

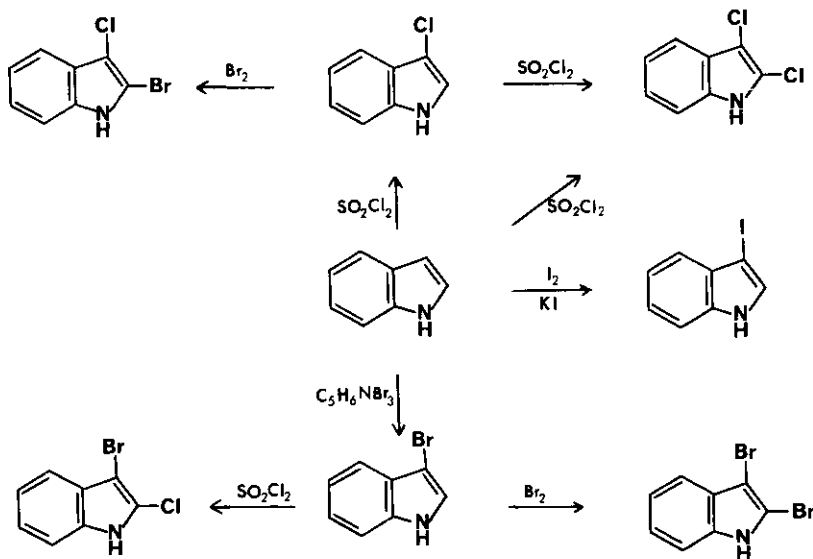
THE PREPARATION AND SPECTRAL CHARACTERIZATION OF 2-HALOINDOLES,
3-HALOINDOLES, AND 2,3-DIHALOINDOLES

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Abstract - The preparation and properties of a series of 2- and 3-haloindoles and 2,3-dihaloindoles are described, and the mechanism of halogenation of 3-halo substituted indoles is briefly discussed.

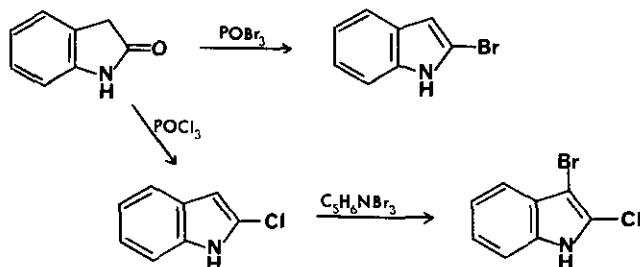
Halogenation in indole systems and the chemistry of the resulting haloindoles have been of interest for some time.¹ However, despite the amount of activity in this area, there is a noticeable lack of spectral data reported for the simple haloindoles. Recent discoveries of such compounds as natural constituents of marine organisms² further emphasizes the need for the establishment of spectral parameters, especially ¹³C nmr parameters, for reference purposes. Several years ago, in order to make structure assignments of tri- and tetrahalo substituted indoles isolated from a marine alga,³ we undertook the preparation and spectral characterization of a series of 2- and 3-halo- and 2,3-dihaloindoles.

3-Chloro-, 3-bromo-, and 3-iodoindole were prepared (Scheme I) by literature procedures with some modifications (see Experimental). These compounds are of very limited stability and cannot be stored for more than a few days without some decomposition occurring. 2-Chloro- and 2-bromoindole are less stable still. Powers⁴ reported the synthesis of the former compound with phosphorus oxychloride through the Vilsmeier salt. We have found that this method can be used for the synthesis of 2-bromoindole as well (Scheme II) if the reaction is carried out at low temperatures in the presence of an acid trap. Yields are poor in both syntheses.



Scheme I

The 2,3-dihaloindoles display greater stability if at least one of the halogens is chlorine. Chlorination of indole or 3-chloroindole with sulfuryl chloride produces 2,3-dichloroindole. Similarly, 3-bromo-2-chloroindole may be prepared by sulfuryl chloride treatment of 3-bromoindole (Scheme I). This reagent, first used by Mazzara and Borgo⁵ for indole chlorinations, affords good yields and clean reactions in these simple cases. An alternate route to 3-bromo-2-chloroindole, used for the verification of structure, is shown in Scheme II. The 2-position of 3-bromoindole and 3-chloroindole can be brominated, also in good yield, with elemental bromine (Scheme I).



Scheme II

The assignment of halogen substitution in the mixed halo compounds becomes a trivial task with ¹³C nmr, but would be most difficult without this spectroscopic tool. Table I contains the ¹³C assignments for the mono- and dihaloindoles prepared here in comparison with indole itself. The 3-carbon is the most upfield signal in the spectrum and is easily recognized. Substitution at this position by chlorine creates a small downfield shift (3.7 ppm), while substitution by bromine or iodine, as expected, leads to large upfield shifts (11.2 and 45.3 ppm respectively). On the other hand, chlorine at the 2-position leads to a small upfield shift of the 3-carbon (2.1 ppm), while a 2-bromo substituent creates a downfield shift of the same magnitude (2.1 ppm) for C-3. Observed δ -values for this carbon in the 2,3-disubstituted derivatives agree quite well with those predicted from the monosubstituted compounds.

Two other carbon signals are systematically affected by the position and nature of the halogen substituent in the pyrrole ring. With a 2-halo substituent, C-4 absorbs near δ 120 ppm. With a 3-chloro substituent, this carbon signal shifts to δ 118 ppm, with a 3-bromo substituent, to δ 119 ppm, and with a 3-iodo substituent, to δ 128 ppm. Similar shifts are observed for the 3a carbon which absorbs near δ 125 ppm with a 3-chloro group, near δ 127 ppm with a 3-bromo group, and at δ 129.5 ppm with a 3-iodo group.

The infrared spectra for the various isomers are very similar for the same substitution types, but subtle differences are noted if one does a careful comparison. One band which may have diagnostic value is a sharp, weak one which occurs at 650 cm⁻¹ when a 3-chloro group is present and at 630-635 cm⁻¹ when a 3-bromo (or 3-iodo) group is present.

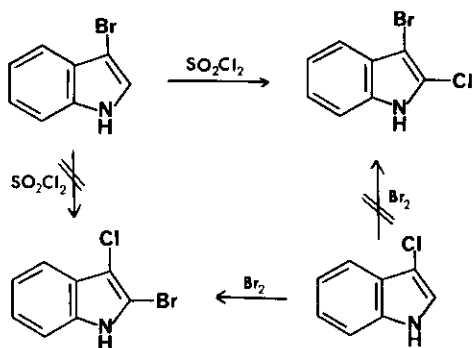
The mechanism of the halogenation of indoles at the 3-position is assumed to be a simple electrophilic substitution reaction. In the present work, when the 3-position is blocked, the incoming halogen goes to the 2-position. Several mechanisms may be envisioned for this process and these are shown in Scheme III.⁶ Jackson and coworkers⁷ have shown that attack at C-3 followed by rearrangement to the 2-position (route b) is the operative mechanism when Z is alkyl or acyl. If activating groups are present in the benzene ring, some direct attack at C-2 by the electrophile (route a) can also occur.⁸ We have not observed any products where the group initially present at the 3-position is transferred to the 2-position as would be expected for this rearrangement

Table I. ^{13}C NMR Spectra of Halogenated Indoles in CDCl_3

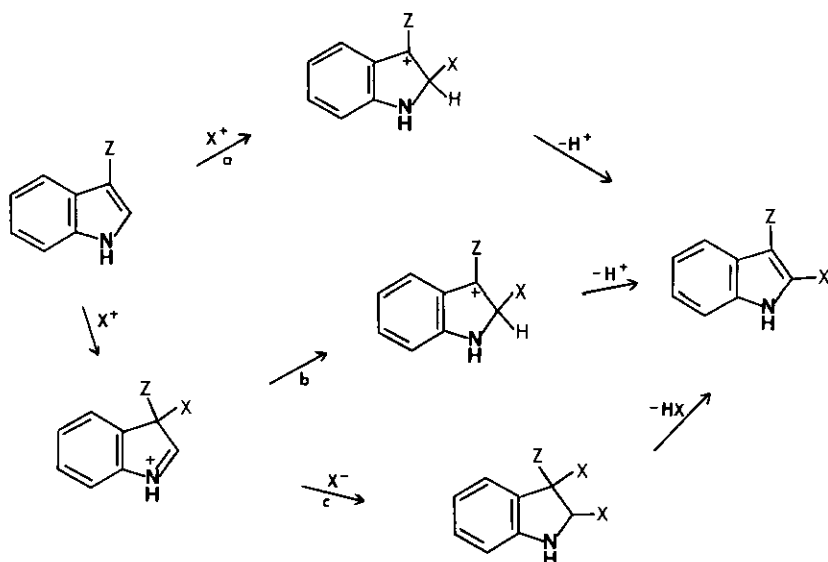
Compound/ Carbon No.	2	3	4	5	6	7	3a	7a
Indole	125.2	102.6	121.3	120.3	122.3	111.8	128.8	136.1
2-Chloroindole	123.2	100.5	119.7	120.4	122.0	110.3	127.9	134.8
3-Chloroindole	120.3*	106.3	118.1	120.7*	123.0	111.4	125.2	134.8
2,3-Dichloroindole	119.9	103.7	117.7	121.0	123.3	110.7	125.4	133.1
2-Bromoindole	108.6	104.7	119.5	120.3	122.1	110.2	128.6	136.3
3-Bromoindole	122.9*	91.4	118.9	120.5	123.2*	111.2	126.7	135.1
2,3-Dibromoindole	109.8	94.3	118.7	121.1	123.3	110.6	127.4	135.4
2-Bromo-3-chloroindole	107.1*	107.4*	117.7	120.9	123.3	110.7	125.6	134.8
3-Bromo-2-chloroindole	122.3	90.2	118.7	121.2	123.4	110.6	127.1	133.8
3-Iodoindole	120.8	57.3	128.3	120.8	123.0	111.2	129.5	135.4

* Assignments may be reversed.

mechanism. Thus, chlorination of 3-bromoindole gives 3-bromo-2-chloroindole exclusively and bromination of 3-chloroindole gives 2-bromo-3-chloroindole exclusively:



An addition-elimination sequence (route c) is also unlikely in view of the fact that HBr would have to be lost exclusively in one case and HCl exclusively in the other in order to explain the results. Direct attack of the electrophile at the 2-position (route a) remains as a viable mechanism for the halogenation.



Scheme III

The incoming electrophile can replace the group originally present at the 3-position. 2,3-Dichloroindole can be detected in the product mixture from the chlorination of 3-bromoindole when excess chlorinating reagent is used, and 3-chloroindole, rather than 2-chloro-3-iodoindole, is formed in good yield when 3-iodoindole is treated with sulfonyl chloride.

EXPERIMENTAL

Melting points were determined on a Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded in CS_2 on Perkin-Elmer Models 137 and 337 spectrophotometers. ^1H nmr spectra were recorded on a Perkin-Elmer R-24B spectrometer at 60 MHz. ^{13}C nmr spectra were obtained on JEOL-PFT-100 or Bruker SXP20-100 spectrometers. Brinkmann silica gel 60 (30-70 mesh) was used for

column chromatography and Brinkmann silica gel HF-254 + 366, Type 60, for tlc. All solvents were reagent grade.

3-Chloroindole.⁹

To a methanol solution of 1.00 g (8.5 mM) of indole was added in small portions 1.30 g (8.5 mM) of N-chlorosuccinimide with stirring and cooling so as to keep the temperature below 25°C. Ice water was added, and the mixture was extracted with ether. The ether layer was dried (MgSO₄) and evaporated to give 1.10 g (84%) of a greenish solid. Silica gel chromatography (20% benzene in hexane) afforded colorless crystals (80% recovery), mp 94-96°C (d) (lit.^{5,9} 91.5°C, 95-97°C); ir ν 3450, 3030, 1400, 1330, 1280, 1240, 1200, 1120, 1100, 1075, 1010, 1000, 780, 760, 735, 650, 570 cm⁻¹; ¹H nmr (CD₃COCD₃) δ 7.1-7.85 ppm.

Mazzara and Borgo⁵ incorrectly report this compound as 2-chloroindole.

3-Bromoindole.¹⁰

To a pyridine solution of 2.00 g (17 mM) of indole cooled in an ice bath was added dropwise and with stirring a pyridine solution of 6.90 g (18 mM) of pyridinium bromide perbromide (80% pure). After complete addition, ice water was added, and the mixture was extracted with ether. The ether extracts were washed successively with ice cold 6 N HCl, 5% NaHCO₃, and NaCl solutions. The ether layer was dried (MgSO₄) and carefully evaporated to give 2.72 g (82%) as pale pink crystals, mp 65°C (d) (lit.^{9,10} 65-67°C, 65-66°C). Further purification may be achieved by crystallization (hexane, keeping the temperature below 60°C) or chromatography on silica gel (20% CH₂Cl₂ in CCl₄). Ir ν 3450, 3030, 1400, 1325, 1280, 1240, 1190, 1120, 1095, 1070, 1010, 980, 785, 760, 735, 630, 570 cm⁻¹; ¹H nmr (CD₃COCD₃) δ 7.05-7.60 ppm. When impure, this compound is subject to spontaneous decomposition.

3-Iodoindole.¹¹

This compound was prepared by the method of Arnold and coworkers.¹¹ The crystals obtained were dried quickly by taking up in ether and drying over MgSO₄. Ir ν 3450, 3030, 1400, 1330, 1320, 1310, 1240, 1195, 1120, 1100, 1075, 1015, 965, 795, 760, 740, 630, 575 cm⁻¹.

2-Chloroindole.⁴

This compound was prepared by the method of Powers⁴ in 26% yield. Chromatography on silica gel (CCl₄) afforded colorless crystals, mp 71-73°C (d) (lit.⁴ 72-76°C); ir ν 3450, 3030, 1400, 1350, 1330, 1320, 1280, 1225, 1190, 1150, 1100, 1010, 940, 920, 775, 740, 730, 610, 595 cm⁻¹; ¹H nmr (CD₃COCD₃) δ 6.44 (1H, dd), 7.0-7.4 (4H) ppm.

2-Bromoindole.

A suspension of oxindole (0.66 g, 5 mM) in 0.73 g (6 mM) of N,N-dimethylaniline was cooled in an ice bath with stirring. To this was added 1.44 g (5 mM) of phosphorus oxybromide in one portion. A semisolid formed within 5 min, and the solution turned brown. Stirring stopped as the mixture thickened. After 72 h at 5°C, cold water was added to break the semisolid. Ether extraction was carried out, and the ether layer was washed successively with cold, dilute HCl, NaHCO₃, and NaCl solutions. After drying (MgSO₄) and removing the ether, 279 mg of a brown oil remained. Silica gel column chromatography (20% benzene in hexane) afforded 153 mg (15%) of 2-bromoindole, mp 82-84°C. Unlike other 2- and 3-halo- and 2,3-dihaloindoles, this compound did not decompose on melting. The melted sample resolidified and remelted sharply at 83°C. Ir ν 3450, 3030, 1400, 1350, 1330, 1320, 1275, 1230, 1190, 1150, 1095, 1010, 925, 775, 740, 730, 605, 570 cm⁻¹; ¹H nmr (CCl₄)₄ δ 7.05-7.3 (m), 7.4-8.0 (m) ppm. 2-Bromoindole decomposes rapidly on standing.

2,3-Dichloroindole.⁵

To an ether solution of 0.29 g (2.5 mM) of indole at ice temperature was added dropwise 0.4 ml (5 mM) of freshly distilled sulfonyl chloride. The mixture was stirred at 0°C for 5 h. It was then

washed successively with cold NaHCO_3 and NaCl solutions, dried (MgSO_4), and the ether removed to give 495 mg of crude product. Chromatography on silica gel (CHCl_3) afforded 406 mg (84%) of colorless plates, mp $95-97^\circ\text{C}$. Recrystallization from hexane gave needles, mp $102-103^\circ\text{C}$ (d) (lit.⁵ $103-104^\circ\text{C}$). $\text{Ir } \nu$ 3450, 3030, 1400, 1350, 1335, 1320, 1280, 1230, 1190, 1150, 1115, 1035, 1010, 925, 910, 740, 650, 615, 570 cm^{-1} ; ^1H nmr (CCl_4) δ 7.05-7.3 (m), 7.4-8.0 (m) ppm.

2,3-Dibromoindole.

To 392 mg (2mM) of 3-bromoindole dissolved in 10 ml of CH_2Cl_2 and cooled in ice was added dropwise 320 mg (2mM) of bromine¹² in CH_2Cl_2 . After complete addition, the mixture was washed with cold aqueous NaHCO_3 and saturated NaCl solutions and dried over MgSO_4 . Removal of the solvent gave a quantitative yield of beige plates, which began to turn green rapidly. Purification was achieved by recrystallization (hexane, keeping the temperature below 60°C), or by silica gel chromatography (20% CH_2Cl_2 in CCl_4). The yield of purified material was 76%, mp $81-83^\circ\text{C}$ (d); $\text{ir } \nu$ 3450, 3030, 1400, 1350, 1335, 1320, 1280, 1225, 1180, 1150, 1115, 1010, 995, 980, 925, 910, 900, 800, 740, 630, 605, 570 cm^{-1} ; ^1H nmr (CD_3COCD_3) δ 7.1-7.7 ppm.

2-Bromo-3-chloroindole.

To a CH_2Cl_2 solution of 305 mg (2 mM) of 3-chloroindole cooled in ice was added dropwise and with stirring 320 mg (2 mM) of bromine¹² in CH_2Cl_2 . The reaction mixture was processed as described for 2,3-dibromoindole to give pink crystals (550 mg). Recrystallization from hexane afforded 409 mg (88%) of colorless crystals, mp 93°C (d) (lit.⁵ 92°C). Purification may also be achieved with silica gel chromatography (20% CH_2Cl_2 in CCl_4). $\text{Ir } \nu$ 3450, 3030, 1400, 1350, 1335, 1320, 1280, 1230, 1185, 1150, 1115, 1020, 1010, 930, 905, 740, 650, 610, 570 cm^{-1} ; ^1H nmr (CD_3COCD_3) δ 7.1-7.8 ppm. Mazzara and Borgo⁵ incorrectly report this compound as the 2-chloro-3-bromo isomer.

3-Bromo-2-chloroindole.

A. From 3-Bromoindole. To 196 mg (1 mM) of 3-bromoindole dissolved in anhydrous ether at 0°C was added 80 μl (1 mM) of freshly distilled sulfonyl chloride. After stirring at 0°C for 1 h, the solution was washed with cold NaHCO_3 and NaCl solutions and dried (MgSO_4). Removal of the ether gave pink crystals. Chromatography on silica gel with 20% benzene in hexane afforded an 85% yield of colorless crystals, mp $99-100^\circ\text{C}$ (d); $\text{ir } \nu$ 3450, 3030, 1400, 1350, 1335, 1320, 1280, 1230, 1185, 1150, 1115, 1015, 1000, 990, 925, 915, 905, 820, 740, 635, 610, 570 cm^{-1} ; ^1H nmr (CD_3COCD_3) δ 7.1-7.7 ppm.

B. From 2-Chloroindole. 2-Chloroindole was brominated in the same fashion as that used in the preparation of 3-bromoindole. The product was identical to that obtained from the chlorination of 3-bromoindole.

Reaction of 3-Iodoindole with Sulfonyl Chloride.

To a solution of 0.5 g (2.2 mM) of 3-iodoindole in 25 ml of anhydrous ether containing 0.12 g of 2,6-dimethylphenol was added dropwise 372 μl (2.2 mM) of SO_2Cl_2 (freshly distilled) at 0°C . Stirring was continued for 1 h, then the reaction mixture was washed successively with aqueous NaOH and saturated NaCl solutions and the ether dried (MgSO_4) and evaporated to give a 95% yield of crude 3-chloroindole and 84% yield after chromatography. Very minor amounts of 2,3-dichloroindole could be detected in the ^{13}C nmr spectrum.

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