ELECTROPHILIC SUBSTITUTION IN SKATOLE AND ITS DERIVATIVES

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Abstract—Evidence is presented to show that the 2-position is the primary site of electrophilic substitution in skatole and its derivatives. Existing data in the literature are reconciled with this view.

THE product from the strong acid-catalyzed reaction of skatole with benzaldehyde is formulated as 3,3'-dimethyl-2,2'-benzylidenebisindole (Ia).[1,2,3,4] This product was first assigned[5] the basic indolenine structure (II), although it is obtained in free form from strongly acidic solution. As recently as 1952, in an authoritative review,[6] the product was said "undoubtedly" to have structure (II). In agreement with structure (Ia), however, it was shown in 1948 that the product, as well as several closely related derivatives, have two hydrogen atoms that react instantly with a Grignard reagent.[3] Likewise, we find that structure (Ia) has NH $<$ stretching absorption in the infrared region. Further, 1,3-dimethylindole forms a bisindole (Ib), analogous to (Ia), thus showing that an open 1-position is not required for bisindole formation. The ultraviolet spectra of (Ia) and (Ib) show typical indole absorption. They are compared in Table 1 with the spectrum of closely related 2-2'-dimethyl-3,3'-benzylidenebisindole

TABLE 1. ULTRAVIOLET ABSORPTION MAXIMA OF 3,3'-DIMETHYL-2,2'-BENZYLIDENEBISINDOLE AND RELATED COMPOUNDS

Compound	Wave lengths in 95% ethanol (mμ) and intensities (log ε)		
(Ia)	224 (4·82)	286 (4·31)	291 (4·29)
(Ib)	230 (4·84)	289 (4·29)	297 (4·27)
(III)	227 (4·79)	284 (4·15)	292 (4·10)
2,3-Dimethylindole	227 (4·79)*	283 (4·13)*	290 (4·08)*

* Log 2ε.

[1] M. Passerini and T. Bonciani, *Gazz. Chim. Ital.* **63**, 138 (1933).
[2] V. Dostál, *Chem. Listy* **32**, 13 (1938).
[3] A. Étienne and R. Heymès, *Bull. Soc. Chim. Fr.* 841 (1948).
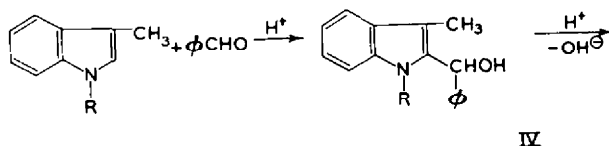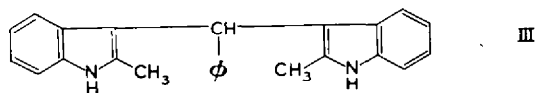[4] H. von Dobeneck and G. Maresch, *Hoppe-Seyl. Z.* **289**, 271 (1952).
[5] M. Freund and G. Lebach, *Ber. Dtsch. Chem. Ges.* **38**, 2640 (1905).
[6] P. L. Julian, E. W. Meyer and H. C. Printy, *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 3, p. 95. Wiley, New York (1952).

I a, R = H
I b, R = CH$_3$

II

III

IV

I

V   VI
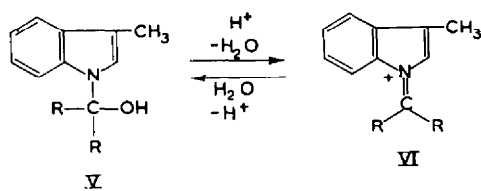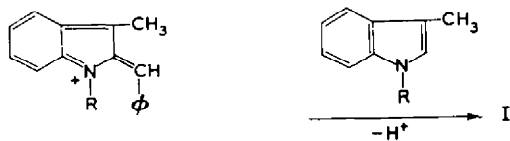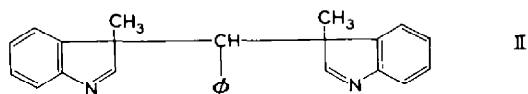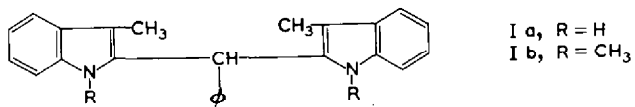
(III). 2,3-Dimethylindole did not react with benzaldehyde under the conditions under which Ia was formed. All these facts support assignment of the 2-position as the point of attachment of the bridging carbon atom in (Ia) and (Ib). It would be expected that the 3-methyl group of skatole would activate the 2-position toward electrophilic substitution relative to the 2-position of indole in the same way as the methyl group of toluene activates the *o*- and *p*-positions relative to any position of benzene.

The mechanism of formation of bisindoles of type I probably involves an intermediate alcohol (IV). The isolation of a pale yellow amorphous substance, $C_{16}H_{15}NO$, corresponding in elemental analysis to (IV R = H), has been reported[7] from the reaction of skatole with benzaldehyde under conditions similar to those under which (Ia) is formed. Proof of structure for this possible intermediate appears, however, to be lacking.

The internal Mannich reaction suggested by Woodward[8] as a possible step in the biogenesis of strychnine involves electrophilic attack at the already occupied 3-position of tryptamine, while the 2-position remains open. It has been noted previously that this suggestion is still not illustrated by any model reaction.[4] In fact, all well authenticated examples of electrophilic carbon substitution in skatole and its derivatives appear to involve initial attack at the 2- and not at the 3-position.[3,4,9-13] Particularly pertinent in this regard is the internal Mannich reaction of *unsym.-N*-phenyl-*N*-skatylhydrazine and benzaldehyde, which has recently been reported to occur (92 per cent yield of crude product) with ring closure at the 2-position of the skatyl nucleus.[14] Consequently, we prefer Woodward's alternative suggestion[8] that in the biogenesis of strychnine preliminary oxidation of the 2-position of the indole nucleus might serve to force the initial attack into the 3-position.

In a series of interesting recent studies[10] of the condensation of skatole and its derivatives with 1,4-dicarbonyl compounds, it has been shown that ring closure occurs at the open 1- and 2-positions to yield benzpyrrocolines. The product from skatole and levulinic aldehyde was shown to be 1,8-dimethyl-2,3-benzpyrrocoline,[10] thus establishing that the more reactive aldehyde carbonyl group had attacked the 1-position of skatole. Consequently, it was proposed[15] that these 1,2-ring closures were initiated by attack on the nitrogen in the 1-position. This proposal can be reconciled with the fact that the 2-position in skatole is the usual point of electrophilic carbonyl attack if it is assumed that skatole (as well as other indoles having an open 1-position) and carbonyl compounds exist in a mobile, but generally unfavorable equilibrium with the corresponding amino alcohol (V) or the equivalent imine (VI). The formation of (V) or (VI) would give the levulinic aldehyde molecule a "beachhead" on the skatole nucleus from which the remaining carbonyl group could carry out the usual electrophilic attack on the 2-position in a sterically much more favorable environment (unimolecular) than would be possible under normal conditions (bimolecular) not involving ring closure.

With indole and 1,4-dicarbonyl compounds ring closure occurs first at the 3- and

[7] M. Hadano, *J. Pharm. Soc. Japan* **48**, 919 (1928).
[8] R. B. Woodward, *Nature, Lond.* **162**, 155 (1948).
[9] G. Magnanini, *Ber. Dtsch. Chem. Ges.* **21**, 1936 (1888).
[10] R. Robinson and J. E. Saxton, *J. Chem. Soc.* 3136 (1950); *Ibid.* 976 (1952).
[11] H. von Dobeneck and I. Maas, *Ber. Dtsch. Chem. Ges.* **87**, 455 (1954).
[12] A. Treibs and E. Herrmann, *Hoppe-Seyl. Z.* **299**, 168 (1955).
[13] J. Szmuszkovicz, *J. Amer. Chem. Soc.* **79**, 2819 (1957).
[14] J. Thesing and C. H. Willersinn, *Ber. Dtsch. Chem. Ges.* **89**, 1195 (1956).

then at the 2-positions, to yield the corresponding carbazoles.[10] With 1,3-dimethylindole ring closure also occurs at the 2- and 3-positions in condensations with hexane-2,5-dione or α,β-unsaturated ketones.[15,16] It was assumed that in these condensations with 1,3-dimethylindole initial electrophilic attack took place at the already occupied 3-position, with *subsequent* ring closure at the 2-position.[15,16] In keeping with the evidence cited in this paper it would appear more probable that the reverse order of attack is involved: initial electrophilic attack at the open 2-position, followed by ring closure at the already occupied 3-position. Consequently, the previously described[15,16] cyclization products having unsymmetrical structures may now have to be reformulated as (VII), (VIII) and (IX). These structures have additional attraction over the previous formulations because they do not involve the formation of bonds between quaternary carbon atoms, a process that would be expected to be quite sterically hindered.
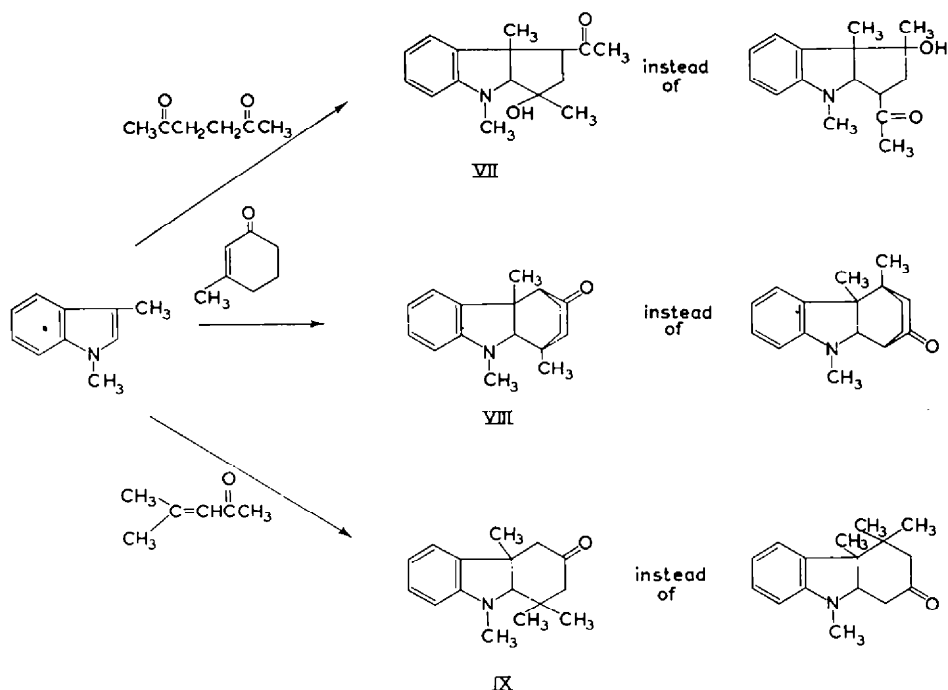
EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

3,3'-Dimethyl-2,2'-benzylidenebisindole (Ia)

This compound has been prepared previously from skatole and benzaldehyde, both in the presence of a small amount of zinc chloride[3,17,18] and in ethanol containing sulfuric[2] or hydrochloric[4] acids. In our hands three attempts with zinc chloride were unsuccessful, but (Ia) was obtained in 44 per cent yield, m.p. 159–161°, by the ethanolic sulfuric acid method.[2] Several recrystallizations from ethanol raised the m.p. to

[15] R. Robinson and J. E. Saxton, *J. Chem. Soc.* 2596 (1953).
[16] D. A. Cockerill, R. Robinson and J. E. Saxton, *J. Chem. Soc.* 4369 (1955).
[17] E. Fischer, *Ber. Dtsch. Chem. Ges.* **19**, 2988 (1886).
[18] M. Wenzing, *Liebigs Ann.* **239**, 239 (1887).

162–163°. Reported: 93 per cent, m.p. 161°.[2] ν_{NH} 3440 (CHCl$_3$), 3430 and 3380 cm^{-1} (Nujol).

1,3-Dimethylindole*

The boron fluoride etherate–acetic acid method[19] was successfully applied to the Fischer indole synthesis of 1,3-dimethylindole[20,21] in 41 per cent yield, n_D^{25} 1·5882.

1,1′,3,3′-Tetramethyl-2,2′-benzylidenebisindole (Ib)

A mixture of 1,3-dimethylindole (7·3 g, 0·0502 mole), benzaldehyde (2·6 g, 0·0245 mole) and zinc chloride (2·0 g) was set aside overnight at room temperature. The red mixture, which was a precipitate mixed with the zinc chloride, was extracted with ether (100 ml) and the ether was evaporated. After standing overnight in the re-frigerator, the red residue had deposited a mass of yellowish crystals (1·5 g, 0·0040 mole, 16 per cent), m.p. 200–203°. Several recrystallizations from acetone–water yielded colorless crystals, m.p. 207–209°. *Anal.* Calcd. for C$_{27}$H$_{26}$N$_2$ (378·49): C, 85·67; H, 6·92; N, 7·40. Found: C, 85·65; H, 6·98; N, 7·33.

Attempted reaction of 2,3-dimethylindole with benzaldehyde

By the method used for the preparation of (Ia),[2] 2,3-dimethylindole[19,22] (5·0 g, 0·0344 mole) and benzaldehyde (1·8 g, 0·0169 mole) were dissolved in ethanol (25 ml), concentrated sulfuric acid (17 drops) was added, and the solution was set aside over-night. No change in the appearance of the solution was noted and a strong odor of benzaldehyde remained. Dilution with water precipitated unreacted 2,3-dimethyl-indole in 93 per cent yield (after drying).

2,2′-Dimethyl-3,3′-benzylidenebisindole (III)

The preparation of this compound in unstated yield by warming 2-methylindole and benzaldehyde at 100° has been reported.[23]

2-Methylindole (2·0 g, 0·015 mole) and benzaldehyde (1·6 g, 0·015 mole) were mixed with glacial acetic acid (20 ml) and set aside. After a few minutes the solution turned red and colorless crystals were precipitated. After the solution had stood overnight, the crystals were collected and washed with ethanol (2·4 g, 0·0068 mole, 91 per cent), m.p. 248–251°. Two recrystallizations from acetone–water raised the m.p. to 252–255°. Reported m.p. 246–247° (uncorr.)[23] and 243°.[24] ν_{NH} 3480 (CHCl$_3$), 3400 cm^{-1} (Nujol).

    * Experiment performed by John J. Baldwin.

[19] H. R. Snyder and C. W. Smith, *J. Amer. Chem. Soc.* **65**, 2452 (1943).
[20] J. Degen, *Liebigs Ann.* **236**, 162 (1886).
[21] L. Marion and C. W. Oldfield, *Canad. J. Res.* B **25**, 1 (1947).
[22] C. M. Atkinson, J. C. E. Simpson and A. Taylor, *J. Chem. Soc.* 165 (1954).
[23] E. Fischer, *Liebigs Ann.* **242**, 372 (1887).
[24] G. O. Burr and R. A. Gortner, *J. Amer. Chem. Soc.* **46**, 1224 (1924).