acetone (30 ml.) and then a solution of ethyl chloroformate (4.35 g., 3.85 ml., 40 mmoles) in acetone (10 ml.). After stirring the mixture at −5° to 0° for 30 min., a solution of sodium azide (3.25 g., 50 mmoles) in water (20 ml.) was added and stirring continued for another hour. The mixture was poured into 500 ml. of ice-cold saturated sodium chloride solution and 250 ml. of ice water, and extracted with five 75-ml. portions of ether. The combined ether extracts were dried over calcium sulfate, evaporated in a vacuum at 30°, and the residual azide was dissolved in 50 ml. of toluene. This solution was warmed slowly to 100° until nitrogen evolution ceased, the solvent removed under reduced pressure, and the residual isocyanate refluxed with 18% hydrochloric acid (35 ml.) for 12 hr. The cooled solution was made basic with 10% sodium hydroxide solution, the amine extracted with ether, the ether extracts were dried over sodium sulfate and evaporated. The oily amine (4.55 g.) boiled at 69°/0.8 mm., 68°/0.55 mm., $n_{\rm D}^{25}$ 1.5498. The yield was 4.15 g. (81%).

The *hydrochloride*, prepared in ether, crystallized from chloroform, m.p. 224–226° (sealed tube).

Anal. Calcd. for $C_{10}H_{13}N.HCl$: C, 65.37; H, 7.68; N, 7.63; Cl, 19.30. Found: C, 65.42; H, 7.71; N, 7.93; Cl, 19.07.

trans-2-Phenylcyclobutylamine. (a) This was prepared from *trans*-2-phenylcyclobutanecarboxylic acid as described for the *cis* isomer above. The yield was 63%, b.p. 72°/0.55 mm., $n_{\rm D}^{25}$ 1.5464. The *hydrochloride* was precipitated with ethereal hydrogen chloride and crystallized from ethanol-ether, m.p. 210–213° dec.

Anal. Calcd. for $C_{10}H_{13}N.HCl$: C, 65.37; H, 7.68; N, 7.63. Found: C, 65.09; H, 7.56; N, 7.75.

The *N-benzoyl derivative* was prepared by the Schotten-Baumann method and crystallized from ethanol, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{17}H_{17}NO$: N, 5.57. Found: N, 5.66.

(b) A solution of oily 2-phenylcyclobutanone oxime (1.6 g.) in absolute ethanol (70 ml.) was reduced by rapid addition of 6 g. of sodium. After the main reaction had ceased (15 min.), the mixture was refluxed for 35 min., the solvent removed under reduced pressure, the residue was treated with water (70 ml.) and the mixture extracted with ether. Basic material was extracted from the ether into 5% hydrochloric acid, the acid solution washed with ether, made alkaline with 40% sodium hydroxide solution, and the amine was extracted into ether. After drying over sodium sulfate and removal of the solvent, an oil remained, the infrared spectrum of which was identical with that of the amine obtained by method (a). The hydrochloride melted at 210–212° dec. and did not depress the melting point of the salt from method (a).

Attempts to reduce 2-phenylcyclobutanone oxime with lithium aluminum hydride or catalytically were unsuccessful.

CHARLOTTESVILLE, Va.

[CONTRIBUTION FROM UNION CARBIDE RESEARCH INSTITUTE AND THE LINDE CO. RESEARCH LABORATORY, UNION CARBIDE CORP.]

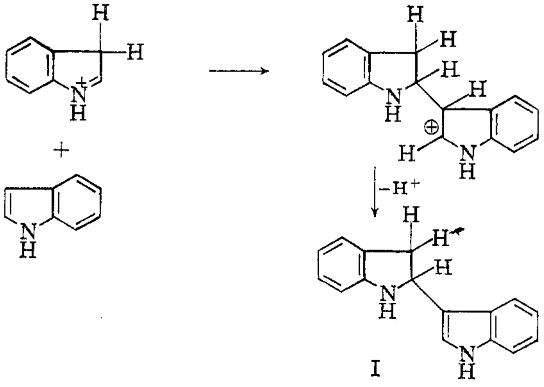
The Structure of Diskatole[1]

RICHARD L. HINMAN[2] AND E. R. SHULL[3]

Formula III has been established by NMR as the correct structure of diskatole. A crossed dimer of skatole and 2-methylindole has been prepared and its structure established as V.

It has been known for many years that indole forms crystalline dimers[4] and trimers[5] in acidic media, but it is only recently that the structures of these products have been established.[6] We became interested in the indole dimers, particularly in diskatole, in the course of studies on the relationship of the oxidation of indoles to their regulatory function in cellular growth.[7,8]

The structure of skatole dimer has not been established. The chemical evidence shows that it resembles diindole (I) in having an anilino nitrogen and an indole nitrogen, and in undergoing thermal depolymerization to the monomer.[9–11] The most recent structure proposed[11] for skatole dimer is shown in formula II. Since dimer formation involves the coupling of a protonated indole nucleus with an unprotonated one,[12] as shown for the formation of diindole (Equation 1), formation of structure II would require protonation of position-2



(1)

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[1] Presented before the Organic Division of the American Chemical Society at the New York meeting, Sept. 9, 1960.

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[3] (a) The Linde Co.; (b) deceased.

[4] O. Schmitz-Dumont and B. Nicolojannis, *Ber.*, **63**, 323 (1930).

[5] K. Keller, *Ber.*, **46**, 726 (1913).

[6] (a) G. F. Smith, *Chem. & Ind.*, 1451 (1954); (b) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957); (c) W. E. Noland and W. C. Kuryla, *J. Org. Chem.*, **25**, 486 (1960).

[7] P. Frost and R. L. Hinman, in *Plant Growth Regulation*, R. Klein, ed., Iowa State University Press, Ames, Iowa, 1961, p. 205.

[8] S. M. Siegel, F. Porto, and P. Frost, *Physiol. Plant.*, **12**, 727 (1959).

[9] B. Oddo and G. B. Crippa, *Gazz. chim. ital.*, **54**, I, 339 (1924).

[10] B. Oddo and Q. Mingoia, *Gazz. chim. ital.*, **57**, I, 480 (1927).

[11] O. Schmitz-Dumont, K. Hamann, and K. H. Geller, *Ann.*, **504**, 1 (1933).

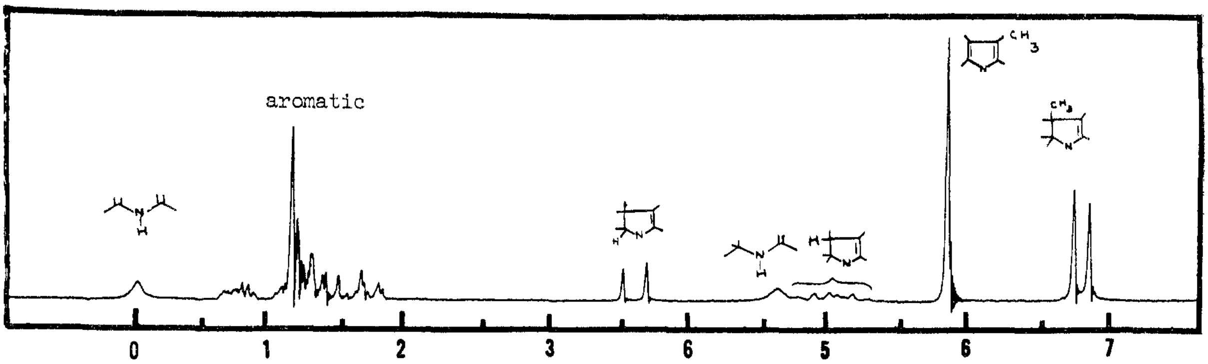
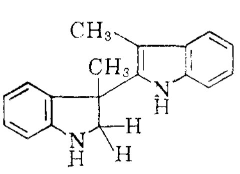
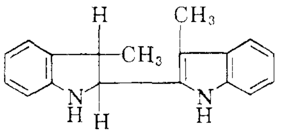


Fig. 1. NMR spectrum at 60 mc. of diskatole in carbon tetrachloride. Scale in ppm. relative to peak at lowest field

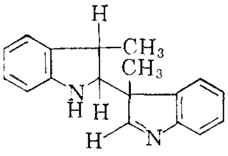
of skatole. We have recently shown, however, that protonation of indole and its simple alkyl derivatives occurs predominantly at the 3-position in solution.[13]



II



III



IV

If the 3-position were protonated, two structures could be envisioned for skatole dimer. One (III) would be formed by attack of the protonated species at position-2 of the unprotonated skatole, while the other (IV) would be formed by attack at the 3-position. As it has recently been shown[14] that substitution of skatole by large electrophilic species generally takes place at the 2-position, structure III seemed most probable.

The infrared spectrum of diskatole showed the presence of two bands at 2.90 and 2.95 μ in the NH region, indicating the presence of both anilino and indolo NH groups, similar to those reported for the dimer of 2-methylindole.[15] The ultraviolet spectrum showed the typical peaks[14] of the indole chromophore at 228, 285, and 293 mμ. The correct structure must therefore contain two NH groups and an indole ring. As structure IV contains only one NH group and the indolenine chromophore, which generally absorbs near 255 mμ,[16] it was eliminated as a possible structure of diskatole.

The two remaining structures (II and III) which differ in the positions of the hydrogens in the reduced hetero ring, could be distinguished by means of proton magnetic resonance. In the 60 mc. spectrum of diskatole (Fig. 1) the resonance lines of the methyl hydrogens are observed as a doublet at $\delta = +6.7$ and 6.8 ppm. (relative to the peak at lowest field strength) and a singlet at + 5.8 ppm., each of area ~ 3. The doublet, which has a coupling constant of ~ 8 cps. clearly indicates that one methyl is bound to a carbon bearing one other hydrogen. This structural feature ($>$ CH—CH_3) is present only in formula III, which is therefore the correct structure of diskatole.[17]

The remainder of the spectrum is interpreted as follows. The complex multiplet (area ~ 8) at $\delta + 1.1$ ppm. is due to the aromatic ring protons. The multiplet at $\delta \sim +5.0$ is assigned to the hydrogen on the 3-carbon of the reduced hetero ring. The resonance of this hydrogen is split by coupling with the methyl hydrogens and with the proton at the 2-position. The doublet of area ~ 1 at $\delta + 5.0$ ppm. is due to the hydrogen at the 2-position of the reduced ring, split by coupling with the hydrogen at the 3-position. The two hydrogens attached to nitrogen are accounted for by the singlet at $\delta = 0$ (the indole NH) and the singlet at $\delta + 4.6$ ppm. (the reduced ring NH). The assignments of the last two peaks were made by comparison with the spectra of skatole and indoline in which the reduced ring NH appears at much higher field strength than the indole NH. The resonance line of the hydrogen bound to nitrogen

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(12) That one indole nucleus must be unprotonated for successful dimerization is shown by the isolation of skatole from its solutions in 15–18*M* sulfuric acid, in which protonation is complete. From the reaction of skatole with dilute solutions of acid only diskatole was isolated.

(13) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960).

(14) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(15) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951).

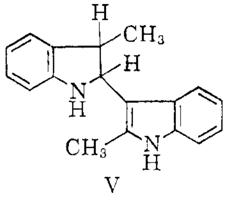
(16) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2188 (1951).

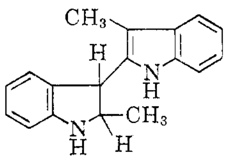
(17) It has been reported [W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960), footnote 17] that the same structure for diskatole has been proved by degradation. No details of the work have appeared.

NOTE ADDED IN PROOF: After this paper had been submitted, diskatole was shown by chemical degradation to have structure III (G. Berti, A. da Settims, and D. Segnini, Tetrahedron Letters, **26**, 13 (1960)).

in pyrrole is also observed at very low fields.[18] The presence of two hydrogens bound to nitrogens is further evidence against the indolenine structure (IV), as are the positions of the methyl resonances. If IV were correct the methyl resonances should appear at about the same field strengths, as both methyls are attached to saturated carbons.

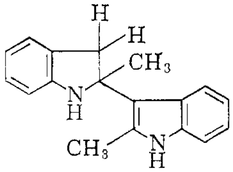
The NMR spectra of two other indole dimers were also determined. The spectrum of diindole was inconclusive, but was in general agreement with the known[6b] structural features of the reduced ring. The other indole dimer examined was a "crossed" dimer formed by the reaction of skatole and 2-methylindole.[19,20] The insolubility of this dimer made it necessary to determine its NMR spectrum in acetone, which absorbs in the same region as the methyl groups of the dimer. Despite this interference, a singlet and a doublet which could be assigned to the methyl groups were clearly distinguishable in the same regions and with about the same separation as the lines due to the two methyl groups in the spectrum of diskatole. Only two structures (V and VI) can be devised which are consistent with the NMR spectrum. Of these only structure V accords with the assumption that dimerization is initiated by protonation of the 3-position of an indole, as in the formation of diskatole and diindole. (Structures of the indolenine type are ruled out because of the indole chromophore in the ultraviolet and two bands in the NH region of the infrared.)


V


VI

In the course of this work we determined the 40 mc. NMR spectra of a number of simple indoles. In general our results agree with the 60 mc. spectra reported recently.[21] In addition to the previously reported observations we found evidence of coupling between the α- or β-ring protons and the hydrogens of alkyl groups at adjacent carbons on the hetero ring. Thus, the methyl resonances of skatole and of 2-methylindole in chloroform, carbon tetrachloride, benzene, or acetone, appeared as doublets with a coupling constant of $\sim$ 1 cps. The resonance of the methylene hydrogens of indole-3-acetic acid in acetone showed similar splitting. In these cases the peaks of the ring protons were more complex than would be expected by coupling with the hydrogen on the pyrrole nitrogen only. In a 60-mc. scan of 1,2-dimethylindole in carbon tetrachloride the coupling between the β-proton and the hydrogens of the 2-methyl group was 0.7 ± 0.2 cps.[22] This splitting affords an additional method[21] for determining the presence of a proton on an adjacent ring carbon.

The major product from the reaction of skatole and 2-methylindole was diskatole. Steric effects and the relative basicities of the monomers favor the formation of this product rather than the "crossed" dimer (V). Molecular models show that the hindrance about the interannular bond in V is much greater than in diskatole. In the dimer (VII) of 2-methylindole,[15] hindrance about the interannular bond is so great that the rings are essentially locked in place. It is this effect which prevents dimerization, since the first step, protonation of 2-methylindole, occurs readily.[13,23]


VII

The formation of the "crossed" dimer (V) requires the reaction of a protonated skatole molecule with an unprotonated 2-methylindole. In other studies under way in this laboratory we have determined that the pK_a of 2-methylindole is -0.3 while that of skatole is -4.3. The more basic 2-methylindole would therefore be protonated first, making it unavailable for reaction with the protonated skatole.[24]

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[18] J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1956, p. 65. It is interesting that the hydrogen on the pyrrole nitrogen of diskatole (and diindole) gives rise to fairly sharp peaks in chloroform whereas the spectra of skatole and other simple indoles show very broad resonance lines or none at all. It has been suggested by Dr. Earl Whipple that the line sharpening in the dimers may be explained by the increase in the effective volume which would increase the correlation time for quadrupole relaxation of the N^{14} spin polarization.

[19] Although 2-substituted indoles, such as 2-methylindole, do not form dimers by treatment with acid [O. Schmitz-Dumont and K. H. Geller, *Ber.*, **66**, 766 (1933)], it seemed likely that "crossed" dimers might be formed by reaction of a 2-substituted indole with a protonated 3-substituted indole.

[20] Shortly after completion of this work, Dr. W. E. Noland informed us of his work on "crossed" dimers, including the dimer from skatole and 2-methylindole, which was not isolated as the free dimer but as the maleyl derivative. We are indebted to Dr. Noland for a copy of this paper[17] prior to its publication.

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

[22] Spectrum obtained by Dr. Earl B. Whipple of the Union Carbide Research Institute.

[23] The proposed structure of this dimer is based on the assumption that it would be formed by 3-protonation. A dimer of 2-methylindole with a 3-3′ interannular bond has been prepared by an indirect route.[15]

[24] As Noland has pointed out,[17] 2-methylindole should be more susceptible than skatole to attack by a protonated skatole. It may be this fact alone which enables the reaction to proceed at all.

The proof of structure of diskatole and the related work on indole dimerization reported in this paper illustrate an important point in indole chemistry. Substitution of indoles by electrophilic species takes place at the 3-position if that position is not occupied. When the 3-position bears a substituent, as in skatole, *small* electrophilic species will still attack the 3-position. Thus, the proton, bromonium ion,[25] and certain electrophilic oxidizing agents[26] attack the 3-position of skatole and its derivatives. If the electrophilic species is large, such as a protonated indole, or in the cases reported by Noland,[14] the electrophile may enter the 2-position.

Finally, attention is called to the similarity of indoles to simple vinylamines in their mode of protonation. The similarity extends to dimerization, since a number of typical vinylamines, particularly the Δ^2-tetrahydropyridines[27a] and Δ^2-pyrrolines,[27b] undergo dimerization through intermediates similar to those of the protonated indoles.

EXPERIMENTAL[28]

Diskatole. Prepared by passing dry hydrogen chloride into a rapidly stirred solution of skatole in dry thiophene-free benzene. The work-up was carried out as described previously,[9] yielding short white needles, m.p. 125–127° (reported[9] m.p. 125–127°). The sample used for spectral studies had an analysis in close agreement with theory. Ultraviolet spectrum (95% ethanol): λ_{max} 228, 285, 293 $m\mu$; ϵ_{max} 39,400, 12,200, 11,500.

2-(2'-Methylindoyl)-3-methylindoline ("crossed" dimer). The reaction was carried out under the conditions described for the preparation of diskatole, using 0.005 mole each of 2-methylindole and skatole. After about 15 min. of reaction a red gelatinous mass was deposited which prevented effective stirring. Introduction of hydrogen chloride was continued with occasional stirring for an additional 45 min. The solvent was removed by distillation *in vacuo,* and the residue was dried overnight in a vacuum desiccator. The red powder which was obtained in this way was triturated with hot 10% sodium hydroxide and extracted with benzene. The combined extracts were dried over sodium sulfate, concentrated to about 50 ml, and heated to boiling. *n*-Hexane was added until the hot solution was turbid, when the solution was allowed to cool to room temperature and was then placed in the refrigerator overnight. The oil which was deposited partially solidified on scratching, and the whole mass was filtered. The semisolid residue was again subjected to the benzene-hexane conditions for crystallization and a small quantity of white powder, m.p. 209–213° dec. was obtained. Recrystallization of this material from 95% ethanol and finally from absolute ethanol (25 ml. for 0.5 g. of solid) produced a white powder, m.p. 214–215° dec.

Anal. Calcd. for C_9H_9N: C, 82.40; H, 6.91; N, 10.68. Found: C, 82.52; H, 7.18; N, 10.78. Ultraviolet spectrum (95% ethanol): λ_{max}227, 285, 291; ϵ_{max} 48,000, 13,500, 12,500. Infrared spectrum (KBr): 3.00, 3.07 μ (NH bands). The "crossed" dimer was much less soluble in all solvents than diskatole and did not show the latter's sensitivity to air and light.

The principal product from this reaction was diskatole, isolated by concentrating the various mother liquors from the crystallizations. Some 2-methylindole was also recovered. Attempts to improve the yield of the "crossed" dimer by using a 3:1 molar ratio of 2-methylindole to skatole, or by adding a solution of skatole dropwise to the stirred solution of 2-methylindole and hydrogen chloride were unsuccessful. No "crossed" dimer was obtained.

NMR studies. The NMR spectra were obtained by E. R. Shull at the Linde Laboratories using a Varian V-4300 B 40 mc. high-resolution NMR spectrometer equipped with a 12 inch electromagnet and super stabilizer. The NMR patterns of the compounds in solution were inserted during continuous scans between the CHO and CH_3 peaks of acetaldehyde, as a means of approximating the chemical shifts. The areas under the NMR peaks were obtained using an Ott planimeter.

Acknowledgment. The authors are indebted to Dr. Earl Whipple of the Union Carbide Research Institute for many helpful discussions of the NMR spectra and their interpretation.

TARRYTOWN, N. Y.

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[25] A. Patchornick, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.,* **80,** 4748 (1958).

[26] (a) B. Witkop, *J. Am. Chem. Soc.,* **72,** 2311 (1950); (b) K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.,* **79,** 3191 (1957).

[27] (a) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.,* **79,** 5279 (1957); (b) N. J. Leonard and A. G. Cook, *J. Am. Chem. Soc.,* **81,** 5627 (1959).

[28] Melting points are uncorrected. Ultraviolet spectra were determined with a Beckman DK-2 recording spectrophotometer and infrared spectra with a Perkin-Elmer 21 instrument equipped with sodium chloride optics.