with those of an authentic sample. No other organic compounds were detectable by vpc.

Synthesis of N-(3-Chloropropyl)formanilide.—Sodium hydride (2.4 g, 0.1 mole) was added to 12.1 g (0.1 mole) of formanilide dissolved in dimethoxyethane. The salt which formed was added to 31.4 g (0.2 mole) of 1-bromo-3-chloropropane dissolved in 100 ml of dimethoxyethane, and the resulting mixture stirred for 18 hr at room temperature. The reaction mixture was poured into water, extracted with chloroform, and fractionated through a 40-cm spinning-band column. The product had bp 135° (10 mm). The nmr spectrum consisted of two triplets (two protons) at τ 6.09 and 6.53, a multiplet (two protons) at 8.02, a five-proton multiplet at 2.74, and a one-proton singlet at 1.67.

Synthesis of N,N'-Diformyl-N,N'-diphenyltrimethylenediamine.—Formanilide (100 g, 0.83 mole) was added dropwise to a suspension of 20 g of sodium hydride in dimethoxyethane over a period of 1 hr. To this was added 167 g (0.83 mole) of 1,3-dibromopropane, and the resulting mixture was stirred for 3 hr, poured into water, and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and evaporated. The product crystallized on cooling and was recrystallized from benzene–hexane giving crystals, mp 105–109°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.47; H, 6.54; N, 10.13.

Preparation of N,N-diphenyltrimethylenediamine from N,N'-Diformyl-N,N'-diphenyltrimethylenediamine.—A mixture of 2.4 g (0.0085 mole) of N,N'-diformyl-N,N'-diphenyltrimethylenediamine and 0.0085 mole of sodium hydride was refluxed for 2 hr in dimethoxyethane until gas evolution had stopped. The reaction mixture was poured into water and extracted with chloroform, the chloroform was washed with dilute hydrochloric acid, and the aqueous solution was basified and extracted with chloroform. The yield after distillation of the diamine was 1.5 g (79%). The product had an identical infrared spectrum and tlc R_f value as an authentic sample.[18]

Reaction of N-(3-Chloropropyl)formanilide with Sodium Hydride.—To 28 g (~0.1 mole) of N-(3-chloropropyl)formanilide dissolved in 200 ml of dimethoxyethane was added 2.4 g (0.1 mole) of sodium hydride. Gas was evolved. The reaction mixture was refluxed for 18 hr, poured into water, and extracted with chloroform. The chloroform was extracted with dilute hydrochloric acid, which was basified and extracted with chloroform. Vapor phase chromatography showed the presence of N-allylformanilide and N-(3-chloropropyl)formanilide in the neutral fraction. No other peaks were observed. In the basic fraction, only N-allyl aniline was identified. The original mixture was shown by vpc analysis to consist of 39% N-allylaniline, 30% N-allylformanilide, and 3% N-(3-chloropropyl)formanilide. No 1-phenyl-2-pyrrolidinone[19] was detected.

Synthesis of N-Benzylaniline.—To a solution of 6 g (0.05 mole) of formanilide in 100 ml of dimethoxyethane at 25° was added 1.2 g (0.05 mole) of sodium hydride, and the mixture was refluxed for 1 hr. Benzyl bromide (5.9 ml, 0.05 mole) was then added and the mixture refluxed for 18 hr. The reaction was poured into water and extracted with ether, which was dried over magnesium sulfate. The solution was concentrated with a rotary evaporator and the product was chromatographed on a column of activated alumina and recrystallized from methanol–water, giving white needles, mp 36–37°.

Acknowledgment.—The authors wish to thank the University of California at Los Angeles Research Committee for financial support.

(18) M. Scholtz, *Ber.*, **32**, 2253 (1899).
(19) W. L. Meyer and W. R. Vaughn, *J. Org. Chem.*, **22**, 1554 (1957).

Chloroindoles[1]

JAMES C. POWERS

Contribution No. 1966 from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

Received December 29, 1965

A systematic investigation of the reaction of simple indoles with chlorinating agents is described. Oxindoles react with phosphorus oxychloride to yield 2-chloroindoles, the first examples of unsubstituted 2-haloindoles. Both 2- and 3-chloroindoles are hydrolyzed to oxindoles, thus demonstrating that acidic hydrolysis is unsuitable for differentiating 2-halo- from 3-haloindoles. N-Chlorosuccimide reacted with 2-methylindole to yield 3-chloro-2-methylindole, and phosphorus pentachloride reacted to yield 3-dichlorophosphoryl-2-methylindole. Skatole reacted with chlorinating agents to give oxindolic products.

The bromination and iodination of simple indoles has been extensively studied.[2,3] These electrophilic substitution reactions preferentially occur at the β position of the indole ring. Blockage of this position allows reaction to take place either α or in the benzenoid system.[3] Because of this selectivity in the reactions of indole, it is not surprising that there are no authentic syntheses of unsubstituted 2-haloindoles.[4] In this paper, we wish to describe the first preparation of 2-chloroindoles, a systematic investigation of the reactions of simple indoles with chlorinating agents and solution of the old problem of hydrolysis of 2- and 3-haloindoles yielding the same product.

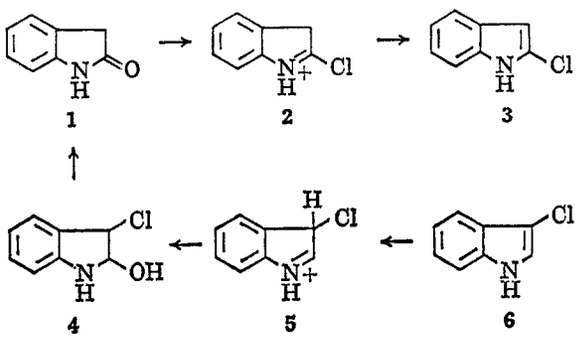
Indole.—Chlorination of indole with sulfuryl chloride produces a mixture of 2,3-dichloroindole and 3-chloroindole (mp 91.5).[5] A cleaner synthetic method for securing the monochloride involves the action of chlorine on 1-benzoylindole followed by alkaline hydrolysis.[6,7] Mazzara and Borgo[5] incorrectly assumed that the monochloride produced in the sulfuryl chloride reaction was substituted at the 2 position since oxindole was obtained from its acidic hydrolysis. This behavior is not unique and several other workers have observed that supposed 3-haloindoles yielded oxindole upon hydrolysis. In order to bury the problem of the structure and hydrolysis of haloindoles, we have prepared authentic 2- and 3-chlorindole and have compared their behavior upon hydrolysis.

The syntheses of 2-chloroindole utilized the Vils-

(1) Presented in part at the Western Regional Meeting of the American Chemical Society, Los Angeles, Calif., Nov 1965.
(2) T. S. Stevens in "The Chemistry of Carbon Compounds," Vol. IVA, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1957, p 85.
(3) K. Piers, C. Meimaroglou, R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, **41**, 2399 (1963); R. M. Acheson and R. W. Snaith, *Proc. Chem. Soc.*, 344 (1963); V. Franzen, *Chem. Ber.*, **87**, 1148 (1954); L. A. Yanovskaya, *Dokl. Akad. Nauk SSSR*, **71**, 693 (1950); *Chem. Abstr.*, **44**, 8354*h* (1950); A. P. Terent'ev, L. I. Belen'Kii, L. A. Yanovskaya, *Zh. Obshch. Khim.*, **24**, 1265 (1954); *Chem. Abstr.*, **49**, 1232*f* (1955); R. D. Arnold, W. M. Nutter, and W. L. Stepp, *J. Org. Chem.*, **24**, 117 (1959); J. Szmuszkovicz, *ibid.*, **29**, 178 (1964).
(4) Halogenation of 3-substituted indoles occasionally yields substituted 2-haloindoles; see, for example, Q. Mingoia, *Gazz. Chim. Ital.*, **60**, 509 (1930).
(5) G. Mazzara and A. Borgo, *ibid.*, **35**, 320, 563 (1905).
(6) R. Weissgerber, *Chem. Ber.*, **46**, 651 (1913).
(7) G. Pappaeardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958).

meyer reaction.[8,9] This involves generation of salts of imino chlorides (Vilsmeyer salts) by interaction of amides with phosphorus chlorides. The Vilsmeyer salt (2) derived from oxindole (1) is simply a protonated form of 2-chlorindole (3)[10] (Scheme I). Since the con-

SCHEME I



version of this salt (2) to 2-chloroindole (3) should be quite easy, this seemed to be a felicitous method for the synthesis of the desired compound. This conception proved to be correct and a new chloroindole (mp 72–76°) was obtained in low yield from the reaction of oxindole and phosphorus oxychloride followed by treatment with sodium bicarbonate. This chloroindole, shown later to be 2-chloroindole, was unstable both in solution and as a pure solid. An analytically pure sample was completely decomposed after standing for 3 days in a sealed vial. N-Benzyl-2-chloroindole, prepared in a similar fashion from N-benzyloxindole, proved to be considerably more stable than 2-chloroindole itself. The N-substituted product could be stored for considerable periods of time with only slight decomposition. Chlorination of indole with sulfuryl chloride produced 3-chloroindole with properties similar to those previously described.[6,7] No 2-chloroindole could be detected among the reaction products.

The structural assignment of 2-chloroindole (3) to the monochloride (m.p 72–76°) obtained from oxindole (1) was substantiated by its nmr spectrum. The spectra of 2- and 3-chloroindole were identical except for the position of the signal due to the hydrogen attached to the heterocyclic ring (see Table I). In 2-chloroindole this was a doublet (J = 2 cps) at τ 3.56. The spectrum of 3-chloroindole likewise contained a doublet (J = 2.5 cps) at τ 2.88. Previous investigations have shown that the signal due to a proton attached to the 3 position of indoles occurs at higher field than that due to the 2-proton.[11,12] As might be expected owing to slight deshielding by the adjacent chlorine atom, the chemical shifts of the 2- and 3-protons of these monochloroindoles occur at lower fields than the corresponding protons in unsubstituted indoles. The coupling between the indolic NH and the

(8) O. Bayer, Houben-Weyl, "Methoden der Organischen Chemie," Vol. 7/1, Georg Thieme Verlag, Stuttgart, 1954, pp 29–38.

(9) H. Eilingsfield, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(10) A. Baeyer [*Ber.*, **12**, 457 (1879); **15**, 786 (1882)] obtained 2,3-dichloroindole by the reaction of phosphorus pentachloride with oxindole. This probably proceeded by way of 2-chloroindole which was further chlorinated under his reaction conditions.

(11) L. A. Cohen, J. W. Daly, J. W. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960).

(12) R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *ibid.*, **85**, 1825 (1963).

TABLE I

NMR SPECTRA OF CHLOROINDOLES[a]

	CH₃	C-2 H	C-3 H
Indole[b]	...	3.32	3.62
3-Chloroindole	...	2.87	...
2-Chloroindole	...	...	3.56
1-Benzyl-2-chloroindole	...	...	3.4
2-Methylindole[b]	7.80	...	3.87
3-Chloro-2-methylindole	7.78	...	...
3-(Dichlorophosphoryl)-2-methylindole	7.62	...	...

[a] Chemical shifts are given as τ values using tetramethylsilane as an internal standard. Data were obtained with a Varian A-60 nmr spectrometer. [b] See ref 12.

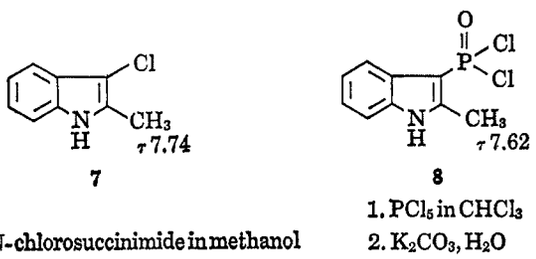
2-proton is 2.5 cps in 3-chloroindole (6) and only 2 cps between the indolic NH and the 3-proton in 2-chloroindole. This is further confirmation for the assigned structures since the coupling constant would be expected with an increasing number of bonds separating the two protons.

N-Benzyl-2-chloroindole was smoothly hydrolyzed by aqueous acid to N-benzyloxindole. This reaction probably proceeds by protonation at the 3 position[13] to produce an indolenenium salt (2, $CH_2C_6H_5$ instead of H) which reacts with water to create oxindole. Surprisingly, acidic hydrolysis of 3-chloroindole (6) likewise yielded oxindole (1).[14] This unusual reaction can be rationalized by assuming that initial 3-protonation produces the indolenium salt **5**, which could add water to give the carbinol amine **4**. Subsequent elimination of hydrogen chloride would then generate a 2-hydroxyindole, the tautomeric form of oxindole 1. Since both 2- and 3-chloroindoles are hydrolyzed to oxindoles, this method should no longer be used as a diagnostic tool in the structure determination of haloindoles.

2-Methylindole turned out to be quite sensitive to chlorination. Attempted chlorination with dilute chlorine or sulfuryl chloride solutions gave polymeric materials. Characterizable products were obtained only with N-chlorosuccinimide and phosphorus pentachloride (see Chart I).

CHART I

2-METHYLINDOLE CHLORINATION PRODUCTS



N-chlorosuccinimide in methanol

1. PCl_5 in $CHCl_3$
2. K_2CO_3, H_2O

Both chlorination products had nearly identical nmr spectra (see Table I). They differed from that of 2-methylindole only in the absence of the signal due to 3-proton of the indole ring. As expected, 3-chloro-2-methylindole (7) was stable to aqueous acidic methanol under conditions which hydrolyzed 3-chloroindole to oxindole. The presence of a methyl group at the 2 position precludes oxindole formation and hydrolysis thus did not occur. The dichloride **8** was probably formed by electrophilic attack of PCl_4^+ on the 2-

(13) R. L. Hinman and J. Lang, *ibid.*, **86**, 3796 (1964), and earlier papers.

(14) Weissgerber[6] reported the hydrolysis of 3-bromoindole to oxindole in dilute aqueous acid.

TABLE II

SPECTRAL CHARACTERISTICS OF CHLOROINDOLES AND OXINDOLES

Compd	Ultraviolet absorption, $\lambda_{max}^{CH_3OH}$, mμ (ε)	Infrared absorption, cm⁻¹ (Nujol) NH region	C=O region
Indole	272 (7900), 278 (6300), 287 (6300)		
3-Chloroindole[b]	219 (32,000), 275 (6300) 279 (6300) 286 (5000)		
2-Chloroindole	215 (50,000), 266 (8800), 277 (7600), 281 (7500), 288 (6200)	3550	
1-Benzyl-2-chloroindole	270 (9700), 280 (8800), 290 (6100)		
3-Chloro-2-methylindole	223 (28,000), 274 (8500), 281 (9300), 289 (8000)	3550	
3-Methyloxindole[a]	207 (27,400), 249 (8700)	3180	1710, 1675
3-Chloro-3-methyloxindole (9)	207 (26,000), 253 (5900)	3150	1720, 1680
3,5-Dichloro-3-methyloxindole (10)	214 (18,800), 258 (6900)	3250	1755, 1695
3-Methoxy-3-methyloxindole (11)	210 (22,000), 253 (6500)	3450	1760, 1720
3-(3-Methyl-2-indolyl)-3-methyloxindole (12)	228 (32,000), 252 infl (7900), 285 (8000), 292 (7400)	3250 3500	1690, 1650

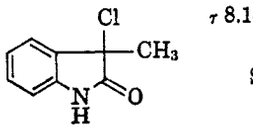
[a] See ref 23. [b] See ref 7.

methylindole followed by partial hydrolysis during the work-up procedure. The structural assignment was substantiated by infrared, ultraviolet, and mass spectral measurements. Attempted hydrolysis of the dichloride **8** with potassium carbonate in water yielded 2-methylindole as the only isolable product. This cleavage reaction is characteristic of the behavior of most 3-substituted indoles in aqueous acid or base.[15]

Skatole.—A rich harvest was reaped from the reactions of skatole with chlorinating agents (see Chart II). The compounds obtained varied with reaction temperature and solvent. Often the same products could not be isolated under seemingly identical reaction conditions.

CHART II

SKATOLE CHLORINATION PRODUCTS

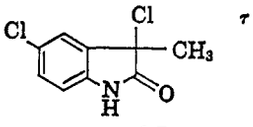


τ 8.14

SO_2Cl_2 in CH_2Cl_2 or PCl_5 in $CHCl_3$

τ −0.7

9

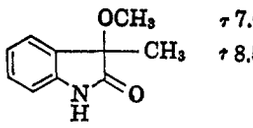


τ 8.15

Cl_2 in CCl_4

τ −0.7

10



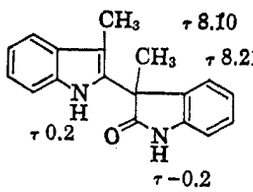
τ 7.04

τ 8.55

N-chlorosuccinimide in methanol[a]

τ −0.42

11



τ 8.10

τ 8.21

N-chlorosuccinimide in methanol

τ 0.2

τ −0.2

12

[a] R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, 29, 1206 (1964). These authors (and those in ref 23) reported the formation of oxindoles by reaction of N-bromosuccinimide with 3-substituted indoles.

(15) J. C. Powers, *Tetrahedron Letters*, 655 (1965).

The spectral properties of all of the above compounds were consistent with the assigned structures (see Table II for infrared and ultraviolet spectra). The dichloride **10** possessed an nmr spectrum than was consistent with either a 3,5-dichloro or a 3,6-dichloroxindole formulation (see Experimental Section). Although electrophilic substitutions on indoles can occur both at the 5 and the 6 position,[16,17] we tend to favor the 5-chloro structure on mechanistic grounds.[17,18] The dimeric compound **12** had ultraviolet and infrared absorptions assignable to both the oxindole and indole portion of the molecule. The structural assignment was substantiated by a mass spectral molecular weight (see Experimental Section for a discussion of the mass spectrum). This dimerization is similar to the formation of indole and skatole dimers under acidic conditions.[19] In these reactions a proton rather than a chloronium ion initiates the process. Bromination of 1-methylindole followed by a basic treatment also yields a dimeric product, 1,1 dimethyl-2,3-diindolyl.[20]

Further work on the chlorination of indoles was terminated when the author developed a severe skin rash from contact with these compounds.

Experimental Section

Microanalyses were performed by Dr. S. Nagy and Associates, Massachusetts Institute of Technology, Microanalytical Laboratory, and by Miss Heather King, University of California at Los Angeles. Melting points were determined on a Kofler hot stage microscope or with a Büchi melting point apparatus and are corrected. Ultraviolet spectra were measured on a Perkin-Elmer recording spectrophotometer, Model II; infrared spectra were measured on a Cary recording spectrophotometer, Model 21, with a sodium chloride prism, or on a Perkin-Elmer, Model 127, Infracord. The listings of infrared bands include those which are relevant to the structural argument and other medium and strong bands. A Varian Associates A-60 instrument was used for recording nmr spectra. Peak positions are given in τ values. The alumina used for chromatography was Alcoa F-20. Mass spectra were obtained on an AIE MS-9 mass spectrometer.

2-Chloroindole (6).—A solution of 1 g of oxindole and 1.5 g of phosphorus oxychloride in 40 ml. of chloroform was

(16) W. Borsch and H. Groth, *Ann.*, **549**, 238 (1941); W. J. Gaudion, W. Hook, and S. Plant, *J. Chem. Soc.*, 1631 (1947).

(17) W. E. Noland, L. R. Smith, and D. C. Johnson, *J. Org. Chem.*, **28**, 2262 (1963); W. E. Noland and K. R. Rush, *ibid.*, **31**, 70 (1966).

(18) Halogenation of 3-substituted indoles occasionally yields compounds containing a halogen atom at the 5 position; see, for example, A. Patchornik, W. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4748 (1958).

(19) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961); G. F. Smith and A. E. Walters, *J. Chem. Soc.*, 940 (1961).

(20) M. Kunori, *Nippon Kagaku Zasshi*, **83**, 836, 839 (1962); *Chem. Abstr.*, 1573c (1963).

heated at reflux for 3 hr. The reaction mixture was then stirred with a dilute sodium bicarbonate solution for 15 min and extracted with chloroform. After drying, the chloroform extracts were evaporated to yield a residue which was dissolved in benzene and passed through a column of alumina. The product, eluted in the first fractions, was recrystallized from hexane to yield 200 mg of white plates, mp 72–76°. This substance decomposed very readily to produce a yellow gum. The 2-chloroindole thus obtained had bands in the infrared (carbon tetrachloride) at 3550, 1595, and 1530 cm^{-1}, and gave a positive Ehrlich's test.

Anal. Calcd for C_8H_6ClN: C, 63.21; H, 3.98; N, 9.22. Found: C, 63.25; H, 4.08; N, 9.38.

1-Benzyloxindole.—Twenty grams of phosphorus pentachloride was added to a suspension of 15 g of 1-benzylisatin[21] in 100 ml of benzene. After stirring overnight, the mixture had become homogeneous and the color of isatin had disappeared. Evaporation of the benzene gave a residue which was filtered through a column of alumina. Elution with benzene followed by evaporation of the solvent gave an oil which crystallized on addition of a small amount of ethanol. The crystals were collected on a filter and washed with ethanol to yield 17 g (92%) of 1-benzyl-3,3-dichlorooxindole.[21]

Catalytic hydrogenation of 1-benzyl-3,3-dichlorooxindole afforded 1-benzyloxindole (81% yield).[22]

1-Benzyl-2-chloroindole (3, $C_6H_5CH_2$ instead of H).—A mixture of 1 g of 1-benzyloxindole, 1.7 g. of phosphorus oxychloride, and 30 ml of chloroform was heated at reflux for 17 hr. Treatment of the reaction mixture with dilute sodium bicarbonate for 5 min followed by extraction with chloroform and evaporation yielded a residue which was chromatographed on alumina. Elution with hexane gave an oil which produced 670 mg of crystals on crystallization from hexane. An analytical sample had mp 73.5–75.5°, and bands in the infrared (chloroform) at 1605, 1520, and 1500 cm^{-1}.

Anal. Calcd for $C_{15}H_{12}ClN$: C, 74.44; H, 5.00; N, 5.78. Found: C, 74.77; H, 5.04; N, 6.14.

Hydrolysis of 1-Benzyl-2-chloroindole.—A solution of 100 mg of 1-benzyl-2-chloroindole, concentrated hydrochloric acid (0.3 ml), water (0.3 ml), benzene (1 ml), and methanol (2 ml) was heated at reflux for 12 hr. The cooled reaction mixture was poured into water and extracted with methylene chloride to yield a crystalline product (50 mg). This was shown to be 1-benzyloxindole by comparison of its infrared spectrum and thin layer chromatographic R_f value with those of an authentic sample.

Hydrolysis of 3-Chloroindole.—A solution of 300 mg of 3-chloroindole, 10 ml of methanol, 0.5 ml of concentrated hydrochloric acid, and 5 ml of water was heated at reflux overnight. After dilution to 100 ml with water, the reaction mixture was extracted with chloroform. Desiccation and concentration of the chloroform extracts furnished a solid residue which was recrystallized to give 100 mg of oxindole. This was characterized by identical infrared solution spectra, melting point, mixture melting point, and R_f value (thin layer chromatography on silica gel) with those of an authentic sample.

3-Chloro-2-methylindole (7).—Solid N-chlorosuccinimide (2.7 g, 0.02 mole) was added to a stirred solution of 2.6 g (0.02 mole) of 2-methylindole in 100 ml. of methanol. The reaction mixture was stirred at room temperature for 7 min while its color turned green and then purple. The solvent was removed on an evaporator and the residual oil chromatographed on a column of 50 g of alumina. Elution with benzene yielded crystalline fractions. These were combined, dissolved in hot hexane, and filtered through Norit to produce a clear solution. Upon cooling 2.61 g (78%) of white plates with mp 97–98 dec were obtained. 3-Chloro-2-methylindole is extremely sensitive to light and heat. A sample is completely destroyed if allowed to remain in contact with a hot water bath for 1 hr. A pure sample had bands in the infrared at 3550 (indole NH) and 780 cm^{-1} (indole ring).

Anal. Calcd for C_9H_8ClN: C, 65.51; H, 4.89; N, 8.44. Found: C, 65.57; H, 4.96; N, 7.78.

3-(Dichlorophosphoryl)-2-methylindole (8).—A solution of 2 g of 2-methylindole in 15 ml of ether was added dropwise to a stirred solution of 2 g of phosphorus pentachloride in 25 ml of ether and 25 ml of chloroform. After standing at room temperature for 1 hr, the reaction mixture was poured into a potassium carbonate solution. The organic layer was separated, washed several times with a dilute sodium hydroxide solution, dried over magnesium sulfate, and evaporated. The residue solidified and was crystallized from chloroform–acetone to yield 400 mg of material with mp 204–207°. An analytical sample was obtained which had mp 210–214°; bands in the infrared (Nujol) at 3350 (indole NH), 1230 (P=O), 745, and 715 cm^{-1} (indole ring); $\lambda_{max}^{CCl_4}$ 257, 279, and 287 mμ (ε 14,500, 8000, and 6800, respectively).

The mass spectrum of **10** provided additional evidence for the assigned structure. Two molecular ion peaks *m/e* 247 and 249 corresponding to $C_9H_8Cl_2{}^{35}NOP$ and $C_9H_8Cl^{35}Cl^{37}NOP$ were observed in the spectrum. The major fragmentation pathway was loss of $POCl_2$ to give $C_9H_8N^+$ (*m/e* 130), the base peak in the spectrum. The other prominate fragment peaks were formed by loss of Cl from the molecular ion to give $C_9H_8ClNOP^+$ (*m/e* 212) followed by loss of HCl to give $C_9H_7NOP^+$ (*m/e* 176). Metastable peaks for both of these processes were observed.

Anal. Calcd for $C_9H_8Cl_2NOP$: C, 43.58; H, 3.25; N, 5.65. Found: C, 43.76; H, 3.31; N, 5.88.

3-Chloro-3-methyloxindole (9).—A solution of 4 g of skatole in 20 ml of methylene chloride was added dropwise to a stirred solution of 21 g of sulfuryl chloride in 60 ml of methylene chloride. The resulting reaction mixture was stirred at room temperature for 1 hr, poured into a potassium carbonate solution, and stirred for an additionl 15 min. Extraction with methylene chloride, desiccation of the organic extracts, and evaporation gave a solid residue. Recrystallization from benzene furnished 4.95 g. (90%) of material with mp 145–147.5°. The nmr spectrum consisted of a three-proton singlet at τ 8.14, a four-proton multiplet at 2.8, and a broad peak (one proton) at τ −0.7 which exchanged when D_2O was added.

Anal. Calcd for C_9H_8ClNO: C, 59.59; H, 4.44; Cl, 19.52. Found: C, 59.97, H. 4.65; Cl, 19.73.

Reaction of skatole with PCl_5 in chloroform at room temperature followed by a sodium carbonate work-up also produced a small amount of 3-chloro-3-methyloxindole.

3-Methoxy-3-methyloxindole (11).—A solution of 4 g (0.03 mole) of skatole and 8.7 g. (0.065 mole) of N-chlorosuccinimide in 100 ml of wet methanol was stirred for 5 min. at room temperature. Thin layer chromatographic investigation of the reaction mixture demonstrated the complete absence of skatole. Evaporation of the methanol furnished a slurry which was poured into water and then extracted with chloroform. Desiccation and evaporation of the chloroform extracts gave an oil, which could be crystallized from benzene–hexane to yield 2.4 g. (45%) of product with mp 120–125°. An analytical sample had mp 124–125°. The nmr spectrum consisted of a three-proton singlet at τ 8.55 (methyl), a three-proton singlet at 7.04 (methoxyl), a four-proton multiplet centered at 2.9 (aromatic hydrogens), and a broad peak at −0.42 (NH).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.85; H, 6.30.

The compound has previously been reported as a product from the reaction of 3-bromo-3-methyloxindole with methanol in the presence of sodium bicarbonate.[23] The melting point of product obtained by that method was 124–125°.

3,5-Dichloro-3-methyloxindole (10).—A solution of chlorine in carbon tetrachloride was added dropwise to a stirred solution of 4 g. (0.03 mole) of skatole in 25 ml of carbon tetrachloride at ice bath temperature. During the addition some tar formed along the sides of the flask. The reaction mixture was stirred for 0.5 hour and then chromatographed on alumina. Elution with a benzene–chloroform mixture gave a solid. Recrystallization of this from benzene gave 600 mg of white plates with mp 163.4–165°. The nmr spectrum of the dichloride in the aromatic region showed a pattern typical of the splitting observed in systems with three independently interacting protons and was consistent with either a 5-chloro or a 6-chlorooxindole formulation.

Anal. Calcd for $C_9H_7Cl_2NO$: C, 50.03; H, 3.27; Cl, 32.82. Found: C, 50.21: H, 3.38; Cl, 32.46.

3-(3-Methyl-2-indolyl)-3-methyloxindole (12).—A mixture of 5.2 g (0.04 mole) of skatole, 8.05 g (0.06 mole) of N-chlorosuccinimide, and 100 ml of methanol was stirred at room temperature for 1.5 hr. Evaporation of the methanol gave a solid residue. This was taken up in benzene and the solid succinimide was removed by filtration. The filtrate was evaporated to give an oil

(21) F. Troxler, F. Seeman, and A. Hofman, *Helv. Chim. Acta*, **42**, 2073 (1959).

(22) A. Hantzch, *Chem. Ber.*, **54**, 1221 (1921).

(23) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 2431 (1964). The spectral properties of a large number of oxindoles were reported in this paper.

which was chromatographed on 50 g of alumina. Elution with benzene yielded skatole. Further elution with $CHCl_3$ gave a white solid which was recrystallized from benzene to give 200 mg of white needles with mp 222–224°. An analytical sample was crystallized from benzene and had mp 224–225°. The nmr spectrum consisted of a singlet (three protons) at τ 8.02, a singlet (three protons) at 8.12, a multiplet (eight protons) at 2.9, and two broad singlets (one proton each) at 0.2 and −0.1.

The mass spectrum of **18** provided additional evidence for the dimeric nature of this compound. The peak for molecular ion appeared at *m/e* 276. The base peak in the spectrum (*m/e* 261) was formed by loss of CH_3. This then lost CO to give another fragment peak at *m/e* 233. Cleavage of the dimer at bond joining the two indolic rings yielded a $C_9H_8N^+$ fragment (*m/e* 130).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 9.93. Found: C, 78.28; H, 5.98; N, 9.98; Cl, less than 0.3.

Acknowledgement.—The author wishes to thank the University of California at Los Angeles Research Committee for financial support and the Public Health Service for a predoctorial fellowship (1962–1963) during whose tenure (at Massachusetts Institute of Technology) some of the initial experiments were performed. The A-60 nmr spectrometer and the MS-9 mass spectrometer used in this work were purchased with funds awarded to UCLA from the National Science Foundation.

Substituted Deuteroporphyrins. I. Reactions at the Periphery of the Porphyrin Ring[1]

WINSLOW S. CAUGHEY,[2a] JAMES O. ALBEN,[2b] WILFRED Y. FUJIMOTO,[2c] AND J. LYNDAL YORK

Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Received December 3, 1965

Variously substituted deuteroporphyrins IX have been obtained from protoporphyrin IX or its iron(III) chloride (protohemin) employing preparative methods which involve reactions of peripheral substituents or substitution directly on the porphyrin ring. Included were oxidation, addition, and displacement reactions of vinyl groups; in contrast to earlier reports no significant differences in the reactivities of the 2- and 4-vinyl groups were observed. Electrophilic substitution reactions (acylation, bromination, nitration) differed in the ring positions selected. Both acylations of deuterohemin and bromination of deuteroporphyrin IX dimethyl ester have been found to take place predominately at the 2 and 4 positions, whereas nitration of the ester in nitric acid–sulfuric acid occurred preferentially at the α and β positions. Selectivity between α and β or between 2 and 4 positions was not noted. It is suggested that relative to the 2,4 positions the *meso* positions are more susceptible to electrophilic attack in the protonated species than in either the neutral species or the hemin. Infrared studies of this series of compounds have permitted vibrational assignments for most of the peripheral ring substituents as well as more equivocal assignments for bands of the porphyrin ring as a whole.

The porphyrins found in hemeproteins can be described as derivatives of deuteroporphyrin IX (Figure 1): protoporphyrin IX with vinyl groups at the 2,4 positions; porphyrin c with thio ether linkages between protein and ethyl groups at the 2,4 positions; porphyrin a with long alkyl, vinyl, and formyl groups at positions 2, 4, and 8, respectively; chlorocruoroporphyrin with 2-formyl and 4-vinyl groups.[3,4] Reactions leading to differently substituted deuteroporphyrins IX have thus been useful for the preparation of compounds most suitable for the evaluation of effects of the differences in structure found among natural porphyrins[3,5–9] and also for considerations of the relative reactivities of positions on the porphyrin ring. Following an approach exploited so successfully by Hans Fischer,[4] we have prepared variously substituted deuteroporphyrins IX from the readily available hemin (protoporphyrin IX iron (III) chloride).

The reactions explored include: oxidations of vinyl groups to formyl and carboxyl groups; additions to vinyl groups to give ethyl, hydroxyethyl, and cyclopropyl groups; replacement of vinyl groups by hydrogen via the resorcinol melt procedure; electrophilic substitution reactions to give acyl, bromo, and nitro compounds. These studies have resulted in the preparation of new deuteroporphyrin IX derivatives, in observations of relative reactivities of ring positions, and in improved preparations and, frequently, more adequate characterizations of several known deuterioporphyrins. Infrared assignments for these, and other, porphyrins have also been considered.

Experimental Section

Melting points were determined on a hot stage (Nalge–Axelrod) apparatus and are corrected. Nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal standard; chemical shifts are reported as δ values. In $CDCl_3$, where chemical shifts are often,[10,11] but not

(1) Initial experiments carried out (by W.S.C.) at Monadnock Research Institute were supported in part by Contract No. SA-43-pH-1914, Cancer Chemotherapy National Service Center, National Cancer Institute National Institutes of Health; concluding experiments were supported by U. S. Public Health Service Grant No. HE-06079. This work was presented in part at the 135th, 138th, and 143rd National Meetings of the American Chemical Society, Boston, Mass., 1959, New York, N. Y., 1960, and Cincinnati, Ohio, 1963, respectively.

(2) (a) Lederle Medical Faculty Award Scholar; (b) U. S. Public Health Service Postdoctoral Research Fellow, 1959–1962; (c) Henry Strong Denison Scholar for 1964–1965.

(3) J. E. Falk, "Porphyrins and Metalloporphyrins," Elsevier Publishing Co., Amsterdam, Holland, 1964.

(4) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 2, 1 Halfe, Akademische Verlagsgesellschafts M.B.H., Leipzig, Austria, 1937: (a) p 416; (b) p 304; (c) p 401; (d) p 447; (e) p 407; (f) p 394; (g) p 612.

(5) W. S. Caughey, R. M. Deal, B. D. McLees, and J. O. Alben, *J. Am. Chem. Soc.*, **84**, 1735 (1962).

(6) W. S. Caughey, J. O. Alben, and C. A. Beaudreau, "Oxidases and Related Redox Systems," T. E. King, H. S. Mason, and M. Morrison, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, p 97.

(7) A. J. Bearden, T. H. Moss, W. S. Caughey, and C. A. Beaudreau, *Proc. Natl. Acad. Sci. U. S.*, **53**, 1246 (1965).

(8) W. S. Caughey and W. S. Koski, *Biochemistry*, **1**, 923 (1962).

(9) R. F. Labbe, N. Hubbard, and W. S. Caughey, *ibid.*, **2**, 372 (1963).

(10) J. L. York and W. S. Caughey, Abstracts of Papers, 143rd National Meeting, American Chemical Society, Cincinnati, Ohio, Jan. 1963, p 31A.

(11) R. J. Abraham, P. A. Burbidge, A. H. Jackson, and G. W. Kenner, *Proc. Chem. Soc.*, 134 (1963).