614. *Addition Reactions of Heterocyclic Compounds. Part XX.* The Bromination and Rearrangement of Trimethyl 1-Methylindole-2,3,4-tricarboxylate.*

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Trimethyl 1-methylindole-2,3,4-tricarboxylate, with bromine in aqueous acetic acid, gave trimethyl 5-bromo-1-methyloxindole-3,3,4-tricarboxylate, the structure of which was established from spectral comparisons and by stepwise degradation to 1-methyloxindole. The mechanism of the 1,2-ester shift is discussed.

Trimethyl 1-methylindole-2,3,4-tricarboxylate (I) with bromine in acetic acid is reported [1] to yield a mixture of the 6-bromo-derivative (II) and a second compound, melting point 187°. The present Paper describes an investigation of this second compound, the oxindole (VI).

Only the 6-bromo-derivative (II) was isolable from the bromination of the indole ester in anhydrous acetic acid but if sufficient water was present the oxindole (VI) became the major product. Hydrogenation of this oxindole removed the bromine atom, and attempted reduction of both oxindoles (V) and (VI) with potassium iodide in acetic acid caused loss of the ester groups at position 3. Heating the oxindole (VII) with zinc, instead of leading to the known methyl 1-methylindole-4-carboxylate as analogies would suggest,[2] gave 1-methyloxindole, thereby showing the presence of this nucleus in the bromination product.

The ultraviolet spectra of the parent compound (VI) and its degradation products were all very similar, indicating that no major structural change took place during the transformations. From the infrared spectra and that of 1-methyloxindole [3] it was concluded that the maxima at about 5·65, 5·73, and 5·80 μ correspond to the 3- and 4-ester groups and to the 2-carbonyl group, respectively. The nuclear magnetic resonance spectra of the oxindoles are given in the Table.

The coupling constants for the aromatic hydrogen atoms in the bromo-compounds (VI) and (VIII) indicate that these atoms are *ortho* to each other, and, consequently, the bromine atom cannot be at position 6. Heacock *et al.*[4] showed that the *N*-methyl proton resonance of 3,5,6-triacetoxy-7-bromo-1-methylindole is shifted 0·52 τ towards low field as compared with the corresponding unbrominated indole, and suggest that this is due to the close proximity of the halogen atom to the *N*-methyl group; a similar down-field shift (0·37 τ) of the *N*-methyl absorption of methyl 3-dimethylaminobenzoate on conversion

* Part XIX, preceding Paper.

[1] Acheson and Vernon, *J.*, 1963, 1907.
[2] Acheson, "Introduction to the Chemistry of Heterocyclic Compounds," Interscience–Wiley, London, 1962, p. 127.
[3] Kellie, O'Sullivan, and Sadler, *J.*, 1956, 3809.
[4] Heacock, Hutzinger, Scott, Daly, and Witkop, *J. Amer. Chem. Soc.*, 1963, **85**, 1825.

Nuclear magnetic resonance spectra in deuterochloroform.

	Assignments [a]						
	Aromatic protons						
Compound	H-5	τ H-6	H-7	*J* (c./sec.)	Other protons	OMe [b]	NMe [b]
(I) [c]	Complex	(3)				5·98, 6·03, 6·05, 6·08 [d]	
(II) [c]	2·08 (?)		2·28 (?)	2		6·01, 6·05, 6·08, 6·09 [d]	
(V)	2·28	2·50	2·91	$J_{5,6} = J_{6,7} = 8·5$, $J_{5,7} = 1·5$		6·10, 6·22 (6)	6·67
(VI)		2·37	3·14	8·5		6·13, 6·22 (6)	6·70
(VII)	2·31	2·61	3·02	$J_{5,6} = J_{6,7} = 8·5$, $J_{5,7} = 1·4$	H-3, 6·21 (2)	6·07	6·77
VIII)		2·42	3·23	8·5	H-3, 6·3 (2)	6·03	6·78
(IX)	2·55	2·90 (2)	3·35 (?) [e]	~8 and 2	H-2, 4·63	6·15, 6·21 (6), 6·34	7·01
(X) [f]	.	2·50	3·60	8·25	H-2, 5·0	6·13, 6·20, 6·25, 6·35	7·06
A [c]	Complex	(4)			H-3, 6·50 (2)		6·79
B	2·34 (?)		2·44 (?)	2		6·02, 6·07, 6·20 [d]	
C		2·31	3·14	8·5	H-3, 5·28	6·07, 6·21	6·75
D			2·69			6·05, 6·21	6·81

A = 1-Methyloxindole, B = dimethyl 3,6-dibromo-1-methylindole-2,4-dicarboxylate, C = dimethyl 5-bromo-1-methyloxindole-3,4-dicarboxylate, D = dimethyl 3,5,6-tribromo-1-methyloxindole-3,4-dicarboxylate.

[a] Numbers of undesignated protons are given in parentheses. [b] 3-Proton peaks unless otherwise indicated. [c] In chloroform. [d] One of these is an NMe group. [e] Double doublet. [f] In nitromethane.

into the dibromo-derivative [1] has been observed. The *N*-methyl resonances of trimethyl 1-methylindole-2,3,4-tricarboxylate (I) and its 6-bromo-derivative (II) are not distinguishable from the ester methyl absorptions but are at a markedly lower field than that of 1-methylindole (6·63 τ).[5] This strongly suggests that the ester groups at position 2 are exerting their usual deshielding effect,[6] and confirms that the position of the *N*-methyl resonance is sensitive to nearby substituents. If it is assumed that a low-field shift of the *N*-methyl resonance will be produced by an *ortho*-bromine atom in oxindoles then the bromine atom must be at position 5 in our compounds. This agrees exactly with the changes in the aromatic proton spectra observed on going from the oxindoles (V) and (VII) to their bromo-derivatives, (VI) and (VIII), respectively, if it is assumed [6] that the low-field proton is at position 5, next to the ester group. Introduction of the bromine at this position causes down-field shifts of the *ortho*-hydrogens (H-6) and up-field shifts of the *meta*-hydrogens (H-7) roughly as predicted from the data (−22 and +11 p.p.m., respectively) of Diehl;[7] the observed changes are not consistent with what would be expected should the bromine have entered position 7. A similar comparison of the spectra of the dihydroindoles (IX) and (X) shows that the bromine atom, previously [1] assigned to position 5 or 7, must be at position 5.

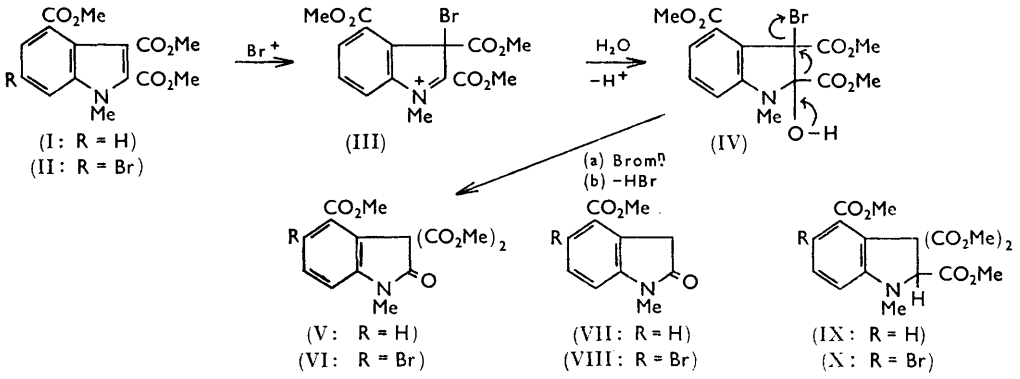
1-Methyloxindole possesses a sharp maximum at 6·50 τ, corresponding to two protons, and no detectable hydroxyl absorption, confirming the deduction [3] from infrared studies that appreciable tautomerism to the 3-hydroxyindole structure does not occur. Similar maxima, but at lower field because of the nearby ester groups, are shown by the oxindoles (VII) and (VIII) and by dimethyl 5-bromo-1-methyloxindole-3,4-dicarboxylate, where the shift is much greater.

The triester (VI) proved difficult to hydrolyse, alcoholic potassium hydroxide yielding only dimethyl 5-bromo-1-methyloxindole-3,4-dicarboxylate, but refluxing hydrogen

[5] Cohen, Daly, Kny, and Witkop, *J. Amer. Chem. Soc.*, 1960, **82**, 2184.
[6] Cf. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon, London, 1959, p. 124.
[7] Diehl, *Helv. Chim. Acta*, 1961, **44**, 829.

bromide gave 5-bromo-1-methyloxindole-4-carboxylic acid which, as expected because the carboxyl group is sterically hindered, was not esterified by methanolic hydrogen chloride.

The formation of the oxindole-3,3-diester (VI) in the original bromination requires a 1,2-shift of an ester group from the 2-position of the indole (I). Few shifts of this type have been described. No mechanism has been established for the saturated-centre rearrangement of methylmalonyl coenzyme A to succinyl coenzyme A [8] whilst nucleophilic attack on the moving ester group accounts [1] for the thermal rearrangement of tetramethyl



3a,7a-dihydro-1-methylindole-2,3,3a,4-tetracarboxylate to the dihydroindole (IX), and for another rearrangement.[9] However, present results are better accommodated in the outlined scheme,[10] which in its early stages resembles the general reaction discussed by Taylor,[11] where the ester group moves with its bonding electrons to a positive centre. This scheme also accounts for the conversion of a number of indoles into 5-bromo-oxindoles by bromination in aqueous media.[12] The possibility that a cyclic bromonium ion of the type suggested by Witkop and his co-workers [12] may be an alternative to the cation (III) in the sequence above, is not excluded. The isomerisation of ethyl 2-hydroxyindoxyl-2-carboxylate by cold alkali to ethyl 3-hydroxyoxindole-3-carboxylate [13] may proceed by a similar path to our rearrangement.

The nuclear bromination appears to occur at some stage prior to the ester shift for, whilst the ester (V) can be brominated in a steam-bath, no reaction occurs under the conditions of the rearrangement. It is possible that the intermediate (IV) is in fact substituted, since 2,3-dihydroindoles are brominated [14] mainly at position 5. Further bromination of the ester (VI) caused loss of one ester group and the formation of dimethyl 3,5,6-tribromo-1-methyloxindole-3,4-dicarboxylate. The ester group lost is almost certainly that at position 3, from spectral data, the knowledge that the 3-ester groups are eliminated under acid conditions, and the assumption that the displacement of the highly hindered 4-ester group by a large bromine atom is improbable. The *N*-methyl resonance of the tribromo-derivative is virtually the same as that of its precursor (VI), indicating no substitution at position 7, and this is confirmed by the position of the resonance of the remaining aromatic proton for, as the introduction of a bromine atom can only cause deshielding of an *ortho*-hydrogen, the remaining proton cannot be at position 6.

Bromination of trimethyl 1-methylindole-2,3,4-tricarboxylate in hot acetic acid gave a

[8] Kellermeyer and Wood, *Biochemistry*, 1962, **1**, 1124.
[9] Fahr and Scheckenbach, *Annalen*, 1962, **655**, 86.
[10] Acheson and Snaith, *Proc. Chem. Soc.*, 1963, 344.
[11] Taylor, *Proc. Chem. Soc.*, 1962, 247.
[12] Lawson, Patchornick, and Witkop, *J. Amer. Chem. Soc.*, 1960, **82**, 5918.
[13] Kalb, *Ber.*, 1911, **44**, 1455.
[14] Thesing, Semler, and Mohr, *Chem. Ber.*, 1962, **95**, 2205.

compound which was probably dimethyl 3,6-dibromo-1-methylindole-2,4-dicarboxylate whilst, on another occasion, when moisture may have entered the apparatus, the product appeared to be dimethyl 3,5-dibromo-1-methyloxindole-3,4-dicarboxylate.

Experimental

Infrared spectra are for Nujol mulls (N) or chloroform solutions (C) and are given for the 5—7 μ region. Ultraviolet spectra are for methanol solutions and are recorded in mμ; 10^{-4} ε being given in parentheses. Inflexions are marked with an asterisk. Nuclear magnetic resonance spectra were measured at 29·92 Mc./sec. as before [1] or in the Dyson Perrins Laboratory using a Perkin-Elmer 60 Mc./sec. spectrometer at 34°.

Bromination of Trimethyl 1-Methylindole-2,3,4-tricarboxylate (I).—(i) The indole (7·2 g.) in glacial acetic acid (36 ml.) and water (4 ml., *ca.* 10 mol.) was cooled to 5° in an ice-bath and bromine (6·0 g., 2 mol.) in glacial acetic acid (15 ml.) was added in three portions, with stirring; the temperature remained about 10°. After 2 hr. at room temperature the mixture was poured into ice–water and the precipitate collected 30 min. later. After washing and drying it was heated with methanol (40 ml.) for 2 min. at about 50°, and filtered hot. The filtrate, on cooling, deposited crude trimethyl 6-bromo-1-methylindole-2,3,4-tricarboxylate (II) (2·0 g., 21%), m. p. 158° (after recrystallisation). The insoluble material gave *trimethyl 5-bromo-1-methyloxindole-3,3,4-tricarboxylate*, (VI) (4·5 g., 45%), m. p. 187° (from methanol) (Found: C, 45·0; H, 3·5; Br, 19·7; N, 3·3; OMe, 23·9. $C_{15}H_{14}BrNO_7$ requires C, 45·0; H, 3·5; Br, 20·0; N, 3·5; 3OMe, 23·2%), $\lambda_{max.}$ 215 (2·10), 267 (1·35), and 312* (0·25), $\nu_{max.}$ (C) 5·65, 5·72 (broad with a suggestion of an inflexion on the long-wavelength side), 6·25, 6·86, 6·90, and 6·98 μ. It gave no Ehrlich reaction.

(ii) The bromination was repeated as above but under anhydrous conditions. Only trimethyl 6-bromo-1-methylindole-2,3,4-tricarboxylate (7·0 g.) was isolable.

(iii) Bromine (3·0 g.) was added all at once to the ester (2·8 g.) in acetic acid (14 ml.) just warm enough to effect solution and, after 15 min., the mixture was heated to 60—70° for 10 min. After 2 hr. at room temperature it was poured into water yielding a yellow tar from which *dimethyl 3,6-dibromo-1-methylindole-2,4-dicarboxylate* (0·6 g.) was obtained, colourless cubes, m. p. 149° (from methanol) (Found: C, 38·5; H, 2·5; Br, 38·3; N, 3·2. $C_{13}H_{11}Br_2NO_4$ requires C, 38·5; H, 2·6; Br, 39·5; N, 3·45%), $\lambda_{max.}$ 243 (2·5) and 316 (1·39); $\nu_{max.}$ (C) 5·82, 6·26, 6·71, 6·88, and 6·97 μ.

(iv) Experiment (iii) was repeated except that the bromine was dissolved in acetic acid (7·5 ml.) before addition. The tar solidified on trituration with hot methanol, and was stirred with hot methanol until the fluffy needles of trimethyl 6-bromo-1-methylindole-2,3,4-tricarboxylate had dissolved. The residue, on crystallisation from methanol, gave probably *dimethyl 3,5-dibromo-1-methyloxindole-3,4-dicarboxylate* (0·2 g.), m. p. 185—187° (decomp.) (Found: C, 37·2; H, 2·7; Br, 38·3; N, 3·2; OMe, 15·3; NMe, 7·5. $C_{13}H_{11}Br_2NO_5$ requires C, 37·2; H, 2·7; Br, 38·3; N, 3·3; 2OMe, 14·8; NMe, 6·9%), $\lambda_{max.}$ ~290* (1·5), 325 (0·55), $\nu_{max.}$ (N) 5·77br, 6·25, 6·71, 6·90, and 6·98 μ.

Bromination of Trimethyl 1-Methyloxindole-3,3,4-tricarboxylate (V).—The ester (V) (0·20 g.) in glacial acetic acid (5 ml.) containing bromine (0·12 ml.) was heated at 100° for 4 hr. The mixture was cooled, poured into water, and the precipitate, after crystallisation from methanol, gave the bromo-derivative (VI) identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen. When the bromination was attempted at room temperature, as above, or with the addition of some hydrobromic acid, only starting material was recovered.

Bromination of Trimethyl 5-Bromo-1-methyloxindole-3,3,4-tricarboxylate (VI).—This ester (0·5 g.) was refluxed with bromine (1·8 g.) in glacial acetic acid (10 ml.) for 4 hr., cooled, and poured into water (50 ml.). Next day, the insoluble material gave *dimethyl 3,5,6-tribromo-1-methyloxindole-3,4-dicarboxylate* as rods (60 mg.), m. p. 170—172° (decomp.) (from methanol) (Found: C, 31·4; H, 2·1; Br, 48·3; N, 2·7; OMe, 12·4. $C_{13}H_{10}Br_3NO_5$ requires C, 31·2; H, 2·0; Br, 48·0; N, 2·8; 2OMe, 12·40%), $\lambda_{max.}$ 280—290* (2·4) and 330 (0·49), $\nu_{max.}$ (C) 5·65, 5·75, 6·27, 6·85, 6·90*, and 6·98 μ.

Trimethyl 1-Methyloxindole-3,3,4-tricarboxylate (V).—The bromo-derivative (VI) (1·0 g.) in methanol (350 ml.) was hydrogenated (4 atm.) over 5% palladised charcoal for 45 hr. After filtration, the catalyst was extracted twice with boiling methanol, and evaporation of the

combined filtrate and extracts gave the *triester* (0·65 g.), prisms, m. p. 203—204° (from methanol) (Found: C, 55·9; H, 4·5; N, 4·5; OMe, 29·1. $C_{15}H_{15}NO_7$ requires C, 56·1; H, 4·7; N, 4·4; 3OMe, 29·0%), $\lambda_{max.}$ 213 (2·05), 262 (0·80), and 313 (0·20), $\nu_{max.}$ (C) 5·60*, 5·65, 5·74*, 5·78, 6·24, 6·71, 6·82, and 6·96 μ. In Nujol clear maxima at 5·60, 5·72, 5·80, and 5·85 μ were observed in the carbonyl region and this change in absorption with the conditions of examination is very similar to that observed with the dihydroindole (IX).[1] It gave a golden-yellow colour with hot Ehrlich's reagent.

Methyl 1-Methyloxindole-4-carboxylate (VII).—The above oxindole (V) (0·1 g.) was refluxed in glacial acetic acid (4 ml.) containing potassium iodide (0·1 g.) for 24 hr., cooled, and diluted with water (20 ml.). After 2 hr. the precipitate was collected and gave the *ester* as needles, m. p. 169° (from methanol) (Found: C, 64·0; H, 5·1; OMe, 15·1. $C_{11}H_{11}NO_3$ requires C, 64·1; H, 5·4; OMe, 15·2%), $\lambda_{max.}$ 255 (1·16) and 315 (0·27), $\nu_{max.}$ (C) 5·65* vw, 5·75*, 5·82, 6·22, 6·72, 6·82, 6·88*, and 6·98 μ.

This compound (0·2 g.) was heated with zinc dust (2·0 g.) for 30 min. so that the organic vapours circulated over the heated metal and did not ascend the air condenser. After cooling, the organic matter was extracted from the zinc with boiling light petroleum (b. p. 60—80°). Evaporation gave a very small quantity of a yellow oil which eventually solidified. Its infrared spectrum (C) was identical with that of an authentic specimen of 1-methyloxindole in the 2·5—15 μ region (16 maxima and corresponding minima) save for two additional weak peaks at 9·5 and 10·1 μ.

Methyl 5-Bromo-1-methyloxindole-4-carboxylate (VIII).—Trimethyl 5-bromo-1-methyloxindole-3,3,4-tricarboxylate (VI) (0·5 g.) was refluxed in glacial acetic acid (20 ml.) with potassium iodide (0·5 g.) for 18 hr., diluted with an equal volume of water, and left 18 hr. The precipitate was collected. The filtrate was evaporated to dryness, and the water-insoluble part of the residue combined with the precipitate. Recrystallisation from methanol gave the *bromo-ester* as needles (0·12 g., 34%), m. p. 149—150° (Found: C, 46·0; H, 3·7; Br, 28·5; OMe, 9·9. $C_{11}H_{10}BrNO_3$ requires C, 46·3; H, 3·5; Br, 28·3; OMe, 10·9%), $\lambda_{max.}$ 262 (1·52) and 312 (0·18); $\nu_{max.}$ (N) 5·75 and 5·83 (unresolved in $CHCl_3$), 6·25, 6·85, and 6·99 μ. It gave a golden-yellow colour with hot Ehrlich's reagent.

Dimethyl 5-Bromo-1-methyloxindole-3,4-dicarboxylate.—Trimethyl 5-bromo-1-methyloxindole-3,3,4-tricarboxylate (VI) (1·14 g.) was refluxed with potassium hydroxide (1·0 g.) in methanol (30 ml.) containing water (2 ml.) for 2 hr. The solvent was evaporated at 40 mm., the residue dissolved in water, and acidification to pH 2 precipitated the *diester* (0·88 g.), prisms, m. p. 192—193° (from aqueous methanol) (Found: C, 45·3, 45·4; H, 3·7, 4·0; N, 3·9, 4·1; OMe, 17·6. $C_{13}H_{12}BrNO_5$ requires C, 45·6; H, 3·5; N, 4·1; 2OMe, 18·1%), $\lambda_{max.}$ 322, 296, and 268 mμ, $\nu_{max.}$ (N) 5·74, 5·85, 6·27, 6·88, 6·92, and 6·99 μ.

5-Bromo-1-methyloxindole-4-carboxylic acid.—Trimethyl 5-bromo-1-methyloxindole-3,3,4-tricarboxylate (VI) (1·0 g.) was refluxed with concentrated aqueous hydrobromic acid (10 ml.) for 24 hr. and the mixture evaporated to dryness at 40 mm. Crystallisation of the residue (0·54 g.) from aqueous methanol gave the *acid* as rhombs, m. p. 275—278° (Found: C, 44·5; H, 2·8. $C_{10}H_8BrNO_3$ requires C, 44·4; H, 3·0%), $\lambda_{max.}$ 307 and 261 mμ, $\nu_{max.}$ (N) 3—4 μ (very broad) 5·82, 6·06, 6·29, 6·36, and 6·92 μ.

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