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# CHLORINATION OF 5-METHOXYINDOLE DERIVATIVES

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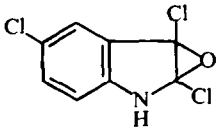
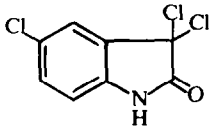
**Abstract** 5-Methoxyindole-2-carboxylic acid and its methyl ester have been subjected to reaction with N,N-dichlorourethane (DCU) in acetic acid, both glacial and aqueous. The probable role of water in these substitution reactions has been elucidated. Novel chlorinated isatins and oxindoles have been obtained and reaction mechanisms for their formation suggested.

IN CONNECTION with an investigation of the reactions of N-monochloro and N,N-dichlorocarbamates, Chabrier claimed[1] that the reaction of N,N-dichlorourethane (DCU) with indol-2-carboxylic acid yielded 2,3,5-trichloro-2,3-epoxyindole (I).



I



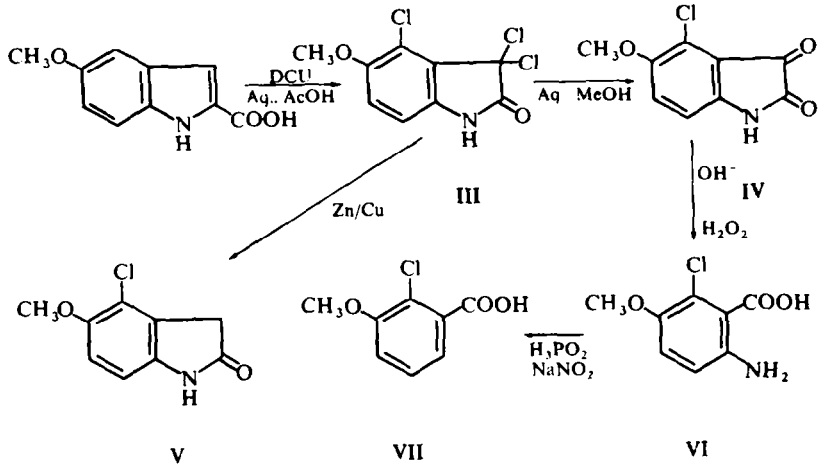
II

Foglia and Swern[2] and Muchowski[3] have recently demonstrated by spectral and degradative methods that the main product from the reaction is the 3,3,5-trichloro-oxindole (II).

The fact that II could be readily hydrolysed to 5-chloroisatin aroused my interest, as the reaction scheme presented a route to 5-methoxyisatins from 5-methoxyindole-2-carboxylic acid. Alkoxyisatins are obtainable in only poor yield by the conventional Sandmeyer synthesis.[4]

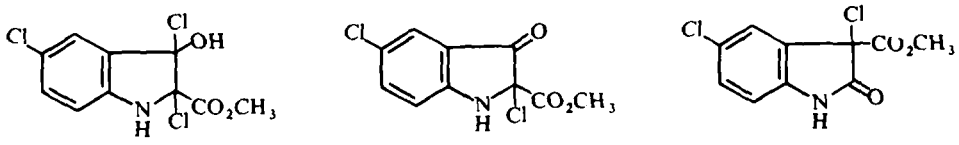
A suspension of 5-methoxyindol-2-carboxylic acid in aqueous acetic acid, gave when treated with 2 equivs. of DCU, a trichloro compound, the structure of which was established as 3,3,4-trichloro-5-methoxyoxindole (III). This assignment was based on the IR and the NMR spectra (Table). The latter showed, by the presence of *ortho*-coupling (8·5 Hz), that chlorine had been introduced at position 4. The presence of three chlorine atoms was confirmed by the mass spectrum $M^+$ 265 (27:27:9:1), peak heights corresponding to the relative abundances of the two chlorine isotopes in the molecular ion. The trichloro-oxindole (III) was reduced by Zn/Cu[5] couple to 4-chloro-5-methoxyoxindole (V) (Table), and hydrolysed smoothly to 4-chloro-5-methoxy-isatin (IV) (Table).

The m.p. 165–168° of the isatin did not agree with that previously reported (261–262°) by B. R. Baker *et al.*[6] The evidence for their structure was based solely on microanalysis of the product from a Sandmeyer reaction on 3-chloro-4-methoxy aniline. They were also unable to obtain a pure sample of the corresponding 6-amino-2-chloro-3-methoxybenzoic acid (VI) by treatment of the isatin with alkaline peroxide.



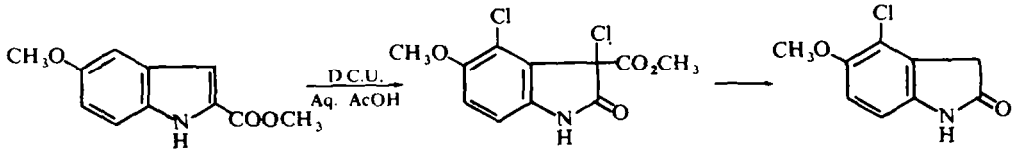

This compound was readily afforded by our material, and then deaminated by hypophosphorous acid to the known[7] 2-chloro-3-methoxybenzoic acid (VII).

Foglia and Swern have re-examined Chabrier's original claim to have prepared the tri-chloro ester (VIII) via the reaction of DCU with methyl-indole-2-carboxylate in aqueous acetic acid and considered the product to have the indoxyl structure (IX). Recently Muchowski has re-examined their conclusions and shown the correct structure to be dichloro-oxindole (X).




The reaction of DCU in aqueous acetic acid with methyl-5-methoxyindole-2-carboxylate (XI) gave a product m.p. 204–205° whose IR and NMR spectra (Table) were consistent with structure XII. That this was an oxindole and not an indoxyl was shown by reduction with Zn/Cu couple to the oxindole (V).

Foglia and Swern have stated that the reaction of indoles with DCU in aqueous acetic acid occurs too fast to allow any intermediates to be isolated. With 5-methoxy indoles this is not so. Using a lower temperature and glacial acetic acid as solvent,



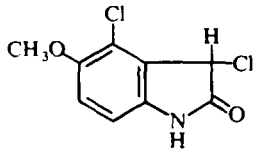
| No. | Infra-red spectra | | NMR spectra (DMSO) τ |
|---|---|---|---|
| | νNH | νC=O | |
| III | 3.120 $cm^{-1}$ broad band | 1.760 $cm^{-1}$ 1·720 $cm^{-1}$ | −1·4 (1H. s. NH); 2·8. 3·08 (2H. q. Ar; $J$ = 8·5 Hz); 6·12 (3H. s. $OCH_3$) |
| IV | 3.290 $cm^{-1}$ broad band | 1.760 $cm^{-1}$ 1.720 $cm^{-1}$ | 2·77, 3·31 (2H, q, Ar; $J$ = 8·0 Hz); 6·23 (3H. s. $OCH_3$); −1·13 (1H, s, NH) |
| V | 3.080 $cm^{-1}$ broad band | 1.710 $cm^{-1}$ 1.765 $cm^{-1}$ | −1·3 (1H. s. NH); 3·18 (2H. m. Ar); 6·2 (3H. s. $OCH_3$); 6·57 (2H. s. $CH_2$) |
| XII | 3.170 $cm^{-1}$ broad band | 1.770 $cm^{-1}$ 1.730 $cm^{-1}$ | 2·97. 3·23 (2H. q. Ar; $J$ = 8·5 Hz); 6·24 (3H. s. $OCH_3$); 6·33 (3H. s. $OCH_3$) |
| XIII | 3.200 $cm^{-1}$ | 1.760 $cm^{-1}$ | −0·80 (1H. s. NH); 3·02. 3·3 (2H. q. Ar; $J$ = 8·5 Hz); |
| | | 1.685 $cm^{-1}$ | 6·23 (3H. s. $OCH_3$); 4·53 (1H. s. $>C<^{H}_{Cl}$) |
| XV | 3.380 $cm^{-1}$ | 1.699 $cm^{-1}$ | −1·86 (1H. s. NH); 2·52. 2·74 (2H. q. Ar; $J$ = 8·5 Hz); 6·1 (3H. s. $OCH_3$) |
| XVI | | 1.728 $cm^{-1}$ | [a] 2·44. 3·02 (2H. q. Ar; $J$ = 8·5 Hz); 5·95 (3H. s. $OCH_3$) 6·02 (3H. s. $OCH_3$) |
| XVIII | 3.160 $cm^{-1}$ broad band | 1.720 $cm^{-1}$ 1.740 $cm^{-1}$ | −1·1 (1H. s. NH); 2·78 (1H. s. Ar); 4·36 (1H. s. $>C<^{H}_{Cl}$); 6·12 (3H. s. $OCH_3$) |
| XIX | | 1.750 $cm^{-1}$ broad band | [b] 2·38. 2·74 (2H. q. Ar: $J$ = 8·5 Hz) 5·98 (3H. s. $OCH_3$) |
| XX | 3.200 $cm^{-1}$ broad band | 1.760 $cm^{-1}$ | 2·84 (1H. s. Ar); 6·18 (3H. s. $OCH_3$) −1·67 (1H. s. NH) |
| XXI | 3.140 $cm^{-1}$ broad band | 1.713 $cm^{-1}$ | −0·83 (H. s. NH); 2·98 (1H. s. Ar); 6·12 (3H. s. $OCH_3$); 6·38 (2H. s. $>CH_2$) |
| XXII | 3.200 $cm^{-1}$ broad band | 1.760 $cm^{-1}$ broad band | −1·45 (1H. s. NH); 2·71 (1H. s. Ar); 6·2 (3H. s. $OCH_3$) |
| XXIV | | 1.640 $cm^{-1}$ broad band | 2·61. 2·66 (2H. q. Ar; $J$ = 3·0 Hz). 6·06 (1H. s. $OCH_3$) |

[a] NMR in $CDCl_3$
[b] NMR in Deutero DMF

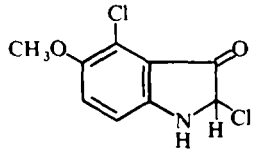
several intermediates have been isolated. In addition it has been possible to determine the role of water in these electrophilic substitutions.

The reaction of the indole ester (XI) with 2 equivs. of DCU in acetic acid gave an unstable ether soluble solid (compound Y) as bright yellow needles. which rapidly became white and powdery on exposure to the atmosphere. Indeed. after about 30 min.. the needles were transformed into an ether insoluble white solid. which could be recrystallised unchanged from acetic acid. Compound Y also gave the same white solid when recrystallised from acetic acid, m.p. 204–6°, analysing for $C_9H_7Cl_2NO_2$. From the mass spectrum $M^+$ 231 (9:6:1) the presence of two chlorine atoms was indicated. The NMR spectrum (Table) showed that one of these was at position 4. The additional singlet at 4·53 τ was consistent with either structure XIII or XIV.

Reduction with Zn/Cu couple gave the oxindole (V) and hence structure XIII was assigned to the substance. A "doublet" in the carbonyl stretching frequency region



XIII



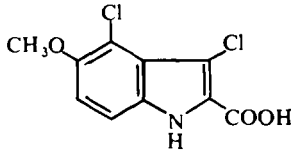
XIV

of the IR spectra of oxindoles has been observed previously[8, 9] and has been ascribed to Fermi resonance. This characteristic doublet was also observed (Table) in the IR spectra of V and XIII and is further conformation of the structural assignment.

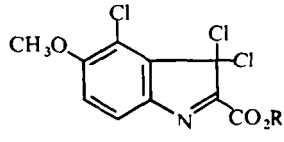
When the unstable yellow product (Y), was treated with water a vigorous evolution of $CO_2$ occurred and the trichlorooxindole (III) was formed.

The formation of III via further chlorination of XIII seemed attractive; a similar scheme having been proposed by Muchowski for the formation of 3,3,5-trichlorooxindole (II). Possible mechanisms for the formation of III and XIII are discussed later.

By reducing the concentration of DCU to 1 equivalent it was possible to isolate a second intermediate which was characterised by IR and NMR spectra (Table) as 3,4-dichloro-5-methoxyindole-2-carboxylic acid (XV). In this case the presence of water did not affect the product obtained, nor did further reduction of the concentration of DCU lead to the isolation of any new product, thus showing that the 3-, and 4-positions of 5-methoxyindole are equally susceptible to electrophilic attack.

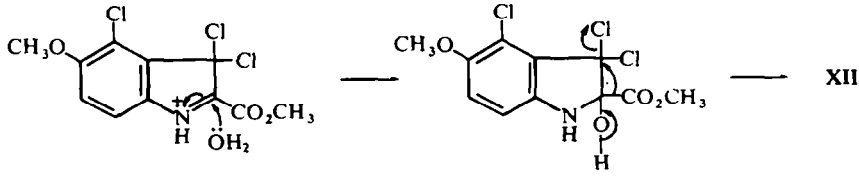


XV



XVI: R = $CH_3$
XVIa: R = H

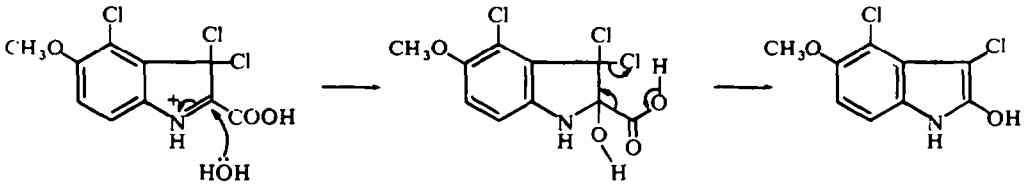
Treatment of compound Y with diazomethane yielded a small quantity of a stable yellow crystalline material, to which the structure XVI (R = $CH_3$) was assigned from IR and NMR spectra (Table ), mass spectrum and X-ray diffraction.[10] The same product was isolated (60% yield) when the indole ester XI was treated with DCU in acetic acid. That XVI was the intermediate in the formation of XII was proved by the easy transformation of the indolenine XVI to the oxindole XII by refluxing for a few minutes in aqueous acetic acid. The mechanism for the formation of the oxindole XII must involve a 1–2 ester shift,* of the type reported by Acheson.[11] and is rationalised as shown;



XII

* A review of intramolecular migrations of ester groups is being prepared by R. M. Acheson

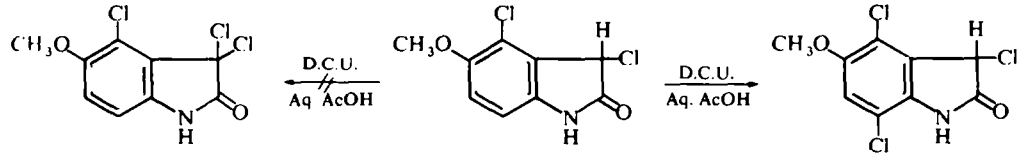
The formation of the 3,4-dichloro-oxindole (XIII) in acetic acid may be accounted for similarly. The structure of compound Y being by inference the indolenine XVIa (R = H) the enol XVII ketonises to give XIII.



XVIa XVII

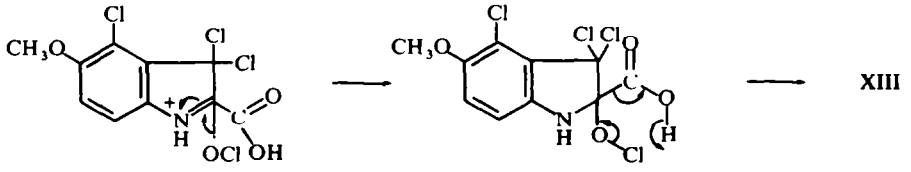
The water in this case presumably coming from the atmosphere. Direct attack by acetic acid seems unlikely, as this is not considered nucleophilic enough. The remaining problem was to find a mechanism that explained the formation of the trichlorooxindole III in aqueous acetic acid. Attempted chlorination of the dichloro-oxindole XIII with excess DCU in aqueous acetic acid at 0–5° led to the recovery of starting material. At 30° chlorination occurred in the aromatic ring to yield the 3.4,7-trichlorooxindole (XVIII) which was characterised by IR, NMR and mass spectra (Table). Halogenation of 3-alkyl indoles has been compared to acid catalysed halogenation of ketones.[12] The presence of a 3-chloro substituent here would hinder the formation of the enolic form and make this mechanism unlikely. In addition no 3,3-dichloro product could be obtained when the chlorination was repeated in acetic acid containing a few drops of sulphuric acid, a method successful with 3-alkyl oxindoles.

Therefore the formation of 3,3-dichlorooxindoles cannot be via the acid catalysed chlorination of a 3-chloro-3H-oxindole.




III XIII XVIII

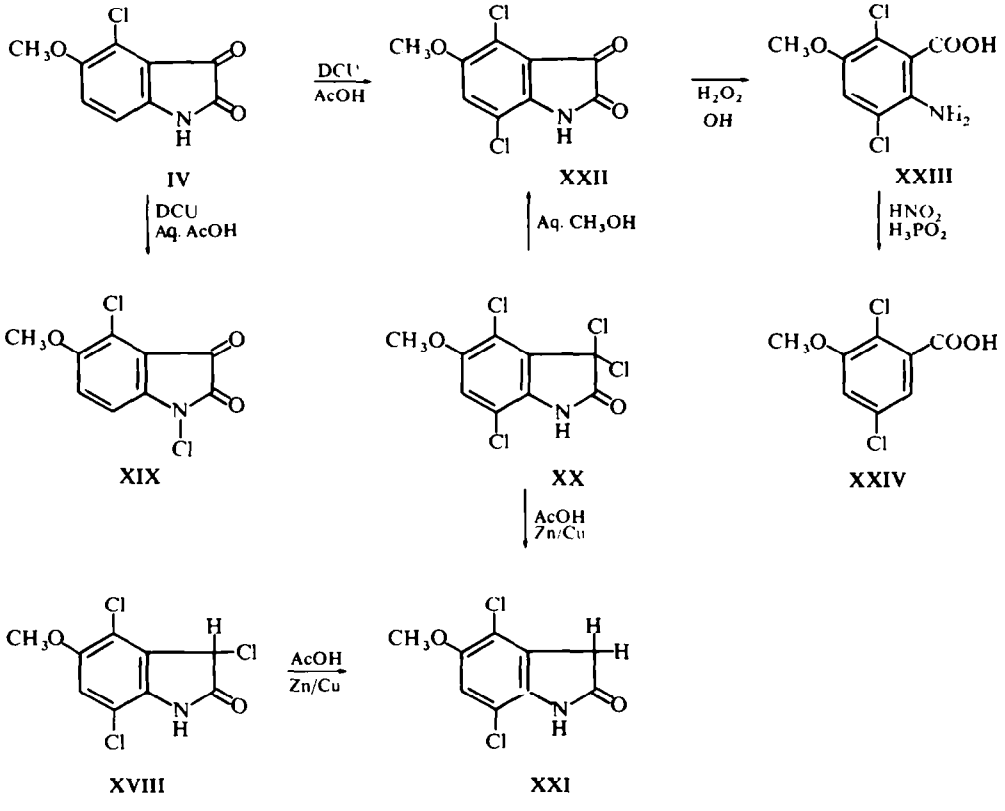
An alternative mechanism is suggested as shown;



XIII

The nucleophilic attack of hypochlorite ion occurs at a faster rate than the corresponding attack by water,[13] and is followed by decarboxylation and loss of HCl. Hypochlorous acid is known to be generated by oxidative chlorinating agents under aqueous conditions.

An unambiguous assignment of the position of the new chlorine atom in XVIII proved to be more difficult than expected. Chlorination of the isatin (IV) with DCU in aqueous acetic acid yielded the N-chloro derivative (XIX) which was fully characterised (Table), the loss of NH being shown by IR, NMR and Mass spectra. Chlorination of the trichlorooxindole (III) under the same conditions also gave the N-chloro derivative, however, chlorination by refluxing in acetic acid gave the desired tetrachlorooxindole (XX). This was reduced to the 4,7-dichlorooxindole (XXI) which was also obtained by the reduction of XVIII. The tetrachlorooxindole (XX) was hydrolysed to 4,7-dichloro-5-methoxyisatin (XXII) which was also obtained in low yield by the chlorination of 4-chloro-5-methoxyisatin (IV) in refluxing acetic acid. The isatin (XXII) was oxidatively degraded to 6-amino-2,5-dichloro-3-methoxybenzoic acid (XXIII) which was then deaminated to 2,5-dichloro-3-methoxybenzoic acid (XXIV).




IV XXII XXIII

XIX XX XXIV

XVIII XXI

The position of the extra chlorine atom was shown to be at C-7 of the aromatic ring, by the presence of meta-coupling in the NMR spectrum (Table) of compound XXIV.

To summarise, the formation of 3,3-dihalo-oxindoles from the treatment of indoles,[2,3] 1-alkylindoles[14] and indole-2-carboxylic acids[2,3] with sources of positive halogens under acidic conditions is believed to arise via the intermediate formation of a 3,3-dihaloindolenine followed by rapid nucleophilic attack of a hypohalite ion.

## EXPERIMENTAL

M.ps were taken on a Buchi m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 237 spectrometer. UV spectra were determined in MeOH with a Perkin–Elmer 137 UV spectrometer. Mass spectra were recorded on an A.E.I. MS12 instrument.

The NMR spectra were determined on a Varian A-60 spectrometer. The chemical shifts (τ) are in p.p.m. from TMS as internal standard. Spectra were obtained in trifluoracetic acid (TFA) deutero chloroform ($CDCl_3$) and in dimethylsulphoxide-$d_6$ (DMSO). Elemental analyses were determined in a Technicon Automatic Analyser.

*5-Methoxy-3.3.4-trichlorooxindole* (III). 5-Methoxyindole-2-carboxylic acid[15] (1·9 g) was suspended in 80% AcOH aq (25 ml) and treated dropwise with DCU (3·2 g) at a temperature below 5°. The acid slowly dissolved and a buff coloured solid precipitated. After 1 hr stirring the solid was filtered. washed with AcOH and recrystallised from $C_6H_6$ to give III. (1·3 g. 50%). m.p. 218–220°. (Found: C. 40·5; H. 2·2; N. 4·9; Cl. 39·9. $C_9H_6Cl_3NO_2$ requires C. 40·5; H. 2·3; N. 5·3; Cl. 40·0%).

*4-Chloro-5-methoxyisatin* (IV). The trichlorooxindole (III) (1·0 g) was refluxed for 18 hr in 50% aqueous MeOH (10·0 ml). On cooling maroon crystals separated; recrystallisation from AcOH gave IV. 0·69 g. 88%). m.p. 165–168°. as rods. (Found: C. 51·4; H. 3·3; N. 6·7. $C_9H_6ClNO_3$ requires: C. 51·1; H. 2·9; N. 6·6%).

*6-Amino-3-methoxy-2-chlorobenzoic acid* (VI). The isatin (IV) (4·0 g) was suspended in N NaOH (50·0 ml) and stirred for 18 hr to give a yellow solution. Hydrogen peroxide (100 vol. 10·0 ml) was added slowly over 30 min and the solution stirred for a further 2 hr. After treatment with decolourising charcoal the solution was acidified and the precipitate filtered and recrystallised from EtOH to give VI. (2·3 g. 60%) m.p. 202–204° as colourless needles. (Found: C. 47·5; H. 4·4; N. 7·2; Cl. 17·8. $C_8H_8ClNO_3$ requires: C. 47·7; H. 4·1; N. 7·0; Cl. 17·7%).

*2-Chloro-3-methoxybenzoic acid* (VII). The acid (VI) (0·6 g) was suspended in a mixture of 5N HCl (5·0 ml) and 50% hypophosphorous acid (7·0 ml). The cold (3°) suspension was treated with a solution of $NaNO_2$ (0·3 g) $H_2O$ (2·0 ml). The solution was stirred for 18 hr at 0°, the precipitate removed and recrystallised from EtOH to give VII. (0·35 g. 63%). m.p. 161–162° (Lit.,[7] 160·5°).

*3.4-Dichloro-3-carbomethoxy-5-methoxy oxindole* (XII). *Method A.* Methyl-5-methoxyindole-2-carboxylate (2·3 g) was suspended in 80% AcOH aq. (40·0 ml). DCU (2·8 ml) was added to the stirred mixture and the temperature rose to 25°. After a further 2·5 hr stirring, the precipitate was separated. and recrystallised from AcOH to give XII. (0·5 g 15%). m.p. 203–205° as micro-needles (Found: C. 45·6; H. 3·1; N. 5·1. $C_{11}H_9NO_4Cl_2$ requires: C. 45·5; H. 3·1; N. 4·8%); $\lambda_{max}$ (MeOH) 212. 255 nm. Log $\varepsilon_{max}$ 4·57; 4·28.
*Method B.* The dichloroindolenine (XVI) (0·6 g) was refluxed with 50% AcOH aq (20·0 ml) for 5 min. On cooling orange crystals separated. filtered and recrystallised from AcOH to give XII. (0·32 g. 55%). The m.p. and m.m.p. of this product with a sample of material prepared by route (A) were identical and the IR spectra superimposable.

*4-Chloro-5-methoxyoxindole* (V). XII (1·1 g) was refluxed in AcOH (25·0 ml) with Zn/Cu couple for 40 hr. The cooled solution was poured into $H_2O$. the precipitated solid filtered and recrystallised from 1 tOAc/petrol to give V. (0·7 g. 94%). m.p. 247–249° as colourless needles. (Found: C. 54·4; H. 4·1; N. 6·9. $C_9H_8ClNO_2$ requires C. 54·7; H. 4·1; N. 7·1%). V was also obtained by analogous reductions of III and XIII.

*3.4-Dichloro-3H-5-methoxy oxindole* (XIII). 5-Methoxyoxindole-2-carboxylic acid (3·8 g). suspended in AcOH (40·0 ml) at 8°. was treated dropwise with DCU (6·4 g). After 30 min stirring the precipitate was removed and recrystallised from AcOH to give XIII. (3·8 g. 80%). m.p. 204–206 as white needles. (Found: C. 47·0; H. 3·3; N. 6·0; Cl. 29·8. $C_9H_7Cl_2NO_2$ requires: C. 46·7; H. 3·1; N. 6·0; Cl. 30·1%). $\lambda_{max}$ (MeOH) 210 inf., 223. 262. 320 inf. nm log $\varepsilon_{max}$ 4·39. 4·43. 4·11. 3·45.

*2-Carboxy-3.4-dichloro-5-methoxyindole* (XV). The reaction was performed as above using 3·2 g of DCU. XV was obtained as pale yellow needles from AcOH (2·2 g. 43%). m.p. 266° dec. (Found: C. 46·3; H. 2·7; N. 5·1; Cl. 27·7. $C_{10}H_7Cl_2NO_3$ requires: C. 46·2; H. 2·7; N. 5·4; Cl. 27·3%) $\lambda_{max}$ (MeOH) 217 sh., 232. 290 sh., 326 inf. nm. log $\varepsilon_{max}$ 4·49. 4·57. 4·20. 4·26. 3·83.

*2-Carbomethoxy-5-methoxy-3.3.4-trichloroindolenine* (XVI). *Method A.* 5-Methoxyindole-2-carboxylic acid (0·95 g). suspended in AcOH (10·0 ml) at 10°. was treated dropwise with DCU (1·6 g). After 30 min stirring the precipitate was removed. washed with AcOH. sucked dry and rapidly dissolved in ether (20·0 ml). Diazomethane (0·7 M. 4·0 ml) in ether was added until evolution of gas ceased. The solution was kept at 5° for 24 hr. Fine yellow needles separated. recrystallisation from iso-propanol gave XVI. (0·2 g. 13%). m.p. 154–156°. (Found: C. 42·7; H. 3·0; N. 4·4; Cl. 34·0. $C_{11}H_8Cl_3NO_3$ requires C. 42·7; H. 2·9; N. 4·5; Cl. 34·4%). $\lambda_{max}$ 212. 263 nm. Log $\varepsilon_{max}$ 4·3. 4·2.

*Method B.* XI (4·1 g) was suspended in AcOH (30·0 ml) at 10° and treated with DCU (6·4 g). After 30 min the precipitate was filtered and recrystallised from iso-propanol to give XVI, (3·7 g, 60%). M.p. and m. m.p. with a sample from route (A) were identical.

3,4,7-*Trichloro*-3H-5-*methoxyoxindole* (XVIII). XIII, (2·4 g) in 80% AcOH aq (40 ml) at 30° was treated with DCU (1·2 ml) and stirred for 30 min. From the cold solution white crystals separated, recrystallisation from AcOH gave XVIII, (1·6 g, 58%), m.p. 220–222°. (Found: C, 41·1; H, 2·2; N, 5·5; Cl, 40·1. $C_9H_6Cl_3NO_2$ requires: C, 40·6; H, 2·3; N, 5·3; Cl, 39·3%).

5-*Methoxy*-3,3,4,7-*tetrachloro-oxindole* (XX). III (5·5 g) refluxed in AcOH (75 ml) with DCU (6·5 ml) for 30 min. The cold solution was poured into $H_2O$ and the yellow precipitate recrystallised from MeOH to give XX, (5·0 g, 80%), m.p. 214–215°. (Found: C, 35·6; H, 1·7; N, 4·7; Cl, 47·5. $C_9H_5Cl_4NO_2$ requires: C, 35·9; H, 1·7; N, 4·7; Cl, 47·2%).

4,7-*Dichloro*-5-*methoxy oxindole* (XXI). XVIII (2·5 g) was reduced with Zn/Cu in refluxing AcOH. On cooling crystals separated, which were recrystallised from iso-propanol to give XXI, (0·85 g, 42%), m.p. 232–234°. (Found: C, 46·8; H, 3·3; N, 5·9; Cl, 30·1. $C_9H_7Cl_2NO_2$ requires: C, 46·6; H, 3·1; N, 5·9; Cl, 30·6%), M + 232 (9:6:1). Reduction of XX gave the same material as shown by m.p. m.m.p. and superimposable IR and mass spectra.

4,7-*Dichloro*-5-*methoxyisatin* (XXII). XX (2·5 g) was refluxed for 12 hr in 50% aqueous MeOH. The MeOH was evaporated and dark red crystals separated, purified by washing with MeOH to give XXII, (1·3 g, 63%), m.p. 277–280° (Found: C, 43·5; H, 2·0; N, 5·7; Cl, 29·7. $C_9H_5Cl_2NO_3$ requires: C, 43·9; H, 2·0; N, 5·7; Cl, 28·8%), $M^+$ 245 (9:6:1). The isatin (1·0 g) in NaOH solution was treated with $H_2O_2$ as described previously for IV to give 6-*amino*-2,5-*dichloro*-3-*methoxybenzoic acid* (XXIII), (0·6 g, 63%), m.p. 181–182°. (Found: C, 40·4; H, 3·0; N, 5·9; Cl, 30·6%) $C_8H_7Cl_2NO_3$ requires: C, 40·7; H, 2·9; N, 5·9; Cl, 30·0%), $M^+$ 235 (9:6:1). Deamination of XXIII (0·6 g) with $H_3PO_2$ gave 2,5-*dichloro*-3-*methoxybenzoic acid* (XXIV) as colourless needles, (0·4 g, 71%), m.p. 173–174°. (Found: C, 43·1; H, 2·8; Cl, 32·7. $C_8H_6Cl_2O_3$ requires C, 43·5; H, 2·7; Cl, 32·1%), $M^+$ 220 (9:6:1).

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