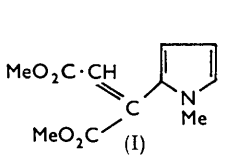
220. *Addition Reactions of Heterocyclic Compounds. Part X.* Products from 1-Alkylpyrroles and Dimethyl Acetylenedicarboxylate, and the Synthesis of Some Indolecarboxylic Esters.†*

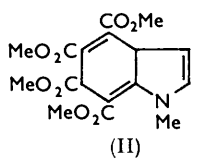
By R. M. Acheson and J. M. Vernon.

1-Methylpyrrole and dimethyl acetylenedicarboxylate gave tetramethyl 3a,7a-dihydro-1-methylindole-2,3,3a,4-tetracarboxylate, which has been degraded to methyl 1-methylindole-4-carboxylate. Under other conditions the reaction gave a mixture of tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate, which was degraded to methyl 1-methylindole-6-carboxylate, trimethyl 1-methylpyrrole-2,3,4-tricarboxylate, and some other products. A mechanism which accounts for these results is suggested, and independent syntheses of methyl 1-methylindole-4- and -6-carboxylate and of dimethyl 1-methylindole-2,3-dicarboxylate are described.

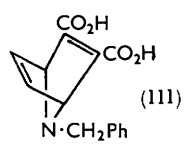
Acetylenedicarboxylic acid undergoes Michael-type addition with some pyrroles; attack occurs preferentially at free α-positions, and the main products are 2-[1,2] or 3-pyrrolyl-fumaric [3] acids or -maleic anhydrides. An additional product from 1-benzylpyrrole is the adduct (III). Similar Michael-type additions have been obtained with dimethyl acetylenedicarboxylate and a number of pyrroles unsubstituted on the nitrogen atom,[4] but in contrast 1-methylpyrrole and the ester give a 2 : 1 molar " yellow adduct " for which Diels, Alder, and Winckler [1] have suggested structure (II). This was based on the assumptions that a maleic ester (I) would be initially formed and would undergo a Diels–Alder reaction yielding (II), and on the observations that the yellow adduct with



(I)



(II)



(III)

bromine and methanol lost a hydrogen atom and an ester group and that the product (described as trimethyl 1-methylindole-4,5,6-tricarboxylate) on hydrolysis and decarboxylation gave 1-methylindole. The failure of the yellow adduct to be oxidised to the corresponding indole tetraester, and the remarkable loss of the ester group, were not explained. The formation of tetramethyl carbazole-1,2,3,4-tetracarboxylate from indole and the acetylenic ester [5] is reminiscent of Diels and Alder's scheme.

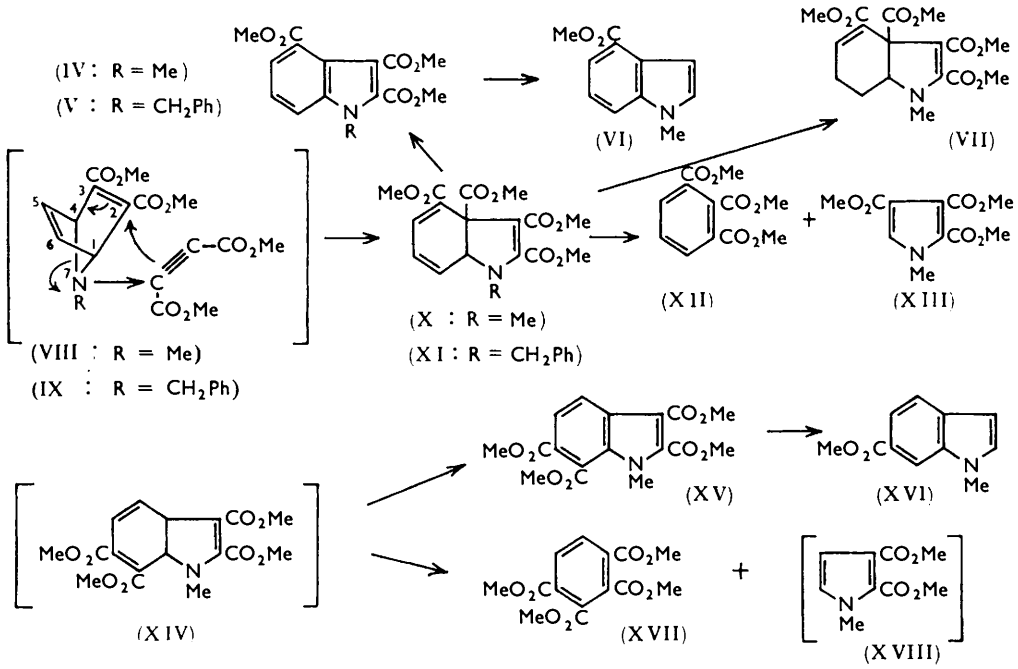
We have found that dimethyl acetylenedicarboxylate and 1-methylpyrrole in the cold gave the 2 : 1 molar yellow adduct as described, but when the preparation was carried out on a larger scale without cooling other products were obtained. The resulting tar, on chromatography over alumina, afforded trimethyl hemimellitate (XII), tetramethyl prehnitate (XVII), trimethyl 1-methylpyrrole-2,3,4-tricarboxylate (XIII), a compound considered to be tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate (XV), and an unidentified crystalline material. The first three products were identical in mixed melting point and infrared absorption spectra with authentic specimens. The ultraviolet

* Part IX, *J.*, 1962, 748.
† Cf. Acheson, Hands, and Vernon, *Proc. Chem. Soc.*, 1961, 164.

[1] Diels, Alder, and Winckler, *Annalen*, 1931, **490**, 267.
[2] Mandell and Blanchard, *J. Amer. Chem. Soc.*, 1957, **79**, 6198.
[3] Fischer, Hartmann, and Riedl, *Annalen*, 1932, **494**, 246.
[4] Diels, Alder, Winckler, and Petersen, *Annalen*, 1932, **498**, 1.
[5] Noland, Kuryla, and Lange, *J. Amer. Chem. Soc.*, 1959, **81**, 6010.

absorption spectrum of the pyrrole (XIII) was very similar to that of trimethyl pyrrole-2,3,4-tricarboxylate,[6] and before synthetic material became available a provisional identification was based on this and on the results of successive hydrolysis and decarboxylation to a mixture of pyrrole and 1-methylpyrrole; another case of *N*-demethylation accompanying decarboxylation is known.[5] None of the yellow adduct could be detected in the mixture although its chromatographic behaviour, independently investigated, should have permitted this had any been present.

Trimethyl 1-methylpyrrole-2,3,4-tricarboxylate (XIII) and hemimellitate (XII) were also obtained when the yellow adduct was heated with dimethyl acetylenedicarboxylate. The occurrence of these triesters among the products of uncontrolled addition of the acetylenic ester to 1-methylpyrrole may therefore account for the absence of the yellow adduct itself.



The structure of the compound considered to be tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate (XV) was first suggested by the reaction scheme discussed above and is consistent with the following observations. Successive hydrolysis, selective decarboxylation to an indolemonocarboxylic acid, and treatment with diazomethane gave methyl 1-methylindole-6-carboxylate (XVI). As the tetraester gave no reaction with Ehrlich's reagent in the cold, and a questionable reaction on heating, while both the monocarboxylic acid and ester gave purple colours in the cold, it seemed probable that decarboxylation had occurred at the 2,3-positions as in the partial decarboxylation of 1-methylindole-2,3,4-tricarboxylic acid; indole-2-carboxylic acid gives a purple colour only with hot Ehrlich's reagent and dimethyl 1-methylindole-2,3-dicarboxylate reacts on prolonged heating. Also as 3-aminophthalic acid readily loses the 2-carboxyl group [7] the loss of the similarly placed 7-carboxyl group of the tetraester (XV) during the degradation is understandable.

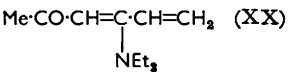
The yellow adduct, on oxidation with bromine in methanol, gave as described [1] a trimethyl 1-methylindoletricarboxylate. This had a typically indolic ultraviolet absorption spectrum, gave a purple colour on prolonged heating with Ehrlich's reagent, and on

[6] Nicolaus and Mangoni, *Gazzetta*, 1956, **86**, 358.
[7] Bogert and Jouard, *J. Amer. Chem. Soc.*, 1909, **31**, 483.

hydrolysis and selective decarboxylation yielded 1-methylindole-4-carboxylic acid which was identified as its methyl ester (VI). The nuclear magnetic resonance spectrum of the indole triester in nitromethane excludes the 4,5,6-structure first proposed,[1] as the simple AB type spectrum expected from the 2,3-hydrogen atoms is not observed. The spectrum is not inconsistent with that expected of the 2,3,4-triester formulation (IV).

On the basis of the reactions described above, the structure of the yellow adduct can be written as (X). This is in agreement with the compound's nuclear magnetic resonance spectrum, and its ultraviolet absorption spectrum is roughly the sum of those of the nearest spectral models found in the literature, sorbic acid [8] (XIX) and 4-diethylamino-hexa-3,5-dien-2-one [9] (XX), for the two chromophoric groups in the molecule. The loss of the angular ester group on aromatisation is to be expected. Hydrogenation of the yellow adduct gives a dihydro-derivative and hexahydro-compounds. The nuclear magnetic resonance spectra in the ester-methyl region, and the infrared absorption spectra in the carbonyl region, of the yellow adduct (X) and its dihydro-derivative were virtually identical, showing that the immediate environment of the ester groups is the same in both. The ultraviolet absorption spectrum of the dihydro-derivative has a single maximum (3070 Å) which corresponds to the shoulder (*ca.* 3000 Å) in the spectrum of the yellow adduct and, from an inspection of the data in the Table, is due to the nitrogen-containing chromophore. The dihydro-derivative therefore has structure (VII).

(XIX)



(XX)

The formation of the yellow adduct (X) and compounds (XII), (XIII), (XV), and (XVII) is explained by a scheme involving initial addition to 1-methylpyrrole to give the Diels–Alder adduct (VIII). Although this adduct was not isolated, another adduct (III) of the same type is known,[2] and the intermediate formation of such adducts in other reactions of 1-substituted pyrroles has been suggested.[10,11] The adduct (VIII) then adds, we suggest, a second molecule of dimethyl acetylenedicarboxylate across the 2,7-positions with scission of the 4,7-bond and consequent electronic movements yielding the yellow adduct (X). This can react with a third molecule of the acetylenic ester across its 4,7-positions and decomposition of the product then affords the aromatic benzene (XII) and pyrrole (XIII) derivatives. A *cis*-ring junction in the yellow adduct (X) is likely from its suggested mode of formation, but Dreiding models of the *cis*- and the *trans*-structure showed that in the latter the angular ester group is not obstructed by the ester groups at the adjacent 3- and 4-positions, and that the molecule is flatter with the 4,6-diene grouping more accessible to reaction with the third molecule of acetylenic ester.

Dimethyl acetylenedicarboxylate can add to the initial adduct (VIII) in an alternative sense, across the 5,7-positions, and a similar scheme to that proposed for the formation of the yellow adduct leads to the dihydroindole (XIV). This structure is exactly analogous to that of the 2 : 1 adduct of benzyne and 1-methylpyrrole,[11] and to that of an intermediate in the formation of 2,3,6,7-tetrakistrifluoromethylnaphthalene from benzene and bistrifluoromethylacetylene.[12] The dihydroindole (XIV) has not been isolated, but it is dehydrogenated and appears as tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate (XV), or it reacts with a third molecule of the acetylenic ester, as does the yellow adduct (X), giving tetramethyl prehnitate (XVII); the other product (XVIII) expected of this last reaction was not detected.

1-Benzylpyrrole with dimethyl acetylenedicarboxylate gave a 1 : 2 adduct (XI)

[8] Hausser, Kuhn, Smakula, and Hoffer, *Z. phys. Chem.*, 1935, *B*, **29**, 371.
[9] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45.
[10] Acheson and Vernon, *J.*, 1961, 457.
[11] Wittig and Behnisch, *Chem. Ber.*, 1958, **91**, 2358.
[12] Krespan, McKusick, and Cairns, *J. Amer. Chem. Soc.*, 1961, **83**, 3428.

analogous to that obtained from 1-methylpyrrole, and this was similarly oxidised by bromine to trimethyl 1-benzylindole-2,3,4-tricarboxylate (V). In order to test the proposed mechanism for the addition of the acetylenic ester to 1-alkylpyrroles the Diels–Alder adduct (III), along with 1-benzyl-2-pyrrolylfumaric acid and the corresponding maleic anhydride, were prepared from 1-benzylpyrrole and acetylenedicarboxylic acid.[2] It was hoped to convert the dimethyl ester (IX) into the adduct (XI) with dimethyl acetylenedicarboxylate. The adduct (III) is a zwitterion and reacted slowly with diazomethane. Removal of the solvents left a yellow oil, which smelled strongly of 1-benzylpyrrole and gave an intense Ehrlich colour in the cold. Gas–liquid chromatography of the oil alongside authentic materials established the presence of 1-benzylpyrrole and dimethyl acetylenedicarboxylate, and gave no indication of a less volatile material which might have been the desired dimethyl ester (IX). When the acid (III) was treated with diazomethane and then with dimethyl acetylenedicarboxylate the 1-benzylpyrrole adduct (XI) was obtained, but in view of the disproportionation of the postulated intermediate (IX) this does not constitute evidence in support of the proposed mechanism. The instability of the intermediate (IX) is consistent with our failure to trap its analogue (VIII) as methiodide when the acetylenic ester and 1-methylpyrrole were mixed in the presence of a large quantity of methyl iodide.

1-Methyl-1-phenylhydrazine and dimethyl acetylenedicarboxylate gave a 1 : 1 molar adduct (XXI, or tautomer; the infrared spectrum showed the absence of N–H absorption). Sulphuric acid, effectively used by Diels and Reese [13] for the cyclisation of a similar adduct to an indole, caused cleavage to dimethyl oxaloacetate which formed a 2,4-dinitrophenylhydrazone identical with that obtained from 2,4-dinitrophenylhydrazine and the acetylenic ester. Cyclisation of the adduct (XXI) with zinc chloride gave methyl hydrogen 1-methylindole-2,3-dicarboxylate. Treatment with diazomethane gave the dimethyl ester (XXII), which was required for the ultraviolet-absorption comparisons. The initial formation of the half ester is paralleled by the production of methyl hydrogen indole-2,3-dicarboxylate from the 1 : 1 molar adduct of phenylhydroxylamine with dimethyl acetylenedicarboxylate.[14]

Ultraviolet absorption spectra.

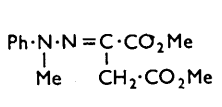
Compound	Solvent *	Absorption maxima (Å) ($10^{-4}\varepsilon$)		
1-Alkylindole esters				
(IV)	M	2260 (2·26)	3120 (1·30)	
(V)	M	2230 (2·65)	3120 (1·55)	
(VI)	M	2330 (2·50)	3170 (0·80)	
(XV)	M	2530 (3·20)	2925 (1·14)	3130 (0·63) †
(XVI)	M	2410 (2·70)	2895 (1·20)	3230 (0·62)
(XXII)	M	2315 (1·80)	2940 (1·10)	
Adducts and derivatives				
(VII)	M	3070 (1·0)		
(X)	M	2750 (1·6)	3000 (0·7) †	
(XI)	M	2770 (1·8)	3000 (0·9) †	
(XIII)	M	2175 (2·9)	2640 (1·2)	
Reference compounds				
(XIX) [8]	H	2610 (5·9)		
	E	2540 (5·7)		
(XX) [9]	E	3080 (1·85)		
Me_3 Pyrrole-2,3,4-tricarboxylate [6]	E	2640 (1·4)		

* Solvents: M = methanol, E = ethanol, H = hexane. † Inflection.

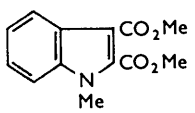
For the 2 : 1 adduct of dimethyl acetylenedicarboxylate and 1,2-dimethylimidazole Diels and his co-workers [4] suggested the structure (XXIII) analogous to that (II) for the 1-methylpyrrole adduct. However, if the addition to the imidazole resembles that to the

[13] Diels and Reese, *Annalen*, 1934, **511**, 168.
[14] Huntress, Lesslie, and Hearon, *J. Amer. Chem. Soc.*, 1956, **78**, 419.

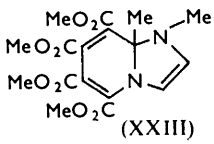
pyrrole, the adduct might instead have the structure (XXIV) which could also give an indolizine-tetraester with acid. We have confirmed the reported oxidation of the 1,2-dimethylimidazole adduct to a methylpyridinetetracarboxylic ester [4] which supports Diels's formation (XXIII), since a methylpyridine-diester would be expected from structure (XXIV).



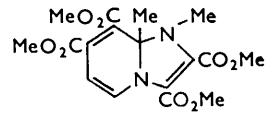
(XXI)



(XXII)



(XXIII)



(XXIV)

Methyl 1-methylindole-4- (VI) and -6-carboxylate (XVI) were synthesised by treatment of the corresponding nitriles with sodamide and methyl iodide in liquid ammonia, followed by hydrolysis of the nitrile groups and esterification with diazomethane. 4-Cyanoindole was obtained as described by Uhle,[15] but the decarboxylation of 6-cyanoindole-2-carboxylic acid by heating it with soda-lime [16] gave only 2% of 6-cyanoindole; better results were obtained by distillation with copper oxide or heating with copper in quinoline. An attempt was made to obtain 6-cyanoindole from 3-cyanoaniline, which was converted successively into *m*-cyanophenylhydrazine and pyruvic acid *m*-cyanophenylhydrazone. The hydrazone failed to cyclise in hot acetic or hot aqueous hydrochloric acid, and heating it with zinc chloride gave Ehrlich-positive material from which neither 6-cyanoindole nor the 2-carboxylic acid could be isolated.

Several attempts were made to prepare dimethyl 3-methylaminophthalate for a possible synthesis of the tetraester (XV) involving addition of dimethyl acetylenedicarboxylate to dimethyl 3-(1-methylhydrazino)phthalate before the synthesis of methyl 1-methylindole-6-carboxylate afforded reasonable proof of its structure (XV). Attempts to methylate 3-acetamidophthalic anhydride by sodium and dimethyl sulphate in boiling toluene,[17] or sodamide and methyl iodide in liquid ammonia, were unsuccessful. Dimethyl 3-aminophthalate with benzaldehyde gave a Schiff's base which failed to undergo methylation.[18] Reductive methylation of dimethyl 3-nitrophthalate under conditions in which methylaniline is obtained from nitrobenzene [19] gave a viscous oil. This was largely dimethyl 3-dimethylaminophthalate as attempted acylation gave 3-dimethylaminophthalic anhydride.

Experimental

Alumina used for chromatography was Spence's grade H, deactivated by being shaken for 24 hr. with 5% of its weight of 10% aqueous acetic acid. Ehrlich's reagent was *p*-dimethylaminobenzaldehyde (2%) in concentrated hydrochloric acid–ethanol–water (*ca.* 1 : 3 : 6 v/v). Infrared absorption spectra were determined for liquid films or paraffin pastes.

Reaction of 1-*Methylpyrrole and Dimethyl Acetylenedicarboxylate.*—(i) 1-Methylpyrrole (2 g.) and dimethyl acetylenedicarboxylate (7 g.) were mixed at 0° and left for 48 hr. at room temperature. Decantation of the oil followed by crystallisation of the residual solid from methanol gave *tetramethyl 3a,7a-dihydro-1-methylindole-2,3,3a,4-tetracarboxylate* (X) as yellow prisms (6·3 g., 70%), m. p. 145—147° (Found: C, 56·1; H, 5·4; N, 4·1; OMe, 33·5. $C_{17}H_{19}NO_8$ requires C, 56·1; H, 5·2; N, 3·8; 4OMe, 34·0%) (lit.,[1] m. p. 145—148°).

(ii) A mixture of ten times the above quantities of the same reactants was cooled in ice for 1 hr. and then left at room temperature for 48 hr. At some stage a violent reaction occurred, forming a partly crystalline black tar which was dissolved in warm benzene and chromatographed on an alumina column prepared in light petroleum (b. p. 40—60°). Fractions 1—3 were eluted with light petroleum–benzene (b. p. 40—60°, 1 : 1; 1 l., 800 ml., and 2·5 l.,

[15] Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761.
[16] Kermack, *J.*, 1924, **125**, 2285.
[17] Cf. Corwin, Bailey, and Viohl, *J. Amer. Chem. Soc.*, 1942, **64**, 1267.
[18] Cf. Decker and Becker, *Annalen*, 1913, **395**, 362.
[19] Emerson and Mohrman, *J. Amer. Chem. Soc.*, 1940, **62**, 69.

respectively), and fraction 4 with benzene (3 l.). Evaporation of the eluates gave yellow to brown oils which crystallised, and all fractions were fractionally recrystallised from methanol.

Fraction 1 first deposited hexagonal prisms of an unidentified material, m. p. 107°, and subsequently needles of trimethyl hemimellitate (XII) (0·2 g.), m. p. 101° (Found: C, 57·2; H, 4·9. Calc. for $C_{12}H_{12}O_6$: C, 57·2; H, 4·8%).

Fraction 2 was recrystallised and the hexagonal plates were hand-picked; further recrystallisation of these gave more of the unidentified material, m. p. 107° (total yield 2·5 g.). The remaining solid was agitated with methanol, and the suspension of needles quickly decanted. Recrystallisation of these needles gave tetramethyl prehnitate (XVII), m. p. 130—131° (Found: C, 54·3; H, 4·9; OMe, 39·2%; *M*, 310. Calc. for $C_{14}H_{14}O_8$: C, 54·2; H, 4·6; 4OMe, 40·0%; *M*, 310).

Fraction 3 gave further tetramethyl prehnitate (total yield, 4 g.) by the same flotation technique, and by hand-picking followed by recrystallisation hard pale yellow prisms of *tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate* (XV), m. p. 165·5° (Found: C, 56·0; H, 4·8; N, 4·2; OMe, 34·2. $C_{17}H_{17}NO_8$ requires C, 56·1; H, 4·7; N, 3·9; 4OMe, 34·2%).

Fraction 4, after crystallisation, gave on hand-picking more of the last indole (total yield 2·5 g.), and by flotation feathery needles of trimethyl 1-methylpyrrole-2,3,4-tricarboxylate (XIII) (2·0 g.) m. p. 163° (Found: C, 51·7; H, 5·1; N, 5·6; OMe, 35·5%; *M*, 250. Calc. for $C_{11}H_{13}NO_6$: C, 51·7; H, 5·1; N, 5·5; 3OMe, 36·5%; *M*, 255).

The yields recorded are of the pure products. Considerable losses were incurred in the repeated crystallisations, and some mixtures were obtained which could not be resolved and may have contained other materials such as (XVIII).

Reaction of Tetramethyl 3a,7a-Dihydro-1-methylindole-2,3,3a-4-tetracarboxylate and Dimethyl Acetylenedicarboxylate.—The dihydroindole (X) (2·0 g.) and the acetylene (1·0 g.) were heated for 2 hr. at 200°. When cold the tarry product was chromatographed in benzene on alumina (120 ml.). Elution with benzene (800 ml.) afforded trimethyl hemimellitate (50 mg.), needles (from aqueous methanol), m. p. and mixed m. p. 101·5°. Further elution with benzene (1·6 l.) gave trimethyl 1-methylpyrrole-2,3,4-tricarboxylate (120 mg.), obtained as needles (from methanol), m. p. and mixed m. p. 163°.

Tetramethyl 3a,6,7,7a-Tetrahydro-1-methylindole-2,3,3a,4-tetracarboxylate (VII).—The yellow adduct (X) (10 g.) in ethyl acetate (150 ml.) was shaken over Raney nickel under hydrogen (3 atm.) until no further absorption occurred. Filtration and evaporation gave the *tetrahydroindole* which separated from methanol in colourless prisms (8 g., 80%), m. p. 115—117° (Found: C, 55·8; H, 5·7; N, 3·9; OMe, 33·9. $C_{17}H_{21}NO_8$ requires C, 55·6; H, 5·7; N, 3·8; 4OMe, 33·8%). It gave no Ehrlich reaction and no colour with acids (lit.,[1] m. p. 114—116°).

Tetramethyl Octahydro-1-methylindole-2,3,3a,4-tetracarboxylates.—The yellow adduct (X) (5·0 g.) in methanol (170 ml.) was hydrogenated at 200°/170 atm. for 6 hr. over Raney nickel. Filtration and evaporation gave a yellow oil, which during some days partly solidified (1·2 g., 24%). Recrystallisation from methanol gave colourless prisms of an *octahydroindole*, m. p. 105° (Found: C, 55·1; H, 6·7; N, 4·1. $C_{17}H_{25}NO_8$ requires C, 55·0; H, 6·8; N, 3·8%). Further solidification of the yellow oil eventually took place, and crystallisation of the product from methanol gave an isomeric *octahydroindole* as hexagonal prisms (0·5 g., 10%), m. p. 125° (Found: C, 55·5; H, 6·5%). Its infrared absorption spectrum differed from that of the first product.

Hydrogenation of the yellow adduct (X) at ordinary temperature with Adams catalyst in glacial acetic acid gave an oil which was taken up in methanol. The solution was kept at 0° and eventually deposited plates, m. p. 155°, presumably the hexahydro-derivative of (X), m. p. 155—157°, obtained by Diels *et al.*[1] by hydrogenation over platinum black in acetic acid.

Hydrolysis and Decarboxylation of Trimethyl 1-Methylpyrrole-2,3,4-tricarboxylate (XIII).—The ester (XIII) (2·0 g.) was refluxed with potassium hydroxide (3 g.) in water (25 ml.) for 4 hr., and the solution cooled and acidified. 1-Methylpyrrole-2,3,4-tricarboxylic acid was precipitated; it separated from methanol as a white powder (1·5 g., 90%), which melted sharply in the range 139—142° (decomp.) (Found: C, 45·0; H, 3·2; N, 6·8. Calc. for $C_8H_7NO_6$: C, 45·0; H, 3·3; N, 6·6%).

This acid (1·0 g.) was intimately mixed with dry powdered soda-lime (10 g.) and heated gradually to dull redness in a slow stream of nitrogen. Sodium chloride and ether (1 ml.) were added to the distillate, and distillation of the dried ($MgSO_4$) ether extract gave a colourless oil (0·3 g., 70%) with a pyrrole-like odour. It gave an immediate intense purple colour with Ehrlich's reagent and was shown to contain only pyrrole (<20%) and 1-methylpyrrole by gas–

liquid chromatography with argon eluant on a polyester column at 80° alongside authentic materials.

Degradation of Tetramethyl 1-Methylindole-2,3,6,7-tetracarboxylate (XV) *to Methyl 1-Methylindole-6-carboxylate.*—The ester (XV) (1·5 g.) was refluxed with potassium hydroxide (5 g.) in water (5 ml.) and methanol (15 ml.) for 5 hr.; a white precipitate appeared after about 20 min. The precipitate was collected, washed with methanol, and sucked dry. It dissolved in water (2 ml.) and acidification with dilute hydrochloric acid gave a white precipitate, which after being washed with water and dried had m. p. 255—265° (1·25 g.). This product was heated in redistilled quinoline (10 ml.) with precipitated copper powder (*ca.* 1 g.) at 200° for 45 min. while carbon dioxide was evolved. When cold the liquid was decanted into an excess of dilute aqueous hydrochloric acid, and the greenish oily precipitate collected. Reprecipitation from aqueous sodium hydroxide solution by hydrochloric acid followed by crystallisation from aqueous acetone gave 1-methylindole-6-carboxylic acid (80 mg.), m. p. 192°, which gave a purple Ehrlich reaction in the cold.

This acid in methanol was treated with ethereal diazomethane, and evaporation, washing of the residue successively with aqueous sodium hydrogen carbonate and water, and four recrystallisations from aqueous methanol afforded methyl 1-methylindole-6-carboxylate (XVI) as buff needles, m. p. 89°, which gave a purple Ehrlich reaction in the cold.

6-Cyanoindole.—6-Cyanoindole-2-carboxylic acid was obtained by hydrolysis of the ethyl ester which was prepared in 57% yield from 4-cyano-2-nitrotoluene by Reissert's synthesis.[16]

(i) Distillation of the acid with soda-lime, as described,[16] gave only 2% of 6-cyanoindole, m. p. 126° (lit.,[16] 129—130°).

(ii) 6-Cyanoindole-2-carboxylic acid (4 g.) was ground with dry cupric oxide (6 g.) and heated gradually to a dull red heat at *ca.* 20 mm. The distillate was collected in a trap at −80°, and crystallisation from aqueous ethanol (charcoal) gave 6-cyanoindole as needles, m. p. 126° (0·6 g., 20%).

(iii) 6-Cyanoindole-2-carboxylic acid (10 g.), quinoline (50 ml.), and precipitated copper powder (0·5 g.) were heated at 220—240° for 2 hr.; the mixture darkened but there was no obvious decarboxylation. The hot solution was decanted from copper residues into concentrated hydrochloric acid (35 ml.) and crushed ice. The slimy brown precipitate was washed with dilute hydrochloric acid and with water; extraction with aqueous sodium hydrogen carbonate and acidification of this extract gave back some of the original acid (2·5 g.).

The aqueous filtrates and washings containing the quinoline hydrochloride were extracted continuously with ether, and the ether-soluble material separated from aqueous ethanol (charcoal) as a solid (3·25 g.) which showed weak carbonyl (5·93 μ) and bonded hydroxyl (in the region of 3·7 μ) absorption in the infrared spectrum. Extraction with aqueous sodium hydroxide removed further 6-cyanoindole-2-carboxylic acid (1·3 g.), and recrystallisation of the alkali-insoluble material from aqueous ethanol gave 6-cyanoindole as plates, having m. p. 126° (1·8 g., 24%), $\nu_{max.}$ at 2·92 (N–H) and at 4·49 μ (C≡N), and no absorption in the carbonyl region.

6-Cyano-1-methylindole.[20]—6-Cyanoindole (2·8 g.) in dry ether (15 ml.) was added with stirring to a solution of sodamide prepared by dissolving sodium (0·46 g.) in liquid ammonia (150 ml.) in the presence of a crystal of ferric nitrate. After 15 min. methyl iodide (3·0 g.) in ether (10 ml.) was added dropwise and stirring continued for another 15 min. When the ammonia had evaporated water (30 ml.) was added and the mixture extracted with ether (2 × 30 ml.). Evaporation of the dried ($MgSO_4$) extract and crystallisation of the residue from ether–light petroleum (b. p. 40—60°) gave 6-cyano-1-methylindole as crystal clusters, m. p. 55° (3·0 g.). It showed $\nu_{max.}$ at 4·49 (C≡N), and a small peak at 2·93 μ (N–H) which indicated the presence of some unmethylated material.

Methyl 1-Methylindole-6-carboxylate (XVI).—6-Cyano-1-methylindole (3·0 g.) was refluxed with potassium hydroxide (6 g.) in water (24 ml.) for 24 hr. After cooling and extraction with ether (30 ml.) the aqueous layer was acidified and the precipitate collected. After recrystallisation from aqueous acetone (charcoal) 1-methylindole-6-carboxylic acid (1·9 g., 60%) was obtained as almost colourless needles, m. p. 190°.

This acid (1·0 g.) in methanol (10 ml.) with ethereal diazomethane gave *methyl 1-methylindole-6-carboxylate* (XVI) which separated from aqueous methanol as plates, m. p. alone and mixed with the degradation product of tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate,

[20] Cf. Potts and Saxton, *J.*, 1954, 2641.

89° (Found: C, 69·9; H, 6·1; N, 7·6; OMe, 16·5. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·8; N, 7·4; OMe, 16·4%). The infrared and ultraviolet absorption spectra of the two samples were identical.

Degradation of Tetramethyl 3a,7a-Dihydro-1-methylindole-2,3,3a,4-tetracarboxylate (X).—This tetraester with bromine in methanol gave *trimethyl 1-methylindole-2,3,4-tricarboxylate* (IV), prisms (from methanol), m. p. 124—126° (Found: C, 59·1; H, 5·1; N, 4·8; OMe, 31·2. $C_{15}H_{15}NO_6$ requires C, 59·0; H, 5·0; N, 4·6; 3OMe, 30·5%), which was saponified to the tricarboxylic acid, m. p. 293° (decomp.), as described by Diels *et al.*[1]

The tricarboxylic acid (1 g.) and precipitated copper powder were heated in quinoline (5 ml.). Carbon dioxide evolution began at *ca.* 200° and was complete after 1 hr. at 200—220°. After cooling, the liquid was decanted from the copper into an excess of dilute hydrochloric acid, and the precipitate was collected, washed, and dissolved in aqueous sodium hydrogen carbonate. Acidification precipitated *1-methylindole-4-carboxylic acid*, which separated from aqueous acetone in needles, m. p. 243° (Found: C, 68·3; H, 5·1; N, 8·0; active H, 0·7. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·1; N, 8·0; active H, 0·6%). The methyl ester (VI), obtained with diazomethane, separated from ether–light petroleum (b. p. 40—60°) in flakes, m. p. 53°.

4-Cyanoindole.—6-Chloro-2-nitrophenylpyruvic acid (22% yield) was obtained from 6-chloro-2-nitrotoluene according to Uhle's directions,[15] but by using dimethyl oxalate and sodium methoxide; 70% of the toluene was recovered. The pyruvic acid, m. p. 105—107°, without purification, was reduced by ferrous sulphate and ammonia. The resulting crude 4-chloroindole-2-carboxylic acid (m. p. 252°; 53% yield) with cuprous chloride in quinoline gave 4-cyanoindole, obtained as needles (from much water), m. p. 117—118° (33% yield) (lit.,[15] m. p. 120—121°).

Methyl 1-Methylindole-4-carboxylate (VI).—4-Cyanoindole (1·3 g.) was methylated in the same way as the 6-isomer, and a crystalline product of very unsharp m. p. was obtained which could not be purified by recrystallisation (cf. 6-cyano-1-methylindole). It showed reduced N–H absorption at 3·0 μ, as compared with 4-cyanoindole. The crude 4-cyano-1-methylindole (1·0 g.) was hydrolysed, as for the 6-isomer, and 1-methylindole-4-carboxylic acid was obtained as brownish needles (from aqueous ethanol), m. p. 236° (0·6 g., 60%). Treatment with diazomethane gave *methyl 1-methylindole-4-carboxylate* which separated from ether–light petroleum (b. p. 40—60°) in flakes, m. p. and mixed m. p. with the sample obtained by the degradation of the yellow adduct (X), 53° (Found: C, 69·6; H, 5·9; N, 7·5; OMe, 16·4. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·8; N, 7·4; OMe, 16·4%). The ultraviolet and infrared absorption spectra of the two samples were identical. Both 1-methylindole-4-carboxylic acid and the ester gave immediate purple Ehrlich colours in the cold.

Tetramethyl 1-Benzyl-3a,7a-dihydroindole-2,3,3a,4-tetracarboxylate (XI).—The *tetraester* (XI), obtained from 1-benzylpyrrole (1·6 g.) and dimethyl acetylenedicarboxylate (2·9 g.) in 48 hr. at room temperature, separated from methanol in very pale primrose-yellow needles, m. p. 135° (1·6 g., 36% yield) (Found: C, 62·3; H, 5·5; N, 3·3; OMe, 27·5. $C_{23}H_{23}NO_8$ requires C, 62·6; H, 5·2; N, 3·2; 4OMe, 28·2%). Like the corresponding adduct from 1-methylpyrrole it slowly gave a purple colour ($\lambda_{max.}$ 5360 Å) with acids.

Trimethyl 1-Benzylindole-2,3,4-tricarboxylate (V).—Bromine (0·1 g.) was added to the tetraester (XI) (0·22 g.) in methanol (5 ml.). After 24 hr. at room temperature, then cooling to 0°, the *triester* was precipitated (0·13 g., 70%); it recrystallised from methanol in needles, m. p. 114° (Found: C, 66·2; H, 5·1; N, 4·1; OMe, 24·6. $C_{21}H_{19}NO_6$ requires C, 66·2; N, 5·0; N, 3·7; 3OMe, 24·4%).

Test of the Mechanism of Formation of Tetramethyl 1-Benzyl-3a,7a-dihydroindole-2,3,3a,4-tetracarboxylate (XI).—A suspension of the dicarboxylic acid [2] (III) (0·4 g.) in ether was treated with an excess of ethereal diazomethane and gently warmed. Filtration and evaporation at room temperature gave a yellow oil, which smelled strongly of 1-benzylpyrrole, gave an immediate purple Ehrlich reaction, and showed very weak absorption at 4·76 μ (monosubstituted acetylene). A sample was chromatographed on an Apiezon column at 200° with argon eluant. Two elution peaks were obtained which were exactly matched by a mixture of 1-benzylpyrrole and dimethyl acetylenedicarboxylate.

The major portion of the oil was treated with dimethyl acetylenedicarboxylate (4 drops); after 48 hr. the mixture solidified on trituration with ether and methanol. The yellow solid had m. p. 130—132° and its infrared absorption spectrum was identical with that of the tetraester (XI).

Dimethyl 1-*Benzyl-2-pyrrolyl maleate and Dimethyl Acetylenedicarboxylate.*—1-Benzyl-2-pyrrolylmaleic acid [2] (0·25 g.) in methanol was treated with an excess of diazomethane in ether; filtration and evaporation gave the ester as a pale yellow oil. Dimethyl acetylenedicarboxylate (0·1 g.) was added and the ultraviolet absorption spectrum of portions of the mixture, suitably diluted with methanol so as to keep the absorption maximum of the maleic ester at *ca.* 3300 Å roughly constant, was examined at intervals during 10 days. There was no significant change in absorption spectrum and in particular no increase near 2770 Å.

Dimethyl Oxaloacetate Derivatives.—1-Methyl-1-phenylhydrazine (2·2 g.) in methanol (10 ml.) and dimethyl acetylenedicarboxylate (2·5 g.) in methanol (3 ml.) were mixed and left for 24 hr. The dark solution was mostly evaporated and the solid product collected and washed with a little ether. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave colourless *dimethyl oxaloacetate* 1-*methyl*-1-*phenylhydrazone* (XXI) (3·5 g., 75%), melting at 54° to a yellow oil and giving a yellow solution in methanol (Found: C, 58·8; H, 6·1; N, 10·8. $C_{13}H_{16}N_2O_4$ requires C, 59·1; H, 6·2; N, 10·6%).

An attempt to cyclise this phenylhydrazone (1·0 g.) by heating it with xylene at 170° for 4 hr., followed by evaporation *in vacuo* and vigorous shaking with 50% aqueous sulphuric acid (3 ml.) gave a paste of crystals, which when washed with water, dried, and recrystallised from ether–light petroleum (b. p. 40—60°) gave dimethyl oxaloacetate, m. p. 80—82° (Found: C, 45·1; H, 5·1; OMe, 38·4. Calc. for $C_6H_8O_5$: C, 45·0; H, 5·0; 2OMe, 38·7%). It gave a pale red ferric chloride colour. The same product was obtained from the 1-methyl-1-phenylhydrazone and 80% sulphuric acid.

Dimethyl oxaloacetate 2,4-*dinitrophenylhydrazone* was precipitated when dimethyl acetylenedicarboxylate (0·15 g.) was left with 2,4-dinitrophenylhydrazine (0·2 g.) in methanol (saturated at 30°) for 1 hr. and formed yellow needles, m. p. 161°, from methanol (Found: C, 42·5; H, 3·7; N, 16·5; OMe, 17·9. $C_{12}H_{12}N_4O_8$ requires C, 42·4; H, 3·5; N, 16·5; 2OMe, 18·2%). It had the same infrared absorption spectrum as a specimen, m. p. 156—158° alone or mixed with the above, prepared from dimethyl oxaloacetate and 2,4-dinitrophenylhydrazine in methanolic sulphuric acid.

Dimethyl 1-*Methylindole*-2,3-*dicarboxylate* (XXII).—Dimethyl oxaloacetate 1-methyl-1-phenylhydrazone (XXI) (1·0 g.) and powdered anhydrous zinc chloride (2 g.) were heated in an oil-bath initially at 100° with occasional stirring. Effervescence began at 150° and reaction was completed by heating at 170° for 1·5 hr. When cold the dark mass was warmed with dilute sulphuric acid to dissolve the zinc salts, cooled, and extracted with ether (3 × 50 ml.). Evaporation of the dried (Na_2SO_4) extract, which had an unpleasant fæcal odour, gave a solid which crystallised from methanol (charcoal), yielding *methyl hydrogen* 1-*methylindole*-2,3-*dicarboxylate* as needles (0·12 g., 13%), m. p. 176° (Found: C, 61·9; H, 4·9; N, 5·9; OMe, 13·2. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·7; N, 6·0; OMe, 13·3%). It gave a purple Ehrlich colour after several minutes' heating.

The *dimethyl ester* (XXII), obtained with diazomethane, separated from ether–light petroleum (b. p. 40—60°) as a solid, m. p. 35° (Found: C, 62·9; H, 5·2. $C_{13}H_{13}NO_4$ requires C, 63·2; H, 5·5%). It gave a purple Ehrlich colour after prolonged heating on a water-bath.

m-*Cyanophenylhydrazine Derivatives.*—*m*-Cyanoaniline [21] (4·4 g.) in concentrated hydrochloric acid (10 ml.) and water (10 ml.) was cooled to −5° with vigorous stirring. Sodium nitrite (3 g.) in water (5 ml.) was added slowly, and stirring continued for 5 min. The solution was filtered and added in 5 min. with stirring to sodium sulphite heptahydrate (20 g.) and sodium hydroxide (2 g.) in water (60 ml.) at 0°. After 5 minutes' further stirring, concentrated hydrochloric acid (35 ml.) was added, and the mixture heated to 55° for 3 min., then kept overnight, filtered, and shaken with ether. Sodium hydroxide (20 g.) was added to the aqueous layer, which was extracted with ether (2 × 100 ml.). The dried (Na_2SO_4) ether extract was evaporated; the residue of yellowish crystals (0·7 g., 14%), m. p. 92—94°, had an odour like that of benzaldehyde. Recrystallisation from benzene–light petroleum (b. p. 40—60°), gave *m*-cyanophenylhydrazine, m. p. 110°, which deteriorated rapidly. It showed $\nu_{max.}$ at 3·06 (N–H) and 4·49 μ (C≡N).

Benzaldehyde (0·1 g.) was shaken with *m*-cyanophenylhydrazine (0·12 g.) in 50% acetic acid (2 ml.). After 10 min. the precipitate was collected and crystallised from aqueous ethanol, to give *benzaldehyde* m-*cyanophenylhydrazone*, m. p. 156° (Found: C, 76·0; H, 5·0. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0%).

[21] Dyson, George, and Hunter, *J*, 1927, 436.

m-Cyanophenylhydrazine (0·4 g.) in warm glacial acetic acid (0·6 g.) was diluted with water (0·6 g.). Addition of sodium pyruvate (0·33 g.) in water (1 g.) precipitated *pyruvic acid* m-*cyanophenylhydrazone* quantitatively as a buff powder which, crystallised from aqueous ethanol, had m. p. 216° (Found: N, 20·3. $C_{10}H_9N_3O_2$ requires N, 20·7%).

Dimethyl 3-*Benzylideneaminophthalate*.—Dimethyl 3-nitrophthalate, m. p. 68—69° (lit.,[22] m. p. 67—69°) was obtained from 3-nitrophthalic acid (3·2 g.) with diazomethane. In methanol (60 ml.) it was shaken with Adams catalyst under hydrogen (4 atm.) for 0·5 hr., absorption being then complete. Filtration and evaporation gave a yellow-brown oil of dimethyl 3-aminophthalate.[22] Benzaldehyde (1·5 g.) was added and the mixture heated for 2 hr. at 100°. Ether (40 ml.) was added and the extract filtered, dried ($MgSO_4$), and evaporated. The residue crystallised from methanol to give pale yellow *dimethyl* 3-*benzylideneaminophthalate* (3 g., 66% overall yield), m. p. 97—97·5° (Found: C, 68·8; H, 5·1; N, 4·8; OMe, 20·3. $C_{17}H_{15}NO_4$ requires C, 68·7; H, 5·2; N, 4·7; 2OMe, 20·8%).

3-*Dimethylaminophthalic Anhydride*.—Dimethyl 3-nitrophthalate (4·8 g.), methanol (50 ml.), 40% aqueous formaldehyde (4·5 g.), anhydrous sodium acetate (0·4 g.), and Raney nickel catalyst (*ca.* 1 g.) were shaken under hydrogen (3 atm.) for 6 hr., absorption then ceasing. Filtration and evaporation gave a yellow-green oil which was heated at 100° for 1 hr. with an equal weight of acetic anhydride. After being kept at 0° the precipitated 3-*dimethylaminophthalic anhydride* was collected and washed with acetic anhydride and with light petroleum (b. p. 40—60°). It crystallised from aqueous methanol as yellow needles (0·8 g., 21%), m. p. 140—141° (Found: C, 62·8; H, 4·7; N, 7·4. Calc. for $C_{10}H_9NO_3$: C, 62·8; H, 4·7; N, 7·3%). It showed $\nu_{max.}$ at 5·47, 5·68 μ (anhydride) but no absorption in the region for N–H.

We are indebted to Professor R. A. Nicolaus for a sample of the pyrrole (XIII), Dr. E. C. Kornfeld for two other pyrroles, Dr. P. Higham for the measurement and interpretation of the nuclear magnetic resonance spectra, Mr. N. J. Earl for some preliminary experiments, Dr. A. R. Hands for many helpful discussions, and to the D.S.I.R. for a studentship (to J. M. V.). This work was supported in part by grants from the Rockefeller Foundation and from the United States Public Health Service to the Department of Biochemistry, University of Oxford.

Department of Biochemistry, University of Oxford. [*Received, October 24th*, 1961.]

[22] Twiss and Heinzelmann, *J. Org. Chem.*, 1950, **15**, 496.