J. Org. Chem. 1981, 46, 2054–2059

ethyl)phencyclidine (**19**) in 90% by adding it to LAH in refluxing ether.

1-[1-(4-Methylphenyl)cyclohexyl]piperidine (35). 4-Methylphencyclidine was synthesized as described:[1] bp 120–130 °C (0.1 mm); mp 65–67 °C [lit.[1] mp 66–67 °C]; ^{1}H NMR ($CDCl_3$) δ 1.1–1.7 (m, 8), 1.8–2.1 (m, 4), 2.1–2.4 (m, 4), 2.22 (s, 3), 7.30 (s, 4); ^{13}C NMR ($CDCl_3$) δ 137.1 (s), 135.3 (s), 128.1 (d), 127.2 (d), 60.7 (s), 46.5 (t), 33.8 (t), 27.2 (t), 26.5 (t), 22.5 (t), 20.9 (q).

Acknowledgment. We wish to thank the National Institutes of Health Biomedical Science Support Program (Grant No. 5-55511-318) and the National Institutes of Health (Grant No. DA 02037) for support of this work.

Registry No. **1**, 77-10-1; **2**, 60658-01-7; **3**, 70227-29-1; **5**, 72242-00-3; **8**, 76916-10-4; **9**, 76916-11-5; **10**, 76916-12-6; **11**, 2201-33-4; **12**, 76916-13-7; **13**, 76916-14-8; **15**, 76916-15-9; **16**, 66568-87-4; **17**, 76916-16-0; **18**, 76916-17-1; **19**, 76916-18-2; **20**, 76916-19-3; **21**, 76916-20-6; **22**, 76916-21-7; **23**, 76916-22-8; **24**, 76916-23-9; **26**, 76916-24-0; **27**, 76916-25-1; **28**, 76916-26-2; **30**, 76916-27-3; **32**, 76916-28-4; **33**, 76916-29-5; **34**, 76916-30-8; **35**, 3883-17-8; 4-bromo-*N*,*N*-dimethylaniline, 586-77-6; phenyl isothiocyanate, 103-72-0; *p*-dibromobenzene, 106-37-6; 1-piperidyl-1-cyanocyclohexane, 3867-15-0; potassium phthalimide, 1074-82-4.

Chlorination of 2-Methyl- and 2-Phenylindole with NaOCl. Formation of Intermediates and Their Reactions with Alkaline Methanol[1]

Michael De Rosa,* Lante Carbognani,[2] and Ayheza Febres

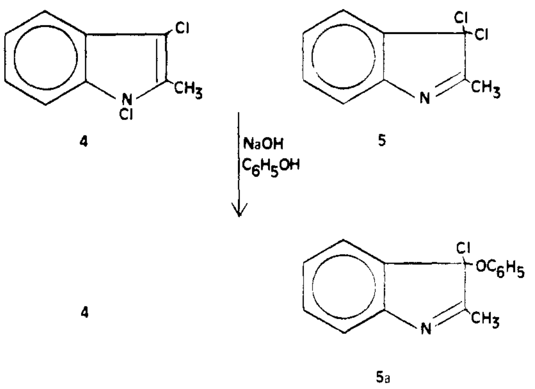
Departamento de Química, Universidad Simón Bolívar, Caracas, Venezuela 1080-A

Received November 21, 1980

Chlorination of 2-methylindole (**1**) in carbon tetrachloride with excess sodium hypochlorite gave a 2:1 mixture of *N*,3-dichloro-2-methylindole (**4**) and 3,3-dichloro-2-methyl-3*H*-indole (**5**) in a total yield of 76–92%. *N*-Chloro-2-methylindole (**2**) was detected when the chlorination was carried out with an indole to NaOCl ratio of 10:1. Sodium hypochlorite was found to promote the rearrangement of *N*-chloroindoles **2** and **4**. The chlorination of 2-phenylindole (**6**) gave a mixture of *N*,3-dichloro-2-phenylindole (**8**) and 3,3-dichloro-2-phenyl-3*H*-indole (**9**) in a total yield of 81–92%. The rearrangement of **8** to **9** was detected by IR and UV. This occurred in the presence or absence of NaOCl. Reactions of the dichloro intermediates with alkaline methanol gave a number of products. It is proposed that the *N*,3-dichloroindoles rearranged to their respective 3*H*-indoles in alkaline methanol and the products were formed by nucleophilic attack on either carbon (C-3) or chlorine of the 3*H*-indole.

Recently we reported the formation of *N*-chloroindole and its subsequent rearrangement in alcohols to 3-chloroindole.[3] The intermediacy of 3-chloro-3*H*-indole was also shown. Studies on the chlorination[4] of 2,3-disubstituted indoles have detected only the formation of 3-chloro-3*H*-indoles.[5-15] The chlorination of 2-methyl- and 3-methylindole with a number of chlorinating agents has been studied and the products depended on the chlorination medium.[16] It was of interest to determine the effect of substitutents on the nature and stability of the initially formed chlorination products. To this end the chlorination of 2-methyl- and 2-phenylindole with sodium hypochlorite was studied, and the reaction of the final intermediates with alkaline methanol was examined.

Scheme I



---

[1] Presented in part at the 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 1979, Abstract no. 183.

[2] From the Tesis Especial de Grado of L. Carbognani, Universidad Simón Bolívar, 1977.

[3] (a) M. De Rosa and J. L. Triana Alonso, *J. Org. Chem.*, **43**, 2639 (1978); (b) M. De Rosa, *J. Chem. Soc., Chem. Commun.*, 482 (1975).

[4] For a review on the chlorination of indoles and its derivatives see: J. C. Powers in "Indoles", Part II, W. J. Houlihan, Ed., Wiley-Interscience, New York, 1972, pp 137–39 and 155–59.

[5] For reviews on the reactions of 3-halo-3*H*-indoles see: M. Ikeda and Y. Tamura, *J. Synth. Org. Chem. Jpn.*, **37**, 568 (1979); M. Ikeda and Y. Tamura, *Heterocycles*, 14, 867 (1980).

[6] P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972).

[7] (a) R. J. Owellen, *J. Org. Chem.*, **39**, 69 (1974); (b) R. J. Owellen and C. A. Hartke, *ibid.*, 41, 102 (1976).

[8] A. Walser, J. F. Blount, and R. I. Fryer, *J. Org. Chem.*, **38**, 3077 (1973).

[9] Y. Tamura, M. W. Chun, H. Nishida, and M. Ikeda, *Heterocycles*, 8, 313 (1977).

[10] T. Hino, M. Endo, M. Tonozuka, Y. Hashimoto, and M. Nakagawa, *Chem. Pharm. Bull.*, **25**, 2350 (1977).

[11] F. M. Hershenson, K. A. Prodan, R. L. Kochman, J. L. Bloss, and C. R. Mackerer, *J. Med. Chem.*, **20**, 1448 (1977).

[12] M. E. Kuehne and R. Hafter, *J. Org. Chem.*, **43**, 3702 (1978).

[13] (a) Y. Tamura, M. W. Chun, H. Nishida, S. Kwon, and M. Ikeda, *Chem. Pharm. Bull.*, **26**, 2866 (1978); (b) Y. Tamura, M. W. Chun, K. Ohno, S. Kwon, and M. Ikeda, *ibid.*, **26**, 2874 (1978).

[14] G. I. Dmitrienko, E. A. Gross, and S. F. Vice, *Can. J. Chem.*, **58**, 808 (1980).

[15] For references to 3-chloro-3*H*-indole derivatives of indole alkaloids see ref 5 and 25.

[16] J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).

0022-3263/81/1946-2054$01.25/0

Formation and Detection of Intermediates. Chlorination of solutions of 2-methylindole (1) in carbon tetrachloride, methylene chloride, *n*-hexane, or benzene with NaOCl gave a 2:1 mixture of *N*,3-dichloro-2-methylindole (4) and 3,3-dichloro-2-methyl-3*H*-indole (5). Iodometric analysis indicated that their total yield was 76–92%. The ^{1}H NMR spectrum of the reaction mixture in carbon tetrachloride showed the presence of two methyl groups at 2.48 and 2.45 ppm in a ratio of 2:1, respectively, and the complete absence of C-3H. The IR spectrum of an *n*-hexane solution of this mixture showed the complete disappearance of the NH stretching frequency and the presence of a band at 1600 cm^{-1} characteristic of the imino group in 3*H*-indoles.[5,14,17] Chlorination of 3-chloro-2-methylindole (3) under the same conditions as 1 gave an identical mixture. Analogous intermediates have been reported to oxidize iodide ion.[3,6,10]

It was not possible to distinguish unambiguously between 4 and 5 by either ^{1}H or ^{13}C NMR spectroscopy.[18] Nucleophiles have been reported to attack 3-chloro-[9] and 3,3-dichloro-3*H*-indoles;[19] indoles, however, generally do not undergo nucleophilic substitution.[20] This difference in reactivity was used to differentiate between 4 and 5 and thus determine their relative yields. A carbon tetrachloride solution containing 4 and 5 was vigorously stirred with an aqueous solution of phenol and NaOH for 24 h at room temperature. The ^{1}H NMR spectrum of the reaction products showed the partial incorporation of phenoxide ion and two methyl singlets at 2.48 and 2.38 ppm in a ratio of 1.6:1, respectively. When the reaction was run for 48 h this ratio changed to 1.25:1.

The peak at 2.45 ppm, which disappeared during the reaction with phenoxide, was assigned to the methyl group of 3,3-dichloro-2-methyl-3*H*-indole (5). The increase in the relative yield of α-chloro ether (5a) with time indicated that another process was also taking place. We have reported the rearrangement of *N*-chloroindole to 3-chloro-3*H*-indole[3a] and the rearrangement of *N*,3-dichloro-2-phenylindole to the 3*H*-indole was also observed in this study (Figure 2). An analogous reaction has been reported for *N*-bromoindoles.[10] A similar rearrangement during the reaction with phenoxide ion would lead to the observed increase in the relative proportion of 5a (Scheme I).

The chlorination of 1 in carbon tetrachloride with a fivefold excess of NaOCl was followed by ^{1}H NMR. A new peak was observed at 2.25 ppm which subsequently disappeared. This indicated that at least one other intermediate preceded the formation of 4 and 5. The position of this new peak was identical with that of the methyl group of 3-chloro-2-methylindole (3). Chlorination of 3 gave the same mixture of 4 and 5 as did 1. These results indicated strongly that 3-chloro-2-methylindole (3) was formed as an intermediate during the chlorination of 1.

The chlorination of 1 in carbon tetrachloride was studied using a ratio of indole to NaOCl of 10:1. The sodium hypochlorite was completely consumed in 40–50 min (aqueous layer gave a negative KI test) and iodometric analysis of the organic phase indicated an 85–100% yield of one or more species able to oxidize iodide ion. The ^{1}H NMR spectrum of the reaction mixture showed no trace of the dichloro species 4 and 5. There were two methyl signals at 2.30 and 2.25 ppm in a ratio of ca. 9:1, respectively. These peaks had been previously assigned to 1 and 3, respectively. Neither indole 1 or 3 can oxidize iodide ion; therefore, the peak which appeared at 2.25 ppm could not be 3-chloro-2-methylindole (3). Another intermediate was formed whose methyl group appeared at the same position as that of 3 and oxidized iodide ion. Iodometric analysis indicated that it rearranged ca. 30% during the period (2–4 min) the mixture was in the NMR probe. This new species appeared to rearrange to 3 as no change was noted in the ^{1}H NMR spectrum. It is proposed that this product was *N*-chloro-2-methylindole (2).

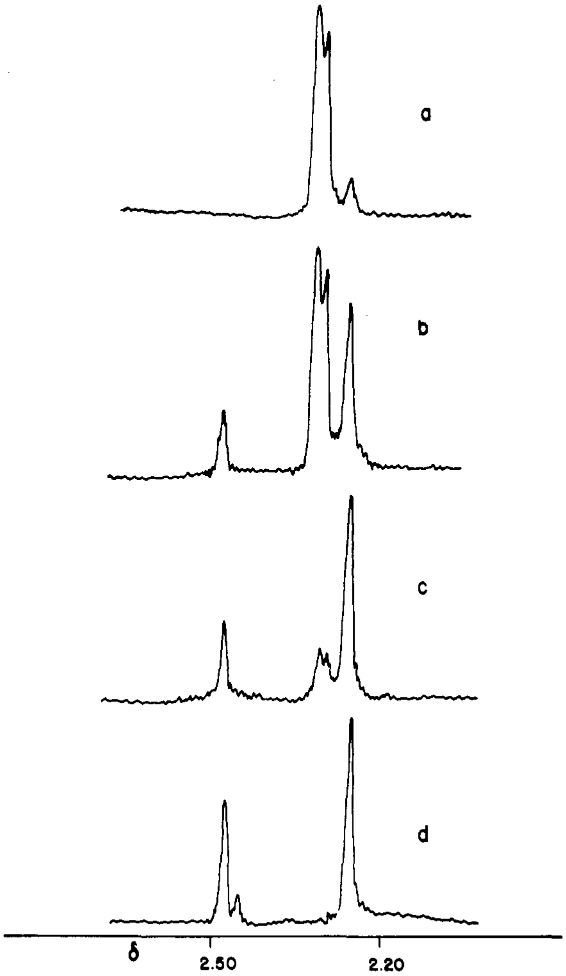


Figure 1. Influence of sodium hypochlorite concentration on chlorination of 2-methylindole (1): 60-MHz ^{1}H NMR, 100-Hz sweep width; 12-h contact time; ratio of 2-methylindole (1) to sodium hypochlorite (a) 10:1, (b) 2:1, (c) 1:1, (d) 1:2.

The chlorination of indole with excess sodium hypochlorite leads only to *N*-chloroindole.[3] This can be contrasted with the results in this study where the *N*-chloro derivative of 1 reacted further in the presence of excess sodium hypochlorite. It can be seen that if 2 was not affected by excess sodium hypochlorite it should have been observed just as readily when the ratio of 1 to NaOCl was 1:5 as when it was 10:1. The effect of the relative concentration of NaOCl can be seen in Figure 1.

No dichloro species were observed when the ratio of indole to NaOCl was 10:1. As the proportion of NaOCl increased, *N*,3-dichloro-2-methylindole (4) was detected. The formation of both 3,3-dichloro-2-methyl-3*H*-indole (5)

---

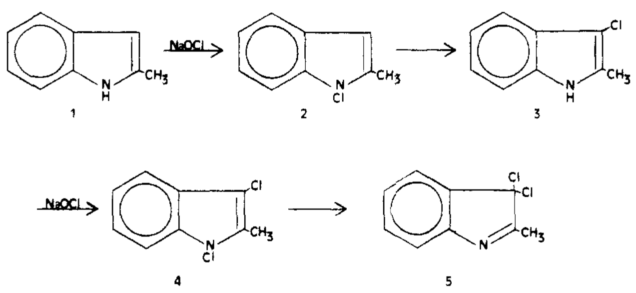
(17) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2188 (1951), and references therein.

(18) The ^{13}C NMR spectrum of the mixture of 4 and 5 presented two methyl signals at 10.26 and 13.35 ppm. In comparison the methyl groups of 2-methylindole (1) and 3-chloro-2-methylindole (3) appeared at 13.05 and 10.98 ppm, respectively. A steric interaction was present and it was not possible to unambiguously assign the signals in the ^{13}C NMR of the mixture. (E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy. Methods and Applications in Organic Chemistry", 2nd ed., Verlag Chemie, New York, 1978, pp 74–75).

(19) G. M. Brooke, R. D. Chambers, W. K. R. Musgrave, R. A. Storey, and J. Yeadon, *J. Chem. Soc., Perkin Trans. 1*, 162 (1976).

(20) For an example of this type of reaction see M. M. Cooper, G. J. Hignett, R. F. Newton, J. A. Joule, M. Harris, and J. D. Hinchley, *J. Chem. Soc., Chem. Commun.*, 432 (1977).

Scheme II



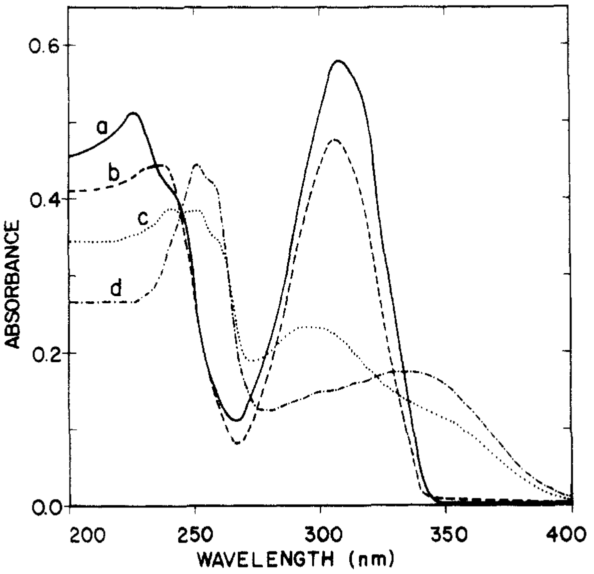


Figure 2. Chlorination of 2-phenylindole (6) with excess sodium hypochlorite: (a) start; (b) 6.5 h (8%); (c) 55 h (84%); (d) 220 h (85%).

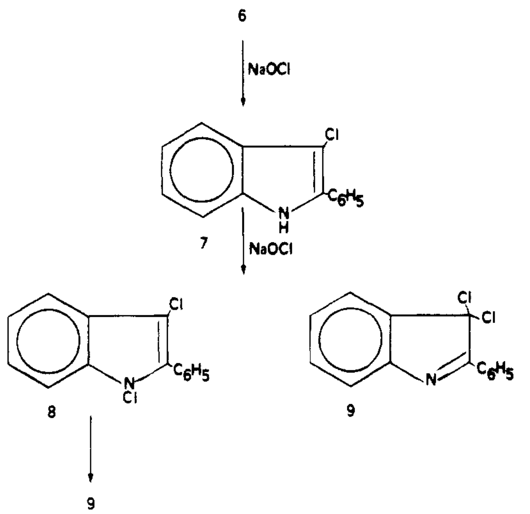
and 4 was observed when the ratio increased to 1:2. It was also observed that 5 only began to form at higher concentrations of NaOCl. This would seem to indicate that *N*-chloroindole 4 was also sensitive to the concentration of NaOCl. Further evidence for this effect was the change in the ratio of 4 and 5 from 2:1 to 1.2:1 which occurred when a tenfold excess of NaOCl was used.

The following appeared to have no major effect on the stability of either 2 or mixtures of 4 and 5: (a) the lot number or salts[21] present in the calcium hypochlorite used to make the solutions of NaOCl; (b) increase in the carbonate concentration in the aqueous solution; (c) changes in pH of 1–2 units. Sodium hypochlorite appeared to promote the rearrangement of *N*-chloroindoles 2 and 4. Its role in this process is unclear.

The results of the various studies are summarized in Scheme II.

The reaction of 2-phenylindole (**6**) in CH_2Cl_2 with excess sodium hypochlorite resulted in an 81–92% yield of a mixture of *N*,3-dichloro-2-phenylindole (**8**) and 3,3-dichloro-2-phenyl-3*H*-indole (**9**). Identical mixtures were obtained, starting with either **6** or 3-chloro-2-phenylindole (**7**). The IR spectrum of the CH_2Cl_2 solution indicated the presence of a 3*H*-indole (C=N at 1540 cm^{-1}).[17] Changes were observed in the IR and UV spectra of the mixture even after no NH was detectable by IR spectroscopy. In the IR spectrum the peak at 1540 cm^{-1} (C=N) increased and in the UV there was a bathochromic shift of the bands.

Scheme III



These changes occurred both in contact with and in the absence of sodium hypochlorite. Little or no change was observed in the total yield of **8** and **9**. This process was then independent of any species present in the aqueous solution.

Figure 2 illustrates the changes that occurred in the UV during the chlorination of **6** with excess sodium hypochlorite. Spectra 3c and 3d show the observed changes after all of indole **6** had been consumed. Similar changes were noted in the UV of solutions of **8** and **9** in the absence of NaOCl. Iodometric analysis indicated that under these conditions the total concentration of intermediates dropped 4%. These results indicated that the chlorination of 2-phenylindole (**6**) leads to a mixture of *N*,3-dichloro-2-phenylindole (**8**) and 3,3-dichloro-2-phenyl-3*H*-indole (**9**). The *N*-chloroindole **8** then slowly rearranged to the 3,3-dichloro-3*H*-indole **9**.

The formation of 3-chloro-2-phenylindole (**7**) was detected by UV and IR spectroscopy. Figure 2b, obtained after 6.5 h of reaction, was almost identical with that of authentic **7**. In the IR spectra taken during the early part of the reaction, there were observed small changes in the region of 3460–3450 and 1350–1355 cm^{-1}. These changes correspond to slight differences in the IR spectra of **6** and **7** in these regions.

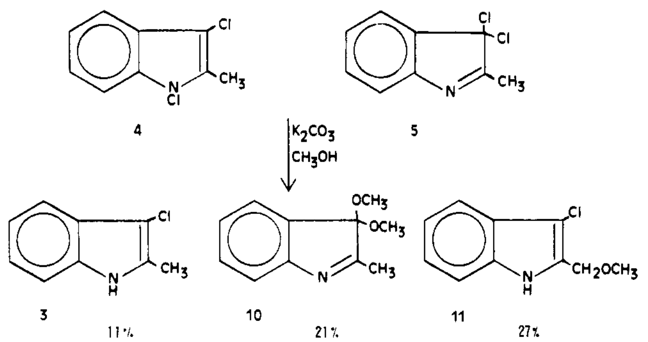
The chlorination of **6** was studied with an equimolar amount of NaOCl. After 24 h of reaction iodometric analysis of the organic layer indicated a 13% yield of one or more species able to oxidize iodide ion. The aqueous solution contained 15% of the original concentration of NaOCl. These values were 10% and 4%, respectively, after 45 h. The IR spectrum of the solution after 45 h indicated the presence of 3-chloro-2-phenylindole (**7**). This was confirmed by TLC. It was not possible to determine if the CH_2Cl_2 solution contained *N*-chloro-2-phenylindole and/or a mixture of the two dichloro species **8** and **9**. The results of the various studies can be seen in Scheme III.

Substitutents at the 2-position of indole appeared to affect the reactivity of the initially formed *N*-chlorindole. This can be seen most clearly in the case of 2-methylindole (**1**) where direct evidence for the formation and rearrangement of *N*-chloro-2-methylindole (**2**) was obtained. No *N*-chloro-2-phenylindole was detected during the chlorination of **6** and hence the direct formation of 3-chloro-2-phenylindole (**7**) can not be ruled out. The 3-chloroindole formed in each system reacted further with the excess NaOCl present to give the final products. The final chlorination products appear to depend not only on

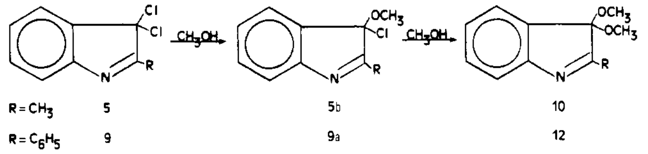
---

[21] The calcium hypochlorite used (70% HTH) contained sodium chloride and impurities present in the lime used in the industrial procedure. (W. J. Sakowski, U.S. Patent 3895099, 1975).

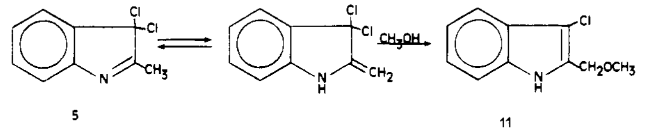
Scheme IV



Scheme V



Scheme VI



the substituent present but also on the relative proportion of NaOCl (Figure 1).

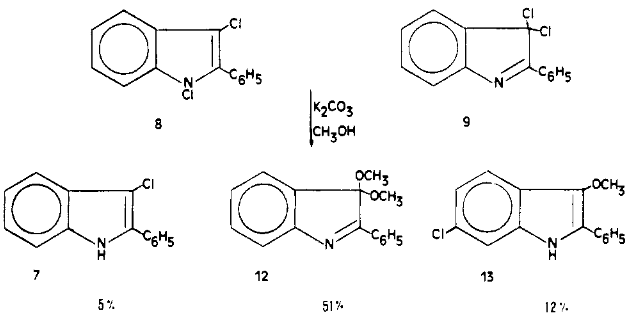
Reactions of Intermediates with Alkaline Methanol. A 2:1 mixture of *N*,3-dichloro-2-methylindole (**4**) and 3,3-dichloro-2-methyl-3*H*-indole (**5**) in *n*-hexane was combined with methanol saturated with potassium carbonate and the solution kept at room temperature for 5 h. A number of products were detected by TLC and it was possible to isolate and identify three components of the complex mixture. The evidence on which these structures are based is contained in the experimental section and summarized in Scheme IV.

Recently it was reported that nucleophiles can attack a 3,3-dichloro-3*H*-indole on either carbon (C-3) or chlorine, depending on the nature of the nucleophile.[19] Similar results have been reported for 3-chloro-3*H*-indoles.[9] Products attributed to both modes of attack were observed. 3*H*-Indole **10** was formed by successive nucleophilic attacks on C-3 (Scheme V).

The α-chloro ether **5b** can give **10** by either an S_N1 or S_N2 process.[5-7a,14] In the reaction of **5** with phenoxide ion an intermediate analogous to **5b** was detected (Scheme I). A similar α-chloro ether was isolated in the reaction of 2,3,3,4,5,6,7-heptachloro-3*H*-indole with isopropoxide.[19] The formation of 3-chloro-2-methylindole (**3**) can come from a nucleophilic attack on a chlorine[9,19] of **5** to give an anion which by proton abstraction gave **3**. Alternatively, the dechlorination of *N*,3-dichloro-2-methylindole (**4**) could lead to the formation of **3**.[22,23] These two paths can not be distinguished.

Products analogous to 3-chloro-2-(methoxymethyl)indole (**11**) have been observed during the reaction of 3-chloro-2,3-disubstituted-3*H*-indoles, which have an α-methylene proton, with nucleophiles. One possibility for the formation of **11** is shown in Scheme VI.[5-7,13b,24,25]

Scheme VII



A mixture of *N*,3-dichloro-2-phenylindole (**8**) and 3,3-dichloro-2-phenyl-3*H*-indole (**9**) in CH_2Cl_2 was kept in contact with methanol saturated with potassium carbonate for 40 h and after this period 7% of the original mixture still remained. At this point, the reaction was stopped and the products were isolated by preparative TLC. The evidence on which structures **7** and **12** are based is presented in the experimental section and summarized in Scheme VII.

It is proposed that 3-chloroindole **7** and 3*H*-indole **12** were formed in processes analogous to those which led to **3** and **10**, respectively.

Indole **13** is most likely either 5-chloro- or 6-chloro-3-methoxy-2-phenylindole.[4,10] The more readily accessible 5-chloro isomer was prepared by the Fischer cyclization of the *p*-chlorophenylhydrazone of α-methoxyacetophenone.[26] Its melting point and spectral properties eliminated the 5-chloro isomer as a possible structure for **13**. These results suggested that **13** was the 6-chloro isomer. The formation of **12** was stepwise (Scheme V). Solvolysis of **9a** could lead to an ion pair in which the cation would be expected to be highly resonance stabilized. Collapse of the ion pair gave **13** where the chloro group is para to C-3, whereas, reaction with solvent gave **12**.

The products observed in this study appeared to be formed by competing nucleophilic attacks on carbon (C-3) and on the chloro groups of the 3,3-dichloro-3*H*-indoles and by the subsequent reaction of initial products which still contained a labile chloro group. These processes are analogous to various reaction pathways which have been reported for 3-chloro-3*H*-indoles.[5] None of the observed products could be attributed to a process unique to an *N*,3-dichloroindole.

It is proposed that the products came from the 3,3-dichloro-3*H*-indole and the *N*,3-dichloroindole rearranged to the 3*H*-indole derivative during the reaction with alkaline methanol. It was possible to observe the rearrangement of *N*,3-dichloro-2-phenylindole **8** to the 3*H*-indole **9**.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 567 and ultraviolet spectra with a Cary 15 spectrophotometer. A Varian T-60 was used for recording ^1H NMR spectra and a Brucker WP-80 for ^{13}C spectra. Routine mass spectra were taken on a

---

(22) The dechlorination of the *N*-chloro derivatives of pyrrole, carbazole, and benzimidazole has been observed in methanol containing K_2CO_3. (M. De Rosa and J. L. Triana Alonso, 174th National Meeting of the American Chemical Society, Chicago, IL, Aug 1977, Abstract no. 155; M. De Rosa, unpublished observations).

(23) It has recently been reported that methoxide effects the dechlorination of *N*-chloro and *N*,*N*-dichloro derivatives of some phosphinic amides (M. J. P. Harger and M. A. Stephen, *J. Chem. Soc., Perkin Trans. 1*, 705 (1980)).

(24) W. I. Taylor, *Proc. Chem. Soc.*, 247 (1962).

(25) (a) G. Büchi and R. E. Manning, *J. Am. Chem. Soc.*, **88**, 2532 (1966); (b) L. J. Dolby and G. W. Gribble, *J. Org. Chem.*, **32**, 1391 (1967); (c) J. P. Kutney, J. Beck, F. Bylsma, and W. J. Cretney, *J. Am. Chem. Soc.*, **90**, 4504 (1968); (d) N. Neuss, M. Gorman, N. J. Cone, and L. L. Huckstep, *Tetrahedron Lett.*, 783 (1968); (e) J. P. Kutney, J. Cook, K. Fuji, A. M. Treasurywala, J. Clardy, J. Fayos, and H. Wright, *Heterocycles*, 3, 205 (1975).

(26) R. Robinson and S. Thornley, *J. Chem. Soc.*, 3144 (1926).

Hitachi Perkin-Elmer RMU-6H instrument. Elemental analyses and exact mass measurements were carried out by Dr. F. Pascher, Mikronanalytisches Laboratorium, Bonn, W. Germany. Melting points were taken on a Fisher-John hot stage and are uncorrected. The indoles (Merck) used in this study were purified by sublimation: 2-methylindole (**1**) sublimed at 50 °C (1 mm), mp 56–58 °C (lit.[27] mp 56–59 °C); 2-phenylindole (**6**) sublimed at 150 °C (1 mm), mp 192–193 °C (lit.[28] mp 187–188 °C).

Caution: Several of us were very sensitive to one or more of the following: 2-methylindole (**1**), 3-chloro-2-methylindole (**3**), 3-chloro-2-phenylindole (**7**), 3-chloro-2-(methoxymethyl)indole (**12**), and the mixture obtained from the chlorination of 2-methylindole. Symptoms included eye irritations, headaches, rashes, and sneezing. Similar effects have been reported during a previous study on the chlorination of indoles.[16]

Aqueous Sodium Hypochlorite Solutions. Solutions of fresh sodium hypochlorite were prepared prior to use as follows: 3.5 g of calcium hypochlorite (70%, HTH) was dissolved in 75 mL of water, to this was added 3.5 g of sodium carbonate, the mixture was stirred for about 5 min, and a 0.40 M solution of sodium hypochlorite was obtained. This solution was diluted as needed.

Chlorination of 2-Methylindole (1) with Excess Sodium Hypochlorite Solution. To a vigorously stirred solution containing 0.760 g (5.8 mmol) of 2-methylindole (**1**) in 100 mL of *n*-hexane was added 75 mL of fresh sodium hypochlorite solution. The reaction mixture at room temperature was stirred in the dark for 5 h. The organic layer was separated, dried (Na_2CO_3), and analyzed iodometrically. A solution was obtained whose chemical (see below) and spectral properties indicated it was a 2:1 mixture of *N*,3-dichloro-2-methylindole (**4**) and 3,3-dichloro-2-methyl-3*H*-indole (**5**) in a combined yield of 76–92%: IR (*n*-hexane) no NH, 1600 (C=N), 1220, 1090, 935, 805, 745 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.45 (s, 3 H), 2.48 (s, 3 H) in a ratio of 1:2, 6.90–7.77 (m, aromatic, 4 H); UV (*n*-hexane) λ_{max} 270 nm. Similar mixtures were obtained when the reactions were run in methylene chloride, *n*-hexane, carbon tetrachloride, and benzene. The same mixture was obtained when a solution containing 0.227 g (1.4 mmol) of 3-chloro-2-methylindole (**3**) in 30 mL of *n*-hexane was stirred with 25 mL of sodium hypochlorite for 140 min at room temperature. The yield was 83% and the spectral properties of the solution (IR, NMR, and UV) were identical with those obtained by starting with **1**.

Chlorination of 2-Phenylindole (6) with Excess Sodium Hypochlorite. To a vigorously stirred solution containing 0.930 g (4.80 mmol) of 2-phenylindole (**6**) in 100 mL of methylene chloride was added 75 mL of fresh sodium hypochlorite solution. The reaction mixture at room temperature was stirred in the dark for 55 h. The organic layer was separated, dried (Na_2CO_3), and analyzed iodometrically. A solution was obtained whose spectral properties indicated it was a mixture of *N*,3-dichloro-2-phenylindole (**8**) and 3,3-dichloro-2-phenyl-3*H*-indole (**9**) in a combined yield of 81–92%: IR (CH_2Cl_2) no NH, 1605, 1540 (C=N), 1190, 940, 830 cm^{-1}; UV (CH_2Cl_2) λ_{max} 240, 250, 258 (sh), 295 (br), 350 (sh) nm (see Figure 2c); ^{1}H NMR (C_4Cl_6) δ 6.83–8.56 (m, aromatic H). The same mixture was obtained in 92% yield when a solution containing 0.915 g (4.02 mmol) of 3-chloro-2-phenylindole (**7**) in 100 mL of methylene chloride was stirred for 40 h with 75 mL of a solution of sodium hypochlorite. This solution had the same spectral properties (IR, UV, NMR) as those from the mixture obtained from **6**.

3-Chloro-2-phenylindole (7). To a stirred solution containing 3.00 g (15.5 mmol) of 2-phenylindole (**6**) in 60 mL of dry ether at room temperature and in the dark was added dropwise over a 3-h period 1.45 mL (17.8 mmol) of sulfuryl chloride[29] in 35 mL of ether. The solution was stirred for an additional 3 h and then 60 mL of an aqueous potassium carbonate solution was added. The organic layer was separated and the aqueous layer extracted with five 20-mL portions of ether. The ether fractions were combined and dried ($CaCl_2$) and the solvent was removed by evaporative distillation at reduced pressure. The crude product was chromatographed on silica gel G-60 (Merck) and elution (followed with a short-wave UV lamp) with methylene chloride gave a solid which was recrystallized from petroleum ether (bp 60–80 °C) to give an 83% yield of **7**: mp 88.5–89 °C; IR (KBr) 3390, 1485, 1455, 1445, 1340, 1315, 1230, 1140, 1005, 770, 745, 695, 650 cm^{-1}; UV (CH_2Cl_2) λ_{max} 238 (log ϵ 4.31), 305 (4.32) nm; ^{1}H NMR ($CDCl_3$) δ 7.06–8.30 (m, 9 H); mass spectrum, *m*/*e* (relative intensity) 229 (M + 2, 34), 228 (M + 1, 17), 227 (M, 100), 192 (M − 35, 12), 165 (13), 123 (13), 113.5 (M^{2+}, 14), 89 (16). It was not possible to get an accurate elemental analysis. This product decomposed both in air and under vacuum and both the solid and solutions were light sensitive.

Reaction of *N*,3-Dichloro-2-methylindole (4) and 3,3-Dichloro-2-methyl-3*H*-indole (5) with Phenoxide Ion. A mixture of the two dichloro species in carbon tetrachloride was prepared as described above. The ^{1}H NMR of this solution showed two methyl singlets at 2.48 and 2.45 ppm in a ratio of 2:1, respectively. To 10.0 mL of this solution was added a solution containing 10.0 mL of water, 3.0 mL of phenol, and 1.0 g of sodium hydroxide. This mixture was stirred for 24 h, and an aliquot was washed twice with a 20% sodium hydroxide solution and then water and dried (K_2CO_3). The ^{1}H NMR showed two methyl singlets at 2.48 and 2.38 ppm in a ratio of 1.6:1. When the reaction was continued for a total of 48 h this ratio was 1.25:1. The singlet at 2.48 ppm was assigned to the methyl group of *N*,3-dichloro-2-methylindole (**4**) and the singlet at 2.45 ppm to the methyl group of 3,3-dichloro-2-methyl-3*H*-indole (**5**).

Reaction of *N*,3-Dichloro-2-methylindole (4) and 3,3-Dichloro-2-methyl-3*H*-indole (5) with Alkaline Methanol. To a solution containing 4.95 mmol of a mixture of **4** and **5** in 72 mL of *n*-hexane was added 200 mL of anhydrous methanol saturated with potassium carbonate. This mixture was stirred at room temperature for 5 h at which time 1% of the original mixture was left. The reaction mixture was concentrated to dryness at room temperature under reduced pressure. To the residue was added enough water to dissolve the K_2CO_3 and then it was extracted with four 20-mL portions of methylene chloride. The organic layer was dried with magnesium sulfate and reduced in volume and the products were separated by preparative TLC (99/1 v/v chloroform/methanol) on three 50 × 20 × 0.2 cm silica gel plates. The following three compounds were isolated: 3-chloro-2-methylindole (**3**), 11%; 3,3-dimethoxy-2-methyl-3*H*-indole (**10**), 21%; 3-chloro-2-(methoxymethyl)indole (**11**), 27%. The evidence on which these structures were based is given below.

3-Chloro-2-methylindole (3). The material obtained by TLC (R_f 0.82) was chromatographed (methylene chloride) on silica gel (this was followed with a long-wave UV lamp) and recrystallized twice from *n*-hexane: mp 97–98 °C (lit.[16] mp 97–98 °C); IR (KBr) 3497, 1453, 1300, 1235, 1220, 1072, 750 cm^{-1}; UV (MeOH) λ_{max} 223 (log ϵ 4.65), 274 (3.85), 280 (3.86), 288 (3.81) nm; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 6.90–7.70 (m, aromatic, 4 H, NH).

3,3-Dimethoxy-2-methyl-3*H*-indole (10). An oil (R_f 0.26) was obtained which decomposed when further purification was attempted by chromatography, recrystallization, or sublimation. The spectral evidence indicated that this oil was ca. 90% pure: IR (neat) 3350 (w, NH impurity), 2940, 2830, 1710 (w, C=O impurity), 1605 (s, C=N), 1455, 1375, 1315, 1260, 1240, 1190, 1120, 1090, 970, 940, 850, 775, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.27 (s, 6.6 H), 7.03–7.63 (m, 4.8 H, aromatic H and NH).

3-Chloro-2-(methoxymethyl)indole (11). This product (R_f 0.48) was stable only in solution. Removal of solvent under reduced pressure gives a short-lived yellow solid which decomposed with the evolution of HCl gas. The lifetime of the solid was increased if glassware previously washed with a sodium carbonate solution was used. The solid was washed three times with hot *n*-hexane and a white crystalline solid was obtained: mp 60–71 °C dec; IR (KBr) 3250, 2930, 2830, 1455, 1338, 1310, 1230, 1190, 1075, 895, 750, 740 cm^{-1}; UV (MeOH) λ_{max} 221 (log ϵ 4.51), 275 (3.88), 282 (3.89), 290 (3.80) nm; ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 3 H), 4.70 (s, 2 H), 7.06–8.63 (m, aromatic, 4 H, NH); mass spectrum, *m*/*e* (relative intensity) 197 (M + 2, 18), 196 (M + 1, 8), 195 (M, 57), 164 (89), 163 (M − 32, 100), 136.5 (m*, 195 → 163), 128 (57), 123 (5), 101 (23), 75 (10); high-resolution mass spectrum calcd for $C_{10}H_{10}{}^{35}ClNO$ 195.0451, found 195.0445.

Reaction of *N*,3-Dichloro-2-phenylindole (8) and 3,3-Dichloro-2-phenyl-3*H*-indole (9) with Alkaline Methanol. To a solution containing 2.66 mmol of a mixture of **8** and **9** in 83 mL

---

(27) A. Kissman, D. Farnsworth, and B. Witkop, *J. Am. Chem. Soc.*, **74**, 3948 (1952).

(28) J. Fitzpatrick and R. Haiser, *J. Org. Chem.*, **22**, 1703 (1957).

(29) G. Mazzara and A. Borgo, *Gazz. Chim. Ital.*, **35**, 320, 563 (1905).

J. Org. Chem. 1981, 46, 2059–2065

of CH_2Cl_2 was added 220 mL of dry methanol saturated with potassium carbonate. After 40 h at room temperature the reaction mixture still contained 7% of the original mixture of 8 and 9. The reaction mixture was evaporated to dryness at room temperature under reduced pressure, water was added to dissolve the K_2CO_3, and the mixture was extracted five times with methylene chloride. The organic layer was dried ($MgSO_4$) and reduced in volume and the products were separated by preparative TLC (benzene) on four 50 × 20 × 0.2 cm silica gel plates. The following three compounds were isolated: 3-chloro-2-phenylindole (**7**), 5%; 3,3-dimethoxy-2-phenyl-3*H*-indole (**12**), 51%; 6-chloro-3-methoxy-2-phenylindole (**13**), 12%. The evidence on which these structures were based is given below.

3-Chloro-2-phenylindole (7). The solid obtained by TLC (R_f 0.74) was recrystallized three times from petroleum ether (bp 60–80 °C) and was identical in all respects with that prepared synthetically.

3,3-Dimethoxy-2-phenyl-3*H*-indole (12). The oil obtained by TLC (R_f 0.34) solidified after 2 h and was recrystallized twice from petroleum ether (bp 60–80 °C) and then sublimed three times at 50 °C (1 mm): mp 80 °C; IR (KBr) 2940, 2830, 1545 (C=N), 1452, 1440, 1235, 1170, 1130, 1090, 990, 890, 770, 760, 695, 652 cm^{-1}; UV (MeOH) λ_{max} 232 (log ϵ 4.25), 240 (4.29), 248 (4.26), 322 (4.12) nm; ^1H NMR ($CDCl_3$) δ 3.20 (s, 6 H), 7.10–8.57 (m, aromatic, 9 H).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.98; N, 5.53; O, 12.63. Found C, 75.75; H, 5.99; N, 5.51; O, 12.75.

6-Chloro-3-methoxy-2-phenylindole (13). The material obtained by TLC (R_f 0.60) was chromatographed (methylene chloride) on silica gel and the solid eluted as a yellow band was recrystallized three times from *n*-hexane: mp 165–176 °C dec; IR (KBr) 3410, 2920, 1625, 1445, 1255, 1200, 1164, 1112, 823, 811, 804, 761, 690 cm^{-1}; UV (MeOH) λ_{max} 206 (log ϵ 4.17), 224 (4.08), 260 (sh, 3.70), 322 (4.04) nm; ^1H NMR (CD_3COCD_3) δ 3.83 (s, 3 H), 6.73–8.03 (m, aromatic, 8 H, NH); mass spectrum, *m/e* (relative abundance) 259 (M + 2, 35), 258 (M + 1, 17), 257 (M, 100), 244 (M + 2 − 15, 36), 242 (M − 15, 100), 214 (M − 15 − 28, 15), 128.5 (M^{2+}, 13).

There was also isolated by TLC a band (R_f 0.25) which represented 13% of the crude reaction mixture. This material was extremely unstable and all attempts at further purification resulted in decomposition. The NMR spectrum indicated at least two components and the possibility that one component contained two different methoxy groups. A broad band (R_f 0.03–0.12) was also obtained which accounted for 10% of the crude reaction mixture and contained at least three components. No pure material was obtained from this mixture.

5-Chloro-3-methoxy-2-phenylindole.[26] To 1.80 g (12.6 mmol) of *p*-chlorophenylhydrazine, obtained from its hydrochloride salt (Aldrich), were added 2.00 g (13.2 mmol) of α-methoxyacetophenone and 20 mL of glacial acetic acid. This solution turned red and was refluxed for 3 h. The reaction mixture was added to 200 mL of water, kept at 0 °C for 12 h, and filtered. The solid was washed with hot *n*-hexane and the filtrate was let cool whereupon a yellow solid formed. It was recrystallized by adding hot *n*-hexane and dried under vacuum and a 30% yield of 5-chloro-3-methoxy-2-phenylindole was obtained. This indole was heat sensitive and discolored during recrystallization. It had the following properties: mp 112–115 °C; IR (KBr) 3370, 3060, 2930, 1600, 1485, 1320, 1240, 1170, 1055, 810, 765, 690 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 3.97 (s, 3 H), 6.97–8.10 (m, 8 H), 10.68 (s, 1 H); high-resolution mass spectrum calcd for $C_{15}H_{12}NCl^{35}O$ 257.0606, found 257.0576.

Acknowledgment. This investigation was supported in part by Grant No. 31-26-S1-0641 from the Consejo Nacional de Investigaciones Cientificas y Tecnológicas (CONICIT). We thank Professors A. Rojas and B. Mendez, Departamento de Química, Facultad de Ciencias, Universidad Central de Venezuela, for the ^{13}C NMR spectra and Dr. J. D. Medina, Lic. V. Sanchez, and Lic. C. Cabello of the Instituto Venezolano de Investigaciones Cientificas (IVIC) for the mass spectra.

Registry No. 1, 95-20-5; **2**, 76794-13-3; **3**, 7164-92-3; **4**, 76794-14-4; **5**, 76794-15-5; **6**, 948-65-2; **7**, 76794-16-6; **8**, 76794-17-7; **9**, 76794-18-8; **10**, 76794-19-9; **11**, 76794-20-2; **12**, 76794-21-3; **13**, 76794-22-4; *p*-chlorophenylhydrazine, 1073-69-4; α-methoxyacetophenone, 4079-52-1; 5-chloro-3-methoxy-2-phenylindole, 76794-23-5; sodium hypochlorite, 7681-52-9.

Synthesis of Functionalized Quinoline Derivatives by Annulation of Pyridines

Eugene Ghera* and Yoshua Ben David

Department of Organic Chemistry,[1] The Weizmann Institute of Science, Rehovot, Israel

Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California

Received January 19, 1981

Thiophenyl and sulfonylphenyl groups were introduced on each methyl group of 2,3-lutidine (**1**), and the reactivity of the adjacent carbanions has been examined. When both methyl groups of **1** were substituted with sulfur groups, regioselective alkylation of the vicinal 2,3 side chains could be performed. The bromosulfones **18** and **19** can be selectively prepared from **1** and were used for an annulation route leading to 6-oxo and 7-oxo derivatives of 5,6,7,8-tetrahydroquinolines.

There is widespread occurrence in nature of compounds which contain structural moieties derived from quinolines and isoquinolines. Most synthetic routes leading to these bicyclic structures consist of cyclization reactions starting from benzene (or cyclohexane) derivatives substituted with nitrogen functions[2] and are subject to the resulting reactivity and isomer restraints. The alternate route, involving the synthesis of quinolines by the annulation of pyridines, has been rarely utilized, and the reported examples are of limited synthetic value. The limitations of

---

[1] Experimental work done in these laboratories.

[2] See: Jones, G. *Chem. Heterocycl. Compd.* **1977**, *32*, 93.

0022-3263/81/1946-2059$01.25/0