diester. To avoid this difficulty caused by the acidity of the imino-hydrogen, the sulphuryl chloride reaction product was refluxed with methanol instead of water. Chromatography now gave the 3,4-dichloro-derivatives of 2,5-diformylpyrrole, methyl 5-formylpyrrole-2-carboxylate (V), and dimethyl pyrrole-2,5-dicarboxylate (VIII), but in yields too low to be of further synthetic use.

Acidity of the Halogenation Products.—The successive introduction of halogen functions into the 2-carbonylpyrrole ring causes cumulative increases in the acidity of the imino-hydrogen which are apparent in the spectroscopic and chemical properties of the halogenation products. The ultraviolet spectra of 2-methoxycarbonyl, 2-formyl-, and 2-acetylpyrrole are unaffected by alkali, but the spectra of their halogenation products, which in neutral solution show small bathochromic shifts relative to the parent compounds, undergo a further, reversible bathochromic shift of about 20 mμ in the presence of alkali owing to the ready formation of the pyrrole anions (cf. Table 2 and Experimental section). Thus the 2-carbonyl-halogenopyrroles dissolve in aqueous alkali, and the di- or tri-halogenated compounds on potentiometric titration give pK_a values comparable with those of simple phenols. This acidity hinders the base-catalysed hydrolysis of the 2-esters; *e.g.*, methyl 4,5-dichloropyrrole-2-carboxylate is recovered after treatment with 10% aqueous methanolic alkali at room temperature overnight, conditions under which the corresponding *N*-methyl-ester and the unsubstituted ester (I) (cf. ref. 17) were completely hydrolysed.

Although infrared spectroscopy indicated that *N*-methoxycarbonyl derivatives were formed in 15—20% yield on treatment of the 3,5- and 4,5-dichloro-esters with methyl chloroformate in pyridine, these derivatives decomposed rapidly on chromatography and

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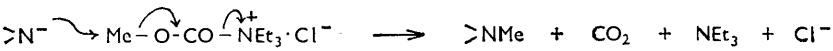
[16] Cf. Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 288; ref. 8, p. 128.

[17] Hodge and Rickards, *J.*, 1963, 2543.

[18] Fischer and Elhardt, *Z. physiol. Chem.*, 1939, **257**, 61.

[19] Colacicchi, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1910, (5), **19** II, 645.

could not be purified in this way. This instability must also be due to the halogen substituents, since dimethyl pyrrole-1,2-dicarboxylate is quite stable.[17] Particularly interesting is the reaction of methyl 3,5-dichloropyrrole-2-carboxylate with methyl chloroformate and triethylamine to give the *N*-methyl-ester in 75% yield. Possibly steric hindrance in both reactants promotes nucleophilic attack of the pyrrole anion at the methyl rather than the carbonyl carbon in the quaternary triethylamine derivative of the formate ester:



$$>N^{-}\ \ \text{Me}-\text{O}-\text{CO}-\overset{+}{\text{N}}\text{Et}_3\cdot\text{Cl}^{-} \longrightarrow\ >\text{NMe} + \text{CO}_2 + \text{NEt}_3 + \text{Cl}^{-}$$

As expected, the acidity and reactivity of the imino-hydrogen varies with the nature and position of the halogen substituent, decreasing in the sequence 5-chloro, 5-bromo, 4-halogeno. Those halogenopyrrole-2-esters which carried at least a 5-chloro-substituent were *N*-methylated in $>90\%$ yield with diazomethane over two days; under the same conditions, the 5-bromo-ester was only 63% *N*-methylated, while the 4-monohalogeno- and 3,4-dihalogeno-2-esters were largely unaffected (cf. Table 3). Ultraviolet spectra of the *N*-methyl derivatives were, in general, closely similar to the spectra of the parent compounds in neutral solution (cf. Tables 2 and 3).

Infrared spectra (considered for carbon tetrachloride solutions in which all compounds were sufficiently soluble) of the ester (I) and the halogeno-esters showed, in addition to several carbonyl absorptions, two NH stretching vibrations, one relatively constant in position around 3430 cm.$^{-1}$, the second variable between 3300—3215 cm.$^{-1}$ (cf. Table 2). This band multiplicity is due [20] to the presence in solution of both free molecules and inter- and intra-molecularly hydrogen-bonded species, the latter giving rise to the lower frequency NH band. An increase in acidity of the imino-hydrogen has little effect on the strength of free NH bonds, but increases the strength of hydrogen bonds, with the result that NH bonds in associated species are weakened and their stretching frequencies are lowered. This is most clearly reflected (cf. Table 2) in the magnitude of $\Delta\nu$, the separation between non-bonded and bonded NH stretching frequencies, which for the parent ester (I) is 149 cm.$^{-1}$. The presence of halogen in the 4- or 3,4-positions causes only a slight increase in this separation (4—9 cm.$^{-1}$), whilst in contrast halogen in the 5-position increases $\Delta\nu$ by *ca.* 40 cm.$^{-1}$, the extreme being reached with methyl 3,4,5-trichloropyrrole-2-carboxylate where $\Delta\nu$ is 205 cm.$^{-1}$.

Halogenation of Some Related 2-Carbonylpyrrole Systems.—The present evidence on the direction of electrophilic halogenation in 2-carbonylpyrrole systems confirms Rinkes's earlier suggestion [7] that the compounds formed on di-iodination (with iodine in alkaline potassium iodide solution) of 2-acylpyrroles [21] and on dibromination (with bromine in acetic acid) of pyrrole-2-carboxamides [22] are, in fact, 4,5-dihalogeno-derivatives. The original 3,4-dihalogeno-formulations [21,22] were based on the formation of dihalogenomaleimides on oxidation with fuming nitric acid, a reaction shown by Rinkes [7] to be of little value in structure determination since 2-acetyl-3,4,5-tri-iodopyrrole is produced in moderate yield during the oxidation of the 2-acetyldi-iodopyrrole. We find that the 2-acetyldi-iodopyrrole is alkali-soluble, as expected for the 4,5-dihalogeno-structure, whilst its n.m.r. spectrum, with ring proton resonance at τ 3·04, indicates substitution in the 4-position. Similarly, the dibromination of 2-acetylpyrrole with bromine in acetic acid [23] would yield 2-acetyl-4,5-dibromopyrrole, not the 3,4-dibromo-derivative as suggested in Beilstein's Handbuch.[24]

The only product isolated from treatment of 2-formylpyrrole with two moles of sulphuryl chloride in ether was a low yield of 5-chloro-2-formylpyrrole, the structure of which was

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[20] Cf. Scrocco and Nicolaus, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1957, **22**, 500; Scrocco, Caglioti, and Caglioti, *ibid.*, 1958, **24**, 316.

[21] Terentjew and Tschelinzew, *Ber.*, 1925, **58**, 66.

[22] Khotinsky and Pictet, *Ber.*, 1904, **37**, 2798.

[23] Ciamician and Dennstedt, *Ber.*, 1883, **16**, 2348.

[24] Beilstein, " Handbuch der Organische Chemie," Springer, Berlin, 1935, Vol. XXI, p. 271.

proved by conversion to the known methyl 5-chloropyrrole-2-carboxylate. As expected, the presence of a 5-chloro-substituent in the chloro-aldehyde was sufficient to confer alkali solubility.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus, and are uncorrected. Infrared spectra were measured on Perkin-Elmer model 21 and Unicam S.P. 200 spectrophotometers, ultraviolet spectra on a Unicam S.P. 500 spectrophotometer and refer to ethanol solutions. N.m.r. spectra were obtained on a Varian Associates A60 machine for *ca.* 11% solutions in carbon tetrachloride containing tetramethylsilane as internal reference, except where otherwise stated. Alumina used was Peter Spence Grade "H"; Florisil was supplied by the Floridin Co., Warren, Pennsylvania.

Table 2 collects data relevant to the methyl halogenopyrrole-2-carboxylates referred to in Table 1. Methyl pyrrole-2-carboxylate (I) was prepared after Hodge and Rickards.[17]

Bromination of Methyl Pyrrole-2-carboxylate (I).—(*a*) *With bromine* (1·1 *moles*). Bromine (640 mg.) in acetic acid (5 ml.) was added dropwise with stirring to the ester (I) (452 mg.) in acetic acid (20 ml.) at room temperature. The bromine colour faded on warming at 60° for 15 min., and the solvent was then removed under reduced pressure. Chromatography of the residue on alumina in benzene gave four main fractions. The first fraction (332 mg.) on rechromatography in the same system gave, in order of elution, *methyl* 5-*bromopyrrole*-2-*carboxylate* (90 mg., 12%), a mixture (175 mg.) of this compound and the 4-bromo-ester, and the 4-bromo-ester (55 mg.). The second fraction contained *methyl* 4-*bromopyrrole*-2-*carboxylate* (224 mg., 30%), and was followed by a mixture (120 mg.) of the 4-bromo- and 4,5-dibromo-esters, and a mixture (110 mg.) of the 4,5-dibromo- and 3,4,5-tribromo-esters.

(*b*) *With bromine* (2·0 *moles*). The residue obtained by treatment of the ester (I) (220 mg.) with bromine (570 mg.) in acetic acid as in (*a*) gave, on crystallisation from aqueous ethanol, *methyl* 4,5-*dibromopyrrole*-2-*carboxylate* (440 mg., 88%), pK_a (in 1 : 1 water–ethanol) 10.

(*c*) *With bromine* (3·0 *moles*). Treatment of the ester (I) (125 mg.) with bromine (480 mg.) in acetic acid as in (*a*) gave a residue which crystallised from hexane, affording methyl 3,4,5-tribromopyrrole-2-carboxylate (340 mg., 93%), pK_a (in 1 : 1 water–ethanol) 10.

Chlorination of Methyl Pyrrole-2-carboxylate (I).—(*a*) *With t-butyl hypochlorite* (1·1 *moles*). t-Butyl hypochlorite (560 mg.) in carbon tetrachloride (20 ml.) was added dropwise with stirring to the ester (I) (590 mg.) in carbon tetrachloride (100 ml.). The pale yellow solution decolourised overnight. Removal of the solvent in vacuum and chromatography of the residue on alumina in benzene gave *methyl* 5-*chloropyrrole*-2-*carboxylate* (500 mg., 80%) and methyl 3,5-dichloropyrrole-2-carboxylate (140 mg., 20%).

(*b*) *With t-butyl hypochlorite* (2·2 *moles*). The residue obtained by treatment of the ester (I) (380 mg.) with t-butyl hypochlorite (740 mg.) as described in (*a*) was chromatographed over alumina. Elution with ether gave successively *methyl* 3,5-*dichloropyrrole*-2-*carboxylate* (500 mg. 82%) and the corresponding 3,4,5-trichloro-ester (90 mg., 17%).

A parallel experiment, in which t-butyl alcohol replaced carbon tetrachloride as solvent, gave similar results.

(*c*) *With sulphuryl chloride* (1·1 *moles*). Sulphuryl chloride (2·30 g.) in ether (50 ml.) was added dropwise with stirring to the ester (I) (2·00 g.) in ether (100 ml.) at 0°. After standing at room temperature overnight, the mixture was evaporated to dryness under reduced pressure. Chromatography of the residue on alumina in benzene gave, in order of elution, methyl 5-chloropyrrole-2-carboxylate (778 mg., 27%), a mixture (426 mg.) of this ester and the 4-chloro-ester, *methyl* 4-*chloropyrrole*-2-*carboxylate* (783 mg., 23%), and a mixture (296 mg.) of the 3,5-dichloro-, 4,5-dichloro-, and 3,4,5-trichloro-esters.

(*d*) *With sulphuryl chloride* (2·0 *moles*). The residue obtained by treatment of the ester (I) (5·00 g.) in ether with sulphuryl chloride (11·0 g.) in ether as in (*c*) was steam-distilled, four arbitrary fractions being collected. The first fraction (1·71 g.), m. p. 100—125°, was shown by the n.m.r. spectrum of its *N*-methylation product (obtained in 96% yield) to be a mixture of the 3,5- and 4,5-dichloro-esters (11 : 10). The fourth fraction (2·70 g.), m. p. 150—170°, was a mixture of the 3,5-dichloro-, 4,5-dichloro, and 3,4,5-trichloro-esters.

The combined second and third fractions were recrystallised from hexane or aqueous ethanol to yield needles of *the* 1 : 1 *solid compound of methyl* 3,5- *and* 4,5-*dichloropyrrole*-2-*carboxylates*

(2·60 g., 34%), m. p. 132—134° (Mazzara and Borgo [5] report 132—134°); $\nu_{max.}$ (in CCl_4) 3401 (free NH), 3215 (bonded NH), 1732, 1710, and 1692 cm.$^{-1}$ (C=O bands); $\lambda_{infl.}$ 240, $\lambda_{max.}$ 270 mμ (log ε 3·80, 4·18); after addition of alkali $\lambda_{max.}$ 290 mμ (log ε 4·30) (Found: C, 37·4; H, 2·7; Cl, 36·8; N, 7·1%; *M* by Rast, 191. $C_6H_5Cl_2NO_2$ requires C, 37·1; H, 2·6; Cl, 36·6; N, 7·2%; *M*, 194). The infrared and n.m.r. spectra of this compound were identical with those of an authentic preparation, m. p. 132—134°, and a mixed m. p. was undepressed.

N-Methylation of this 1 : 1 solid compound (515 mg.) by the method described below gave an oil (495 mg., 90%); $\nu_{max.}$ (in CCl_4) 1706 cm.$^{-1}$; $\lambda_{infl.}$ 244, $\lambda_{max.}$ 271 mμ (log ε 3·82, 4·14) (Found: C, 40·5; H, 3·6; Cl, 33·5; N, 6·4. Calc. for $C_7H_7Cl_2NO_2$: C, 40·4; H, 3·4; Cl, 34·1; N, 6·7%), which was shown by n.m.r. spectroscopy and g.l.c. on a polyester column at 150° to be a 1 : 1 mixture of the corresponding *N*-methyl esters (retention times 51 and 55 min.).

(*e*) *With sulphuryl chloride* (3·5 *moles*) (cf. Mazzara and Borgo [5]). The residue from treatment of the ester (I) (1·30 g.) with sulphuryl chloride (5·00 g.) as in (*c*) was steam-distilled until 300 ml. of distillate had collected. The non-volatile material was recovered by ether extraction and recrystallised from hexane, affording methyl 3,4,5-trichloropyrrole-2-carboxylate (1·00 g., 42%), pK_a (in 1 : 1 water–ethanol) 9·0.

(*f*) *With sulphuryl chloride* (2·3 *moles*) *under peroxide-free conditions*. The ester (I) (253 mg.) in peroxide-free ether (50 ml.) containing 2,6-dimethylphenol (12·5 mg.) was treated as in (*c*) with sulphuryl chloride (621 mg.) in peroxide-free ether (50 ml.) containing 2,6-dimethylphenol (12·5 mg.). Evaporation of the mixture to dryness under reduced pressure gave a residue, the ether-soluble portion (300 mg.) of which was chromatographed on alumina. Elution with benzene gave a mixture (202 mg.) of methyl 4- and 5-chloropyrrole-2-carboxylates (21 and 42% yields, respectively), followed by methyl 3,4,5-trichloropyrrole-2-carboxylate (27 mg., 6%). Further elution with ether gave only oils.

(*g*) *With chlorine* (2·1 *moles*). Chlorine (1·80 g.) in acetic acid (55 ml.) was added dropwise with stirring to the ester (I) (1·50 g.) in acetic acid (100 ml.). After the mixture had been left at room temperature overnight, the solvent was removed under reduced pressure. The crystalline residue, on chromatography over alumina in benzene, afforded in order of elution methyl 5-chloropyrrole-2-carboxylate (100 mg., 5%), the corresponding 4-chloro-ester (145 mg., 8%), *methyl* 4,5-*dichloropyrrole*-2-*carboxylate* (1·67 g., 71%), and the 3,4,5-trichloro-ester (50 mg., 2%).

(*h*) *With chlorine* (1·1 *moles*). A single chromatogram on alumina was insufficient to resolve fully the products obtained from treatment of the ester (I) (3·90 g.) with chlorine (2·30 g.) in acetic acid as described in (*g*). Consequently, the fractions were analysed directly by n.m.r. and infrared spectroscopy, and contained, in order of elution, methyl 5-chloropyrrole-2-carboxylate (20%), recovered ester (I) (35%), the 4-chloro-ester (23%), the 4,5-dichloro-ester (20%), and the 3,4,5-trichloro-ester (1%).

Chlorination of Methyl 1-*Methylpyrrole*-2-*carboxylate with t-Butyl Hypochlorite*.—Chromatography over alumina in hexane of the product obtained from reaction of the *N*-methyl ester [17] (74 mg.) with t-butyl hypochlorite (61 mg., 1 mole) as described above afforded *methyl* 5-*chloro*-1-*methylpyrrole*-2-*carboxylate* (90 mg., 91%), an oil (cf. Table 3).

This ester (120 mg.) on refluxing for 3 hr. with ethanolic potassium hydroxide (5 ml., 10% solution) gave 5-*chloro*-1-*methylpyrrole*-2-*carboxylic acid* (80 mg., 73%), m. p. 156—158° after sublimation at 60°/0·1 mm.; $\nu_{max.}$ (in CCl_4) 3400—2400 (CO_2H) and 1670 (C=O) (Found: C, 44·7; H, 7·1. $C_6H_6ClNO_2$ requires C, 45·1; H, 7·5%).

Chlorination of Methyl 5-*Chloropyrrole*-2-*carboxylate with Sulphuryl Chloride*.—Methyl 5-chloropyrrole-2-carboxylate (210 mg.) was treated with sulphuryl chloride (250 mg., 1·4 moles) as described above. Chromatography of the product over alumina in benzene gave the 1 : 1 solid compound of methyl 3,5- and 4,5-dichloropyrrole-2-carboxylates (125 mg., 49%), m. p. 134—135°, identified by infrared spectrum and mixed m. p. with an authentic preparation.

Chlorination of 2-*Formylpyrrole with Sulphuryl Chloride*.—Sulphuryl chloride (4·80 g.) in ether (10 ml.) was added dropwise with stirring to 2-formylpyrrole (1·65 g.) in ether (100 ml.) at 0°. After 1 hr. at 0°, the mixture was left overnight at room temperature and then poured into ice–water. The ethereal layer was washed with water until neutral, dried, and evaporated. Sublimation of the residue at 110°/0·4 mm. gave a solid (1·70 g.), which on chromatography on alumina in ether afforded, as the only crystalline fraction, 5-*chloro*-2-*formylpyrrole* (210 mg., 9%), needles, m. p. 112—113°, from hexane; $\nu_{max.}$ (in CCl_4) 3458 (free NH), 3232 (bonded NH), 2830 (CHO), and 1660 cm.$^{-1}$ (C=O); $\lambda_{max.}$ 245 and 294 mμ (log ε 3·60, 4·32), after addition of

TABLE 2.

Methyl halogenopyrrole-2-carboxylates.

Sub-stituents in (I)	Infrared absorption (cm.$^{-1}$)[a]				Ultraviolet maxima			
	NH stretching				Neutral		Alkaline	
	Free	Bonded	$\Delta\nu$	C=O stretching	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
None	3445	3296	149	1714, 1685	238 (infl.), 263	3·63, 4·14	As neutral	
4-Br	3441	3283	158	1734, 1706, 1691	233, 269	4·04, 4·24	280	4·19
4-Cl	3439	3282	157	1729, 1706, 1689	233, 269	3·80, 4·11	232, 288	3·60, 4·10
5-Br	3438	3253	185	1729, 1706, 1691	228, 271	3·65, 4·30	291	4·33
5-Cl	3441	3252	189	1724, 1704, 1699	236 (infl.), 269	3·33, 4·21	291	4·30
3,4-Cl_2 ...	3435	3282	153	1730, 1707, 1686	250 (infl.), 264	3·98, 4·09	286	4·23
4,5-Br_2 ...	3426	3240	186	1729, 1709, 1689	233, 279	3·72, 4·15	233, 295	3·45, 4·27
4,5-Cl_2 ...	3429	3235	194	1734, 1709, 1694	233, 274	3·68, 4·17	240, 294	3·45, 4·32
3,5-Cl_2 ...	3425	3234	191	1739, 1699, 1674	266	4·20	287	4·27
3,4,5-Cl_3...	3420	3215	205	1789, 1748, 1699, 1679	245 (infl.), 271	3·80, 4·13	292	4·14
3,4,5-Br_3	3415	3231	184	1739, 1704, 1684	279	4·18	295	4·27

Substituents in (I)	Crystallised from	M. p.	Found (%)				Formula	Required (%)			
			C	H	Hal.	N		C	H	Hal.	N
4-Br	Hexane	98·5—100·5°	35·2	2·9	—	6·7	$C_6H_6BrNO_2$	35·3	2·9	—	6·9
4-Cl	Hexane–ether	101·5—103	45·3	4·0	—	8·6	$C_6H_6ClNO_2$	45·3	3·8	—	8·7
5-Br	Hexane	106·5—108	35·6	3·0	—	6·9	$C_6H_6BrNO_2$	35·3	2·9	—	6·9
5-Cl	Ethanol–water	96·5—98·5[b]	45·2	3·6	—	8·8	$C_6H_6ClNO_2$	45·3	3·8	—	8·7
3,4-Cl_2	Hexane	151·5—153	36·9	2·7	—	7·0	$C_6H_5Cl_2NO_2$	37·1	2·6	—	7·2
4,5-Br_2.........	Ethanol–water	157—158[c]	—	—	—	—	$C_6H_5Br_2NO_2$	—	—	—	—
4,5-Cl_2	Hexane	164—165·5	37·1	2·6	36·9	7·0	$C_6H_5Cl_2NO_2$	37·1	2·6	36·6	7·2
3,5-Cl_2	Hexane	165—167	37·1	2·6	36·8	7·0	$C_6H_5Cl_2NO_2$	37·1	2·6	36·6	7·2
3,4,5-Cl_3	Hexane	196—196·5[d]	31·5	1·8	46·4	6·0	$C_6H_4Cl_3NO_2$	31·5	1·8	46·6	6·1
3,4,5-Br_3	Hexane	212—214[e]	—	—	—	—	$C_6H_4Br_3NO_2$	—	—	—	—

[a] All spectra were measured on a Perkin-Elmer model 21 Spectrophotometer using double scale expansion, for 0·04 molar carbon tetrachloride solutions. In several cases, examination of solutions half and four times this concentration gave $\Delta\nu$ values agreeing with those reported to within ± 4 cm.$^{-1}$. Values for the ester (I) quoted in ref. 17 were obtained on a Unicam S.P. 200 Spectrophotometer. [b] Mazzara and Borgo, ref. 5, quote m. p. 92—94°. [c] Rinkes, ref. 7, records m. p. 153—154°. [d] Mazzara and Borgo, ref. 5, quote m. p. 189°. [e] Ciamician and Silber, ref. 6, report m. p. 209—210°.

alkali $\lambda_{infl.}$ 265 and $\lambda_{max.}$ 320 mμ (log ε 3·33, 4·43) (Found: C, 46·5; H, 3·1; N, 11·3. C_5H_4ClNO requires C, 46·3; H, 3·1; N, 10·8%).

Oxidation of 5-*Chloro*-2-*formylpyrrole*.—To a suspension of silver oxide [prepared [25] by adding, with stirring, silver nitrate (50 mg.) in water (5 ml.) to N-sodium hydroxide (10 ml.)] was added the aldehyde (12 mg.) in ethanol (1 ml.). After the mixture had been stirred for 1 hr. at room temperature, the precipitate was removed by filtration and the filtrate extracted several times with ether. Acidification of the filtrate, extraction with ether, and recovery gave an oil which was treated with excess of ethereal diazomethane for 2 min. Chromatography of the methylated product over alumina in ether gave methyl 5-chloropyrrole-2-carboxylate (6 mg., 41%), m. p. 93—96°, identified by mixed m. p. and infrared spectrum.

2-*Acetyl*-4,5-*di-iodopyrrole*.—2-Acetylpyrrole, prepared after Oddo,[26] was iodinated by Rinkes's method [7] with alkaline potassium tri-iodide, yielding 2-*acetyl*-4,5-*di-iodopyrrole* (60%) as needles, m. p. 173—176°, from hexane (Rinkes [7] reports m. p. 157°, Pieroni and Nocentini [27] 168°); $\nu_{max.}$ (in CCl_4) 3435 (free NH), 3241 (bonded NH), 1672, and 1657 cm.$^{-1}$ (C=O); $\lambda_{max.}$ 259 and 310 mμ (log ε 3·74, 4·12); after addition of alkali, $\lambda_{max.}$ 225 and 333 mμ (log ε 3·91 and 4·32).

Methyl 5-*Formylpyrrole*-2-*carboxylate*.—The Gattermann reaction applied to methyl pyrrole-2-carboxylate, using Reichstein's procedure,[28] gave *methyl* 5-*formylpyrrole*-2-*carboxylate* (40%), needles, m. p. 95—98°, from carbon tetrachloride; $\nu_{max.}$ (in CS_2) 3360 (free NH), 3210 (bonded NH), 2760 (CHO), 1715, and 1668 cm.$^{-1}$ (C=O bands); $\lambda_{max.}$ 220, 224, and 296 mμ (log ε 4·02,

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[25] Cf. Campaigne and Le Suer, *Org. Synth.*, 1953, **33**, 94.

[26] Oddo, *Ber.*, 1910, **43**, 1012; *Gazzetta*, 1912, **42**, 257.

[27] Pieroni and Nocentini, *Gazzetta*, 1925, **55**, 348.

[28] Reichstein, *Helv. Chim. Acta*, 1930, **13**, 349.

4·00, 4·38), after addition of alkali $\lambda_{max.}$ 245 and 326 mμ (log ε 4·02 and 4·43) (Found: C, 54·8; H, 4·4; N, 9·1. $C_7H_7NO_3$ requires C, 54·9; H, 4·8; N, 9·2%).

Dimethyl Pyrrole-2,5-*dicarboxylate*.—Methyl 5-formylpyrrole-2-carboxylate on oxidation with alkaline silver oxide, as described for the corresponding 3,4-dichloro-ester below, gave methyl 5-carboxypyrrole-2-carboxylate (76%), m. p. 270° (lit.,[29] 243°); $\nu_{max.}$ (in Nujol) 3375 (NH), 3300—2300 (CO_2H), and 1675 cm.$^{-1}$. Brief treatment with diazomethane in ether gave dimethyl pyrrole-2,5-dicarboxylate (98%), m. p. 128—130° after sublimation at 100°/0·1 mm. and recrystallisation from aqueous ethanol (Nicolaus and Mangoni [30] quote m. p. 129—130°); $\nu_{max.}$ (in CCl_4) 3385 (free NH), 3250 (bonded NH), 1722, and 1710 cm.$^{-1}$ (C=O bands); $\lambda_{max.}$ 273 and 282 mμ (log ε 4·30 and 4·25), after addition of alkali $\lambda_{infl.}$ 255 and $\lambda_{max.}$ 303 mμ (log ε 4·03, 4·34).

Methyl 3,4-*Dichloro*-5-*formylpyrrole*-2-*carboxylate* (V).—Methyl 5-formylpyrrole-2-carboxylate (400 mg.) was treated with sulphuryl chloride (730 mg., 2 moles) according to the above procedure. Chromatography on alumina of an ethereal solution of the crude product yielded *methyl* 3,4-*dichloro*-5-*formylpyrrole*-2-*carboxylate* (V) (510 mg., 87%), m. p. 163—165° from carbon tetrachloride; $\nu_{max.}$ (in CCl_4) 3365 (free NH), 3215 (bonded NH), 2800 (CHO), 1719, and 1668 cm.$^{-1}$ (C=O bands); $\lambda_{max.}$ 226, 231, and 293 mμ (log ε 4·24, 4·22, and 4·36); after addition of alkali $\lambda_{max.}$ 246 and 323 mμ (log ε 4·23, 4·44) (Found: C, 37·6; H, 2·1; N, 6·7. $C_7H_5Cl_2NO_3$ requires C, 37·8; H, 2·3; N, 6·3%).

Methyl 5-*Carboxy*-3,4-*dichloropyrrole*-2-*carboxylate* (VI).—(*a*) *From the formyl-ester* (V). Methyl 3,4-dichloro-5-formylpyrrole-2-carboxylate (V) (190 mg.) in methanol (3 ml.) was added with stirring to an alkaline suspension of silver oxide [prepared from silver nitrate (2 g.) and N-sodium hydroxide (60 ml.)]. After 3 hr. the solution was acidified with dilute nitric acid and extracted with chloroform. The extract was washed with aqueous potassium hydrogen carbonate. Acidification of the washings, extraction with ether, and recovery gave methyl 5-carboxy-3,4-dichloropyrrole-2-carboxylate (VI) (200 mg., 98%), m. p. >280°; $\nu_{max.}$ (in Nujol) 3500—2200 (CO_2H), 1710, and 1680 cm.$^{-1}$ (C=O bands).

(*b*) *From methyl* 5-*methylpyrrole*-2-*carboxylate*. Reaction of 2-methylpyrrylmagnesium bromide with methyl chloroformate, under the conditions used by Fischer *et al.*[31] for reaction with ethyl chloroformate, gave methyl 5-methylpyrrole-2-carboxylate (45%), prisms m. p. 96—99° from hexane (lit.,[32] m. p. 96—97°); $\nu_{max.}$ (in CS_2) 3370 (free NH), 3201 (bonded NH), and 1720 cm.$^{-1}$ (C=O). To this ester (2·2 g.) in ether (200 ml.) at −70° was added during 1 hr. with stirring sulphuryl chloride (13 ml.) in ether (20 ml.). After 20 hr. at room temperature the reaction was diluted with water. Recovery of the ethereal layer gave an oil (5·5 g.), which was refluxed with water (100 ml.) and diethylene glycol dimethyl ether (10 ml.) for 3 hr. Extraction with ether and separation of the fraction soluble in aqueous potassium hydrogen carbonate gave the methyl ester (VI) (1·8 g., 45%), m. p. >280°. These improvements on Fischer and Elhardt's preparation [18] of the ethyl ester corresponding to (VI) increased the yield from 15%.

Treatment of the methyl ester (VI) with excess of ethereal diazomethane for 5 min. gave *dimethyl* 3,4-*dichloro*-1-*methylpyrrole*-2,5-*dicarboxylate* (95%), m. p. 155—160°, from hexane; $\nu_{max.}$ (in CS_2) 1716 cm.$^{-1}$ (C=O) (Found: C, 40·2; H, 3·1. $C_9H_9Cl_2NO_4$ requires C, 40·6; H, 3·4%).

Methyl 3,4-*Dichloropyrrole*-2-*carboxylate*.—Pyrolysis at 300° of the methyl ester (VI), although effective in 8% yield with the corresponding ethyl ester,[18] caused extensive decomposition and sublimation of unchanged material.

When the crude ester (VI) (1·00 g. as prepared by the modified Fischer–Elhardt route above) was heated in quinoline (5 ml.) with copper powder under nitrogen at 210°, decarboxylation was complete in 1 hr., as judged by evolution of carbon dioxide. The reaction mixture was diluted with ether, and washed successively with dilute hydrochloric acid, aqueous potassium hydrogen carbonate, and water. The remaining neutral material (210 mg.), on chromatography over alumina in hexane–ether, gave 3,4-dichloropyrrole (40 mg.), prisms m. p. 70—72° from hexane (Fischer and Gangl [33] report m. p. 74°); $\nu_{max.}$ (in CS_2) 3412 cm.$^{-1}$ (NH) with no C=O absorption,

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[29] Ciamician and Silber, *Ber.*, 1887, **20**, 2594.
[30] Nicolaus and Mangoni, *Gazzetta*, 1956, **86**, 757.
[31] Fischer, Beller, and Stern, *Ber.*, 1928, **61**, 1074.
[32] Nicolaus and Mangoni, *Ann. Chim.* (*Italy*), 1956, **46**, 847.
[33] Fischer and Gangl, *Z. physiol. Chem.*, 1941, **267**, 188.

showing only end-absorption in the ultraviolet region, and *methyl* 3,4-*dichloropyrrole*-2-*carboxylate* (160 mg., 20%), needles m. p. 151·5—153°, purified by sublimation at 130°/8 mm. and crystallisation from hexane. M. p.s of mixtures of this ester with the corresponding 3,5- or 4,5-dichloro-esters showed considerable depression.

Chlorination of 2,5-*Dimethylpyrrole with Sulphuryl Chloride* (cf. Colacicchi [19]).—(*a*) *With hydrolysis of the reaction product.* The mixture from the dropwise addition at 0° of sulphuryl chloride (13·7 g., 8 moles) in ether (50 ml.) to 2,5-dimethylpyrrole (1·20 g.) in ether (100 ml.) was kept for 2 days, then poured into water. After evaporation of the ether, the mixture was refluxed for 1 hr., basified, and washed with ether. Acidification of the aqueous phase and ether extraction gave, on recovery, a black oil (650 mg.), which was treated for 2 min. with an excess of ethereal diazomethane. Chromatography of the product over alumina in ether gave dimethyl 3,4-dichloro-1-methylpyrrole-2,5-dicarboxylate (210 mg., 7%), m. p. 155—160°, from hexane, together with the diester (VIII) (50 mg., 2%), m. p. 174—177°, from carbon tetrachloride, each identified by comparison with an authentic sample.

(*b*) *With methanolysis of the reaction product.* 2,5-Dimethylpyrrole (2·00 g.) was treated with sulphuryl chloride (23·0 g., 8 moles) in ether as in (*a*). After being poured into water, the product was extracted with ether, recovered, and refluxed in methanol for 6 hr. Evaporation gave a black oil, which after sublimation at 150°/0·01 mm. was chromatographed on alumina. Elution with ether gave dimethyl 3,4-dichloropyrrole-2,5-dicarboxylate (VIII) (80 mg., 2%), needles, m. p. 175—178°, from carbon tetrachloride (Nicolaus and Mangoni [30] report m. p. 147—149°); $\nu_{max.}$ (in $CHCl_3$) 3370 (NH) and 1713 cm.$^{-1}$ (C=O); $\lambda_{max.}$ 217, 220, and 274 mμ (log ε 4·22, 4·23, 4·24), after addition of alkali $\lambda_{max.}$ 237 and 299 mμ (log ε 4·20, 4·35) (Found: C, 38·5; H, 3·1; N, 6·2. Calc. for $C_8H_7Cl_2NO_4$: C, 38·1; H, 2·8; N, 5·6%); followed by 3,4-dichloro-2,5-diformylpyrrole (90 mg., 3%), needles, m. p. 220—223°, from benzene (Colacicchi [19] quotes m. p. 228°); $\nu_{max.}$ (in CCl_4) 3365 (NH), 2780 (CHO), and 1665 cm.$^{-1}$ (C=O); $\lambda_{max.}$ 218, 234 (infl.), 241, 246, and 307 mμ (log ε 3·70, 3·96, 4·09, 4·04, 4·20); after addition of alkali $\lambda_{max.}$ 240 (infl.), 262, and 330 mμ (log ε 3·96, 4·16, 4·34), and methyl 3,4-dichloro-5-formylpyrrole-2-carboxylate (V) (250 mg., 6%), identified by comparison with an authentic sample (see above).

N-*Methylation of Substituted Methyl Pyrrole*-2-*carboxylates.*—The substituted esters were

TABLE 3.

Methyl 1-methylpyrrole-2-carboxylates prepared by *N*-methylation with diazomethane.

No.	Substituents in 1-methyl-(I)	Yield (%)	M. p.	Infrared C=O absorption		Ultraviolet maxima	
				Solvent	$\nu_{max.}$ (cm.$^{-1}$)	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
1	None [a]	—	—	CCl_4	1707	240 (infl.), 265	3·84, 4·18
2	4-Br	33 [b]	Oil	CS_2	1703	—	—
3	4-Cl	0 [c]	—	—	—	—	—
4	5-Br	63	Oil	CS_2	1702	233, 271	4·02, 4·50
5	5-Cl	92	Oil	CCl_4	1705	236 (infl.), 269	3·76, 4·24
6	3,4-Cl_2	0 [c]	—	—	—	—	—
7	4,5-Br_2	93	87—90°	CCl_4	1711	240, 279	3·81, 4·11
8	4,5-Cl_2	96	40—42	CS_2	1711	237, 274	3·76, 4·10
9	3,5-Cl_2	96	56—58	CS_2	1700	266, 272 (infl.)	4·18, 4·15
10	3,4,5-Cl_3	92	73—74·5	CCl_4	1703	245 (infl.), 272	3·83, 4·10
11	5-CO_2Me	70	78—80 [d]	CCl_4	1730, 1710	277, 287	4·34, 4·29
12	5-CHO	75	Oil	CCl_4	1708	—	—

Substituents in 1-methyl-(I)	Found (%)			Formula	Required (%)		
	C	H	N		C	H	N
4-Br	38·2	3·2	—	$C_7H_8BrNO_2$	38·5	3·7	—
5-Br	38·7	3·2	—	$C_7H_8BrNO_2$	38·5	3·7	—
5-Cl	48·2	4·3	8·0	$C_7H_8ClNO_2$ [e]	48·4	4·6	8·1
4,5-Br_2	25·0	1·8	—	$C_7H_7Br_2NO_2$	25·3	2·1	—
4,5-Cl_2	40·5	3·2	6·4	$C_7H_7Cl_2NO_2$	40·4	3·4	6·7
3,5-Cl_2	40·2	3·1	6·5	$C_7H_7Cl_2NO_2$	40·4	3·4	6·7
3,4,5-Cl_3	34·6	2·5	—	$C_7H_6Cl_3NO_2$	34·6	2·5	—
5-CHO	45·2	5·1	—	$C_8H_8NO_3$	45·7	5·4	—

[a] Spectra values taken from Hodge and Rickards, ref. 17. [b] Reaction time 4 days. [c] Starting material (98%) recovered. [d] Shirley, Gross, and Roussel, *J. Org. Chem.*, 1955, **20**, 225, record m. p. 80—81°. [e] (Found: Cl, 20·1. Requires Cl, 20·5%).

kept for 2 days with an excess of ethereal diazomethane containing a trace of methanol. Chromatography on alumina and crystallisation where appropriate from aqueous ethanol afforded the methyl 1-methylpyrrole-2-carboxylates described in Table 3.

Reaction of Methyl 3,5-*Dichloropyrrole*-2-*carboxylate with Methyl Chloroformate*.—The dichloro-ester (600 mg.) and methyl chloroformate (0·5 ml.) in triethylamine (5 ml.) were refluxed for 1 hr. The material obtained after filtration and evaporation of the filtrate was chromatographed in hexane on alumina, affording methyl 3,5-dichloro-1-methylpyrrole-2-carboxylate (460 mg., 75%), identified by infrared and n.m.r. spectra in comparison with an authentic sample, and a second fraction; $\nu_{max.}$ (in CCl_4) 1768 (NCO_2Me) and 1720 cm.$^{-1}$ (CO_2Me); which was probably impure dimethyl 3,5-dichloropyrrole-1,2-dicarboxylate (200 mg., 20%).

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