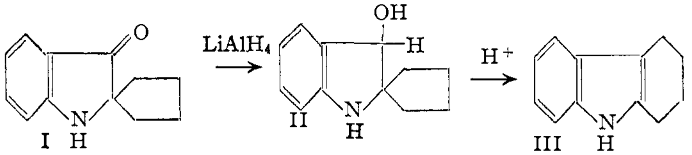
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY AND THE NATIONAL HEART INSTITUTE]

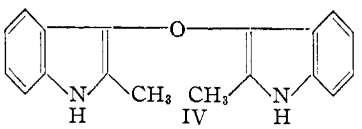
Addition Reactions and Wagner–Meerwein Rearrangements in the Indoxyl Series

BY BERNHARD WITKOP[1] AND J. B. PATRICK[1,2]

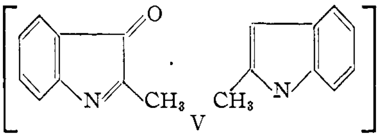
It was shown previously[3] that *spiro*-[cyclopentane-1,2′-*pseudo*indoxyl] (I) can be reduced by lithium aluminum hydride to the dihydro derivative (II), which is noteworthy for the ease with which, in the presence of a trace of acid, it undergoes a Wagner–Meerwein shift to give tetrahydrocarbazole (III). We have now applied this series of reactions to the solution of some structural problems in the chemistry of indoxyl derivatives.



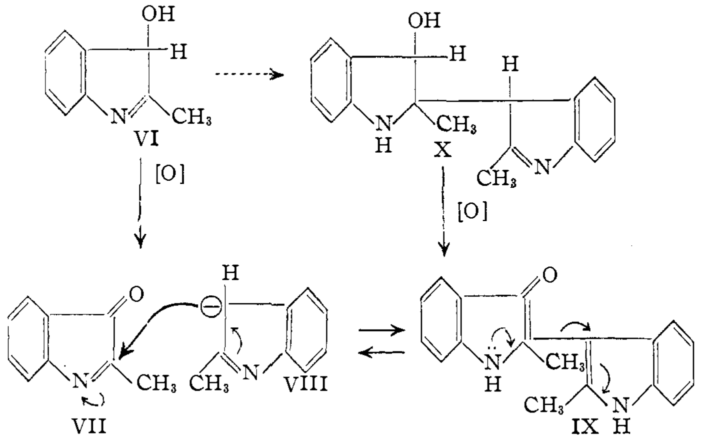
It is known that oxygen,[4] hydrogen peroxide or Caro's acid,[5] air and light,[6] autoxidation in general[7,8] and peracetic acid,[9] convert methylketol (or its magnesium derivative)[7] into a *yellow* compound, $C_{18}H_{16}N_2O$ (IX), which has been regarded as bis-[2-methylindyl-(3)]-ether (IV). Toffoli[10] was the first one to point out that such an ether structure does not account for the yellow color of the compound and suggested a formulation which represents a sort of molecular complex between α-methylindolone and methylketol (V). This formulation is untenable. It represents merely a step in the oxidation, but not the final compound.



IV



V



In accordance with the general course of oxidation of indole compounds[11] the hydroxyindolenine (VI) may be assumed to represent the first intermediate in the reaction of any oxidant with 2-methylindole. Further oxidation yields α-methylindolone (VII). Both VI and VII are capable of adding another molecule of methylketol (VIII, indolenine form). Examples of such additions to the reactive >C=N— double bond of indolenine derivatives[12] as well as the β-reactivity of methylketol[13,14] are known. We prefer to have addition of VIII take place at the indolone stage to give the final yellow oxidation product (IX) rather than proceed from VI *via* X to IX, since X would rearrange to 3,3′-dimethylketyl (XIII) in the acidic medium employed. The process leading to the formation of IX is, of course, reversible (IX, arrows). Grignard reagents, treatment with alkali, and other reactions, carried out with IX invariably lead to the formation of lesser amounts of methylketol and 2-methylindolone.[10] This behavior prompted Toffoli[10] to propose the molecular complex V.

The ultraviolet absorption spectrum of IX is closely related to that of I (Fig. 1) and shows clearly the presence of an indoxyl element. The infrared spectrum (Fig. 2A) records a band at 5.8 μ, characteristic of a carbonyl in a five-membered ring, and one band at 6.2 μ, typical of the structural element $C_6H_5-\underset{|}{N}-C\lessgtr$, where C does not have a double bond. Indoles, like methylketol (Fig. 2C), lack this band.

The reduction of IX with lithium aluminum hydride proceeds smoothly with only negligible cleavage. It is not possible, however, to isolate the intermediate carbinol (corresponding to X). Apparently, the aluminum compound present owing to its electron affinity acts like an acid. The methylketyl residue (R_1, XI) possessing much greater migratory aptitude than the methyl group, migrates to give bis-(α-methyl-β-indyl) (XIII) *via* the intermediates XI ⟷ XII. Such a rearranging action of lithium aluminum hydride has, as far as we are aware, not been reported yet. XIII, showing the properties of a compound obtained in

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(1) National Heart Institute, Bethesda, Maryland.

(2) Research Corporation Fellow, 1950.

(3) Witkop, THIS JOURNAL, **72**, 614 (1950).

(4) Oddo, *Gazz. chim. ital.*, **46**, I, 323 (1916).

(5) Plancher and Colacicchi, *Atti. r. accad. Lincei*, [5] **20**, I, 453 (1911).

(6) Baudisch and Hoschek, *Ber.*, **49**, 453, 2579 (1916).

(7) Toffoli, *Rendiconti Istituto di Sanità Pubblica*, **2**, II, 565 (1939).

(8) Toffoli, *Atti X° congr. intern. Chim.*, **3**, 369 (1939).

(9) Witkop, *Ann.*, **558**, 98 (1947).

(10) Toffoli, *Rendiconti Istituto di Sanità Pubblica*, **2**, II, 676 (1939).

(11) Witkop, THIS JOURNAL, **72**, 1428 (1950).

(12) Witkop, *ibid.*, **72**, 2311 (1950).

(13) Fischer, *Ann.*, **242**, 372 (1887).

(14) Freund and Lebach, *Ber.*, **38**, 2640 (1905).

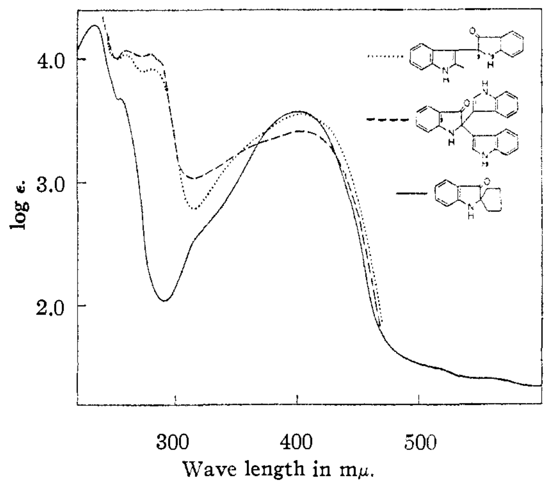
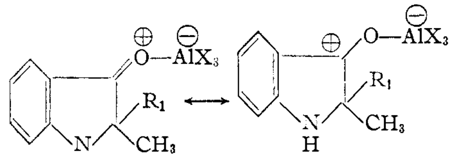
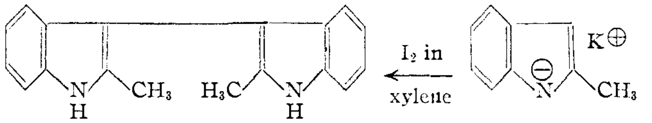


Fig. 1.—Characteristic indoxyl spectra of compounds I, IX and XXII (in ethanol).

very small yield by Toffoli,[8] was synthesized by an adaptation of the method of Knoevenagel. The potassium salt of methylketol (XIV) in xylene reacted with iodine to give XIII in fair yield (infrared spectrum Fig. 2B, ultraviolet spectrum Fig. 3).

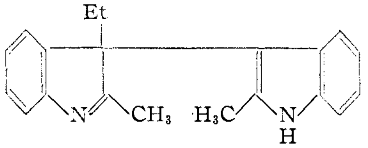


XI XII



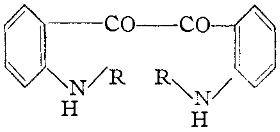
XIII XIV

The attempt to prepare XV by the reaction of ethylmagnesium iodide with IX gave unreacted starting material and methylketol. The carbonyl group in IX, inactivated by conjugation with the amino group, is highly hindered by two bulky ortho substituents.

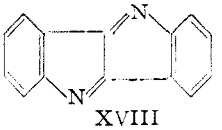


XV

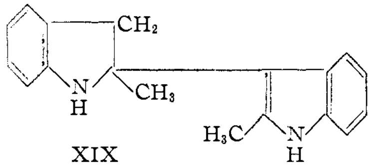
XIII is very stable to ozonolysis, which should lead to *o,o'*-diacetaminobenzil (XVI). By treatment of the crude ozonization product with dilute mineral acid we arrived at a small amount of a hydrochloride, m.p. 316–320° (picrate, m.p. 221°), the analysis of which did not allow of a decision between the possible hydrochlorides of structures XVII and XVIII or a similar condensation product[15,16] containing water of crystallization.



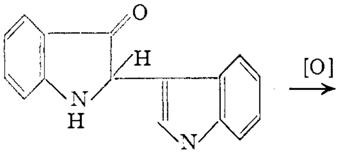
XVI, R = CH_3CO
XVII, R = H



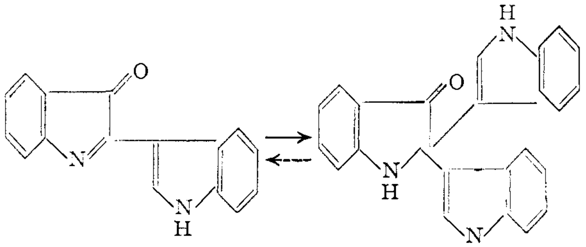
XVIII



XIX



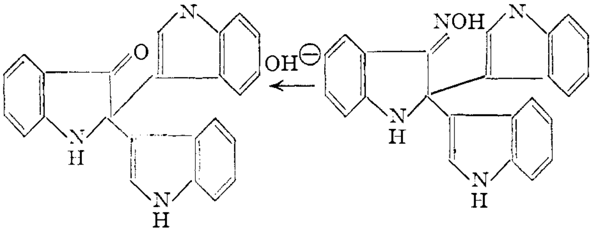
XX, leucoindoxyl red



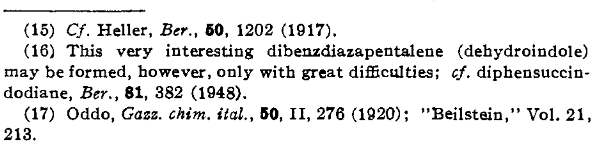
XXI indoxyl red XXII

The action of lithium aluminum hydride on IX furnishes a second reduction product of basic nature; it is 2-methyl-2,3'-[2'-methylindyl]-2,3-dihydroindole XIX. The compound is stable to acid, forms a hydrochloride and chromoisomeric (yellow → red) picrate. The infrared absorption spectrum (Fig. 2D) is interesting, because it shows clearly the difference between the absorption of an anilino-NH (a) and an indole-NH (b) and the effect of salt formation in such a case (Fig. 2E).

The oxidation by air and light[4,6,17] or by peracetic acid[9] of indole itself leads to indoxyl, which can react further to yield either indigo or a trimeric condensation product $C_{24}H_{17}ON_3$ (XXII),



XXIII XXIV indole red



XXII XXV

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(15) *Cf.* Heller, *Ber.*, **50**, 1202 (1917).

(16) This very interesting dibenzdiazapentalene (dehydroindole) may be formed, however, only with great difficulties; *cf.* diphensuccindodiane, *Ber.*, **81**, 382 (1948).

(17) Oddo, *Gazz. chim. ital.*, **50**, II, 276 (1920); "Beilstein," Vol. 21, 213.

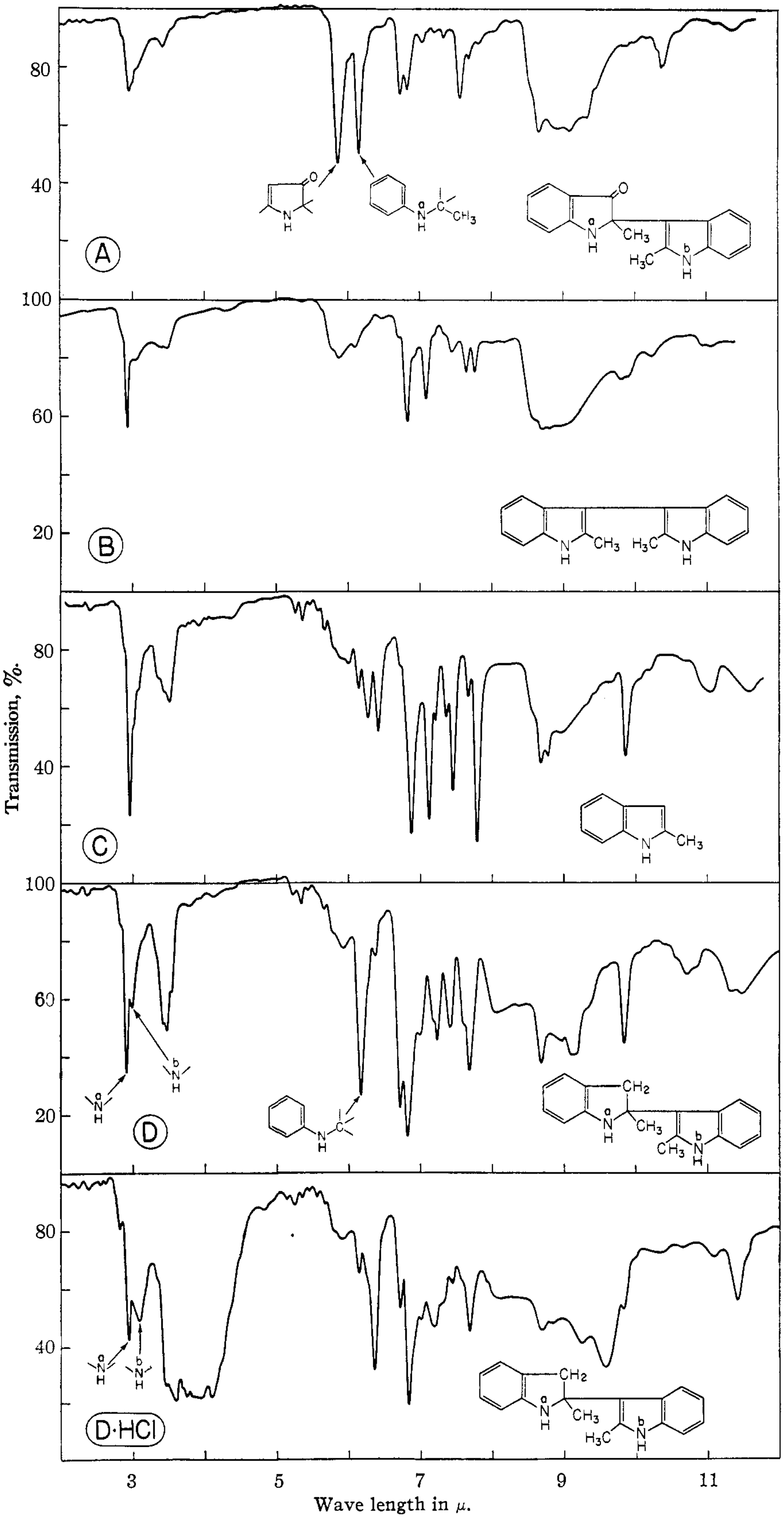

Fig. 2.—Infrared spectra (in chloroform).

probably *via* leucoindoxyl red (XX)[18] and indoxyl red (XXI).[19] The latter is known to be capable of add-

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(18) Seidel, *Ber.*, **77**, 789 (1944).

(19) Seidel, *ibid.*, **77**, 797 (1944).

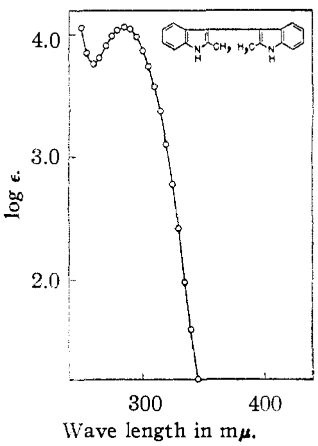
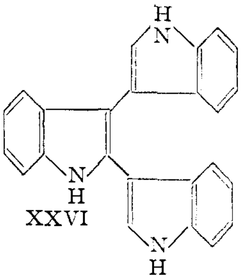
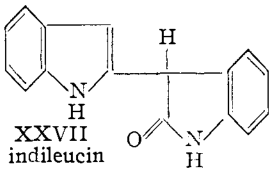


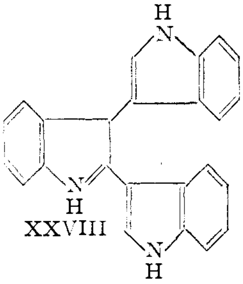
Fig. 3.—Ultraviolet absorption spectrum of β,β′-dimethylketyl (bis-(α-methyl)-β-indyl, XIII). The low values for log ε indicate some steric inhibition of resonance between the two methylketyl residues caused by the two methyl groups.

ing another molecule of indole in glacial acetic acid solution to yield α-diindyl-ψ-indoxyl (XXII).[19,20] We have obtained XXII directly from indole and dilute peracetic acid and identified the compound by comparison with a sample of α-diindyl-ψ-indoxyl synthesized from indole and $^1/_3$ mole of sodium nitrite in dilute sulfuric acid according to Seidel,[21] a sequence of reactions that may well lead through a mononitroso derivative XXIII, and, after hydrolytic removal of the nitroso group followed by nitrosation at position 3 (*cf.* Liebermann nitroso reaction)[22] and dehydrogenation, to indole red (XXIV). The addition of indole to the latter would result in the labile blue-red dye (XXV) which is then converted into XXII by the action of alkali.


XXVI


XXVII
indileucin

We obtained compound XXII in two isomeric forms differing in melting point (204°, 245°).[23] Both forms have practically the same infrared absorption spectrum (Fig. 4A). The ultraviolet spectrum (Fig. 1) shows the presence of the indoxyl chromophor. Both modifications, on reduction with lithium aluminum hydride, did not give dihydro derivatives but again (*vide supra*) under loss of water directly the rearranged compound, presumably 2,3-di-[3′-indyl]-indole (XXVI). The infrared spectrum of this compound is characteristic of an indolic compound and rules out the presence of a dihydroindole element. No basic product was formed in this reduction. A solution of XXVI in ethyl alcohol gave the ultraviolet spectrum shown in Fig. 5 which, however, changed on standing as a consequence of oxidation by air. The compound which was obtained from a solution of XXVI in ether or alcohol on addition of a drop of hydrochloric acid was first thought to be an oxidation product, *e.g.*, indileucin (XXVII).[24,25] This new compound turned out to be the hydrochloride of 2,3-di-[3′-indyl]-ψ-indole (XXVIII). The infrared spectrum (Fig. 4C) of this hydrochloride shows the characteristic indolenine band, usually at 6.10–6.30 μ, displaced to almost 6.40 μ, an effect probably caused by the conjugation of the —C=N bond with the two indyl substituents. Some bathochromic effect of salt formation is shown in the partial shift of absorption to longer wave lengths (Fig. 5). Solutions of XXVIII darken rapidly on exposure to air and light.


XXVIII

The addition of certain oxidants to such a solution produces striking blue to violet colors typical of molecules containing both indole and indolenine elements.[14,26]

Experimental[27]

2-Methyl-3,3′-[2′-methylindyl]-indole (3,3′-Dimethylketyl) (XIII).—Two grams of 2-methyl-2,3′-[2′-methylindyl]-indoxyl (IX), prepared from methylketol (VIII) by the action of hydrogen peroxide in glacial acetic acid in 90% yield according to Witkop,[9] was slowly added to a suspension of 1.1 g. of lithium aluminum hydride in 20 ml. of absolute ether. The mixture after refluxing for 4 hours was almost colorless. After decomposition with ice and water the layers were separated. The ether phase was dried over anhydrous sodium sulfate, concentrated to a volume of 10 ml., and left overnight in the refrigerator. There was obtained 0.8 g. of colorless glistening prisms, m.p. 231–234° (sintering 221°).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20. Found: C, 83.07; H, 6.25.

Synthesis of 2-Methyl-3,3′-[2′-methylindyl]-indole (XIII) from Methylketol (VIII).—To 300 mg. (7.65 millimoles) of potassium metal, chopped into small pieces, in 30 ml. of xylene was added 1.0 g. of 2-methylindole in 40 ml. of xylene. The mixture was refluxed for 12 hours. Some unreacted potassium was removed from the reaction mixture

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[20] Seidel, *Ber.*, **83**, 20 (1950); the name used there for XXII is α-diindylisatin.

[21] Seidel, *ibid.*, **77**, 805 (1944).

[22] Schmitz-Dumont, Hamann and Gellert, *Ann.*, **504**, 3 (1933).

[23] Oddo (ref. 4) reports similar dual melting points (207°, 269°). However, his molecular weights (196, 221, 249), obtained by the cryoscopic method in glacial acetic acid, as well as his analytical figures ($C_{16}H_{12}N_2O$) would indicate the reversible nature of reactions XX $\rightleftarrows$ XXI $\rightleftharpoons$ XXII. In our investigation we did not observe any deviations from the molecular weight (Rast method) and analytical data calculated for α-diindyl-ψ-indoxyl.

[24] *Cf.* Forrer, *Ber.*, **17**, 978 (1884).

[25] Similarly Oddo (ref. 4) claims to have obtained indirubin by the action of hydrochloric acid on his "di-[indyl-3]-ether" (probably XX or XXII).

[26] The possibility of such a sequence of transformations has to be borne in mind when following the fate of indole in enzymatic oxidations, such as in the metabolism of *chromabacterium violaceum* leading to the pigment violacein [Beer, Clarke, Khorana and Robertson, *J. Chem. Soc.*, 885 (1949)].

[27] Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and his associates (Microchemical Laboratories, Massachusetts Institute of Technology) for analyses.

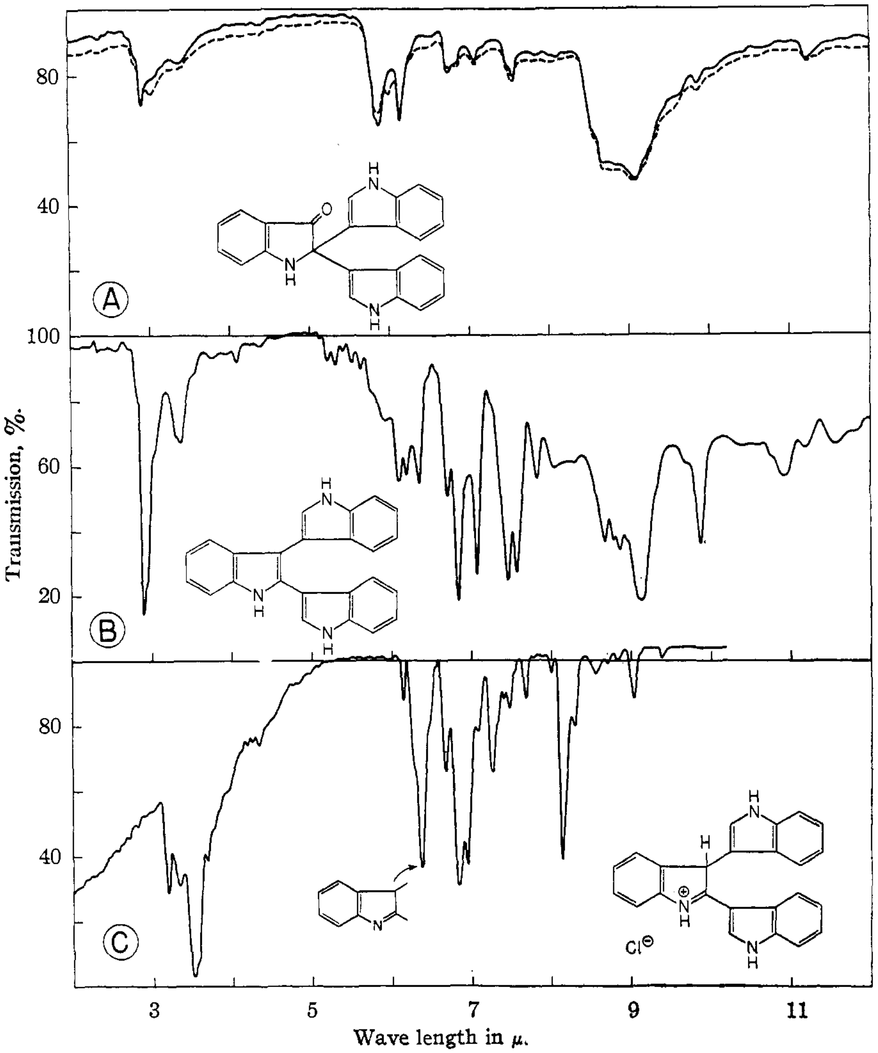

Fig. 4.—Infrared spectra (A and B in chloroform; C in nujol).

and 0.96 g. (3.8 millimoles) of iodine in xylene solution was added to the cool suspension of the potassium salt of the methylindole. After standing for 10 hours at room temperature the reaction mixture was filtered and the xylene removed under vacuum. The dark residue, approximately 0.8 g., was dissolved in chloroform and filtered through a column of aluminum oxide (standardized according to Brockmann), 15 cm. long and 1.2 cm. diameter and eluted with about 50 ml. of chloroform until the elution began to be red in color. The chloroform solution on concentration yielded 0.22 g. of colorless glossy prisms, which were washed several times with chloroform; m.p. 234° (sintering 220°), no depression on admixture with the product from the lithium aluminum hydride reduction of IX.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20. Found: C, 83.21; H, 6.03.

Attempted Ozonolysis of 2-Methyl-3,3′-[2′-methylindyl]-indole.—When a vigorous stream of oxygen containing 3% ozone was bubbled through a solution of 0.6 g. of dimethylketyl (XIII) in 60 ml. of chloroform under cooling, the solution darkened considerably. No excess of ozone was passing the reaction mixture at that time. After concentration of the solution to 10 ml. and cooling 0.23 g. of starting material was recovered. The mother liquor was shaken under hydrogen in the presence of 50 mg. of palladium and took up 8.6 cc. of hydrogen in the course of 10 minutes. This solution was evaporated to dryness and the residue was digested with 2 ml. of an equal mixture of ethyl alcohol and concentrated hydrochloric acid on the steam-bath for 1 hour. The residue crystallized from ethanol in colorless crystals, m.p. 213–216°, colorless melt resolidifies at 220°, 316–320° blackening and sintering. Found: C, 58.50; H, 5.59. The monohydrochloride of *o,o*′-diaminobenzil, or a condensation product containing water of crystallization, would require: C, 60.76; H, 4.70. The paucity of the material did not allow of further investigation. The picrate, pale yellow rods from methanol, melted at 221°, resolidified immediately to feather-like crystals and melted a second time at 240–243° under decomposition.

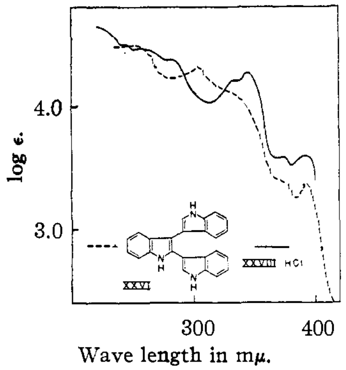

Fig. 5.—Ultraviolet absorption spectra of compounds XXVI and XXVIII in ethyl alcohol.

2-Methyl-2,3′-[2′-methylindyl]-2,3-dihydroindole (XIX).—The ether mother liquor from the lithium aluminum hydride reduction of IX, from which most of the sparingly soluble dimethylketyl (XIII) had been separated by crystallization, was extracted with several portions of 0.1 *N* hydrochloric acid. The combined acid extracts were basified and extracted with ether. After drying over anhydrous sodium sulfate, the ether solution was evaporated to yield 0.43 g. of the free base which crystallized from chloroform–petroleum ether (5:1) in colorless crystals, m.p. 149–151° (sublimation at 140°; opaque melt became clear and colorless at 156°).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92. Found: C, 81.85; H, 6.98.

Hydrochloride.—A solution of the above base in dilute hydrochloric acid on evaporation to dryness in the desiccator left the crystalline hydrochloride, which, after recrystallization from ethyl alcohol containing a few drops of ether, formed colorless prisms, m.p. 198°.

Anal. Calcd. for $C_{18}H_{18}N_2 \cdot HCl$: C, 72.35; H, 6.41. Found: C, 72.05; H, 6.85.

Picrate.—From the aqueous solution of the above hydrochloride an aqueous saturated solution of picric acid precipitated the *yellow* picrate. On recrystallization from absolute methanol this picrate appeared in the form of *bright red* prisms, m.p. 169–171°.

Anal. Calcd. for $C_{18}H_{18}N_2 \cdot C_6H_3O_7N_3$: C, 58.65; H, 4.31. Found: C, 58.64; H, 4.37.

2,2-Bis-[3′-indyl]-indoxyl (2,2-Diindyl-ψ-indoxyl) (XXII).—Ten grams of indole was treated with hydrogen peroxide in glacial acetic acid (30 ml. instead of 20 ml. as in ref. 9) following the previous directions.[9] The dried ether solution of the crude reaction products was filtered through a column containing about 200 g. of aluminum oxide (Brockmann). By fractional elution with small portions of ether two different crystalline fractions were obtained:

A. Low Melting Modification.—The crystalline fraction more easily eluted from the column was recrystallized from methyl alcohol. The dark red mother liquor apparently contained indoxyl red. The yellow crystals melted at 202–204° forming a yellow melt with bubbles, sintering at 195°; crystalline transformation 140–160°; melt resolidified at 212° to tufts of yellow needles within the darkening melt; second m.p. 242–244°.

Anal. Calcd. for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.57; mol. wt., 363. Found: C, 79.14; H, 4.87; N, 10.93; mol. wt., could not be determined because of the intensely dark red color of the solution of the compound in camphor.

B. Higher Melting Modification.—The subsequent ether elutions yielded crystals which, after recrystallization from methanol, melted at 243–245.5° (dec., darkening starting at 210°). A mixed melting point with synthetic α-diindyl-ψ-indoxyl prepared according to Seidel[21] showed no depression.

Anal. Calcd. for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.57; mol. wt., 363. Found: C, 78.80; H, 4.82; N, 11.32; mol. wt., 395 (Rast).

Reduction of α-Diindyl-ψ-indoxyl (XXII) with Lithium Aluminum Hydride.—Powdered diindyl-ψ-indoxyl (420 mg., m.p. 204°) was added cautiously to 500 mg. of lithium aluminum hydride in 20 ml. of ether, producing vigorous reaction and an orange solution. After an hour refluxing the solution was colorless. The mixture was decomposed with ice and water, and the ether layer separated and dried over anhydrous sodium sulfate. On evaporation an almost colorless lacquer was obtained, which was taken up in benzene and filtered through a column of 15 g. of aluminum oxide. Three zones, brown, yellow-green and red-purple, were formed in that order from top to bottom. Elution with benzene, evaporation of the first elution containing all colorless material and recrystallization of the residue from benzene–petroleum ether yielded colorless crystals, m.p. 150–155° (sintering 143°; clear colorless melt).

Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10; mol. wt., 347. Found: C, 82.55; H, 5.51; N, 12.32; mol. wt., 355 (Rast).

2,3-Di-[3′-indyl]-ψ-indole Hydrochloride (XXVIII).—To a methanol solution of the above triindyl was added a drop of concentrated hydrochloric acid. The resulting yellow-brown solution yielded a brown crystalline residue on evaporation in the desiccator. This residue was dissolved in ethanol and decolorized with charcoal. The almost colorless solution displayed a striking blue fluorescence. Crystals were obtained by keeping the solution in a closed test-tube at 60°. The resulting short, glossy needles melted at 212–214°; the quiet yellow melt contained residual needles which melted at 245–250°.

Anal. Calcd. for $C_{24}H_{19}N_3 \cdot HCl$: C, 74.90; H, 5.20; N, 10.90. Found: C, 75.12; H, 5.12; N, 10.73.

When 0.5 g. of the higher melting diindyl-ψ-indoxyl was reduced with lithium aluminum hydride in the same fashion as described above, the crude reduction product in ethereal solution, on the addition of a few drops of ethereal hydrochloric acid, directly deposited a crystalline precipitate which could be washed with ethyl alcohol. The material was identical with the above hydrochloride. The salt can be reconverted into the free base with alkali and ether. The infrared spectrum of the recovered base (in chloroform) is identical with the original base. Oxidants, such as nitric acid, produce a magnificent purple-violet color which fades on addition of excess oxidant. The reaction with chloranil in alcoholic hydrochloric acid (*cf.* ref. 14) did not produce any significant color.

Acknowledgment.—We are indebted to Research Corporation, New York, for financial support of this investigation.

Summary

β-Hydroxyindolenines, indolones and indoxyl derivatives, the intermediates in the oxidation of certain indole compounds, show a remarkable ability of adding nucleophilic elements to their reactive >C=N— double bond.

Lithium aluminum hydride not only reduces disubstituted ψ-indoxyl derivatives, formed from methylketol and indole by this scheme, but also effects a migration of the substituent with the greater migratory aptitude. This rearrangement can be used for the structural elucidation of indoxyl compounds of unknown constitution.

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