distilled azeotropically with 50 cc. of benzene in presence of 0.5 g. of *p*-toluenesulfonic acid. When the expected quantity of water had been liberated, the solution was neutralized with calcium carbonate, filtered and distilled; b.p. 111° (22 mm.); yield 31 g. (70%); $n^{21}D$ 1.5108; $d^{21}{}_4$ 1.085; *MR* calcd. 44.35, *MR* found 43.31.

*Anal.* Calcd. for $C_8H_{14}OS$: C, 60.8; H, 8.8. Found: C, 60.6; H, 8.6.

No reaction took place when the product was refluxed with lithium aluminum hydride in dioxane for 4 hours.

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

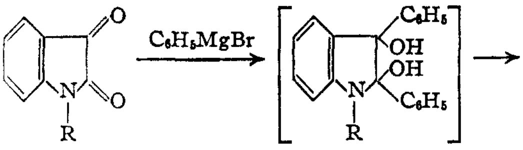
# Twofold Wagner-Meerwein Rearrangements. II

BY BERNHARD WITKOP[1] AND ARVID EK[2]

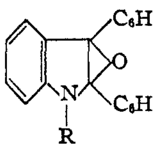
The reaction of N-methylisatin with phenylmagnesium bromide leads to N-methyl-2,2-diphenyl-ψ-indoxyl (VI), previously considered to be 2,3-diphenyl-2,3-epoxy-1-methylindoline (III) and to N-methyl-3,3-diphenyl-ψ-oxindole (XIV). The mechanism of the formation of the two products is discussed and amplified by the direct conversion of the indoxyl (VI) to the oxindole (XIV) by the action of phenyl Grignard reagent as well as of boron trifluoride in ether. N-Unsubstituted ψ-indoxyls, such as 2,2-dibenzyl-ψ-indoxyl (XV), undergo this twofold 1,2-shift not only under acid conditions, but also with sodium hydroxide in isoamyl alcohol. The significance of these transformations is discussed in terms of the possible intermediate indole epoxide structures, a number of cases in the literature is taken up and revised, and the potential usefulness of these twofold rearrangements with regard to synthetic studies in the strychnine and gelsemine series is pointed out.

Although the double bond in the pyrrole part of indoles possesses some individual character and independence,[3] no indole epoxide has ever been prepared.[4] Where such structures have been proposed, as for the alkaloid quinamine,[5] subsequent revision[6] led to a different formulation. However, the literature still lists a number of indole epoxides. Although such epoxides have never been isolated as such, they may have some significance as the hypothetical transitory intermediates in a number of interesting, hitherto-unrecognized twofold Wagner-Meerwein rearrangements.

When N-substituted isatins (I) react with phenylmagnesium bromide[7-10] two products are formed which have been presented as 2,3-diphenyl-2,3-epoxy-1-methylindoline (III), resulting by dehydration from the parent glycol (II), and 3,3-diphenyl-1-methyloxindole (XIV). When we repeated this reaction under carefully controlled conditions, we obtained the two products as yellow rods, m.p. 174-175° (the literature[9] records 137.5-138.5°),



I II



III, R = $CH_3$
IV, R = $C_2H$
V, R = $C_6H$

and colorless needles, m.p. 177.5 (previous m.p. 171-171.5°).

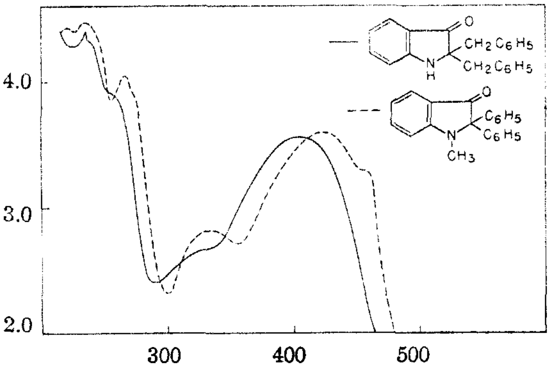
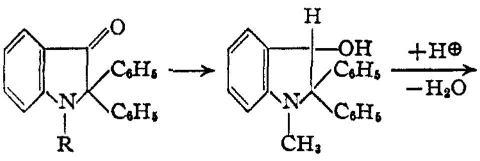


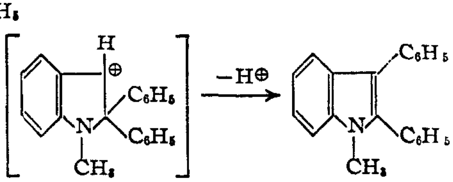
Fig. 1.—Ultraviolet spectra in ethyl alcohol.

The ultraviolet (Fig. 1) and infrared (Fig. 2A) spectra of the yellow compound showed it to be the indoxyl derivative VI. Using the method previously employed in the structural elucidation of



VI, R = $CH_3$
VII, R = $C_2H_5$
VIII, R = $C_6H_5$

IX



X XI

indoxyl compounds of unknown constitution[11,12] we reduced VI to the alkamine IX which, on treatment with hydrogen chloride in ether, underwent a Wagner-Meerwein rearrangement to yield, *via* the intermediate X, 1-methyl-2,3-diphenylindole

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[1] National Heart Institute, Washington 14, D. C.

[2] Research Corporation Fellow 1949-1950.

[3] B. Witkop, *Ann.*, **556**, 105 (1944).

[4] B. Witkop and H. Fiedler, *ibid.*, **558**, 91 (1947).

[5] R. Goutarel, M. M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

[6] B. Witkop, THIS JOURNAL, **72**, 2311 (1950).

[7] M. Kohn and A. Ostersetzer, *Monatsh.*, **34**, 787 (1913).

[8] R. Stollé, *J. prakt. Chem.*, **135**, 345 (1932).

[9] F. J. Myers and H. G. Lindwall, THIS JOURNAL, **60**, 2153 (1938).

[10] W. C. Sumpter, *ibid.*, **64**, 1736 (1942).

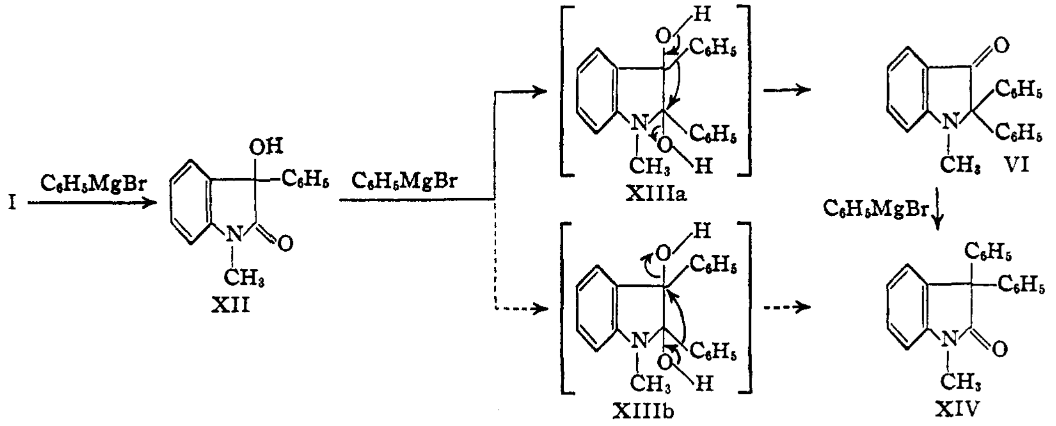
[11] B. Witkop, *ibid.*, **72**, 614 (1950).

[12] B. Witkop and J. B. Patrick, *ibid.*, **73**, 713 (1951).

(XI, Fig. 2C) identical with a specimen synthesized from benzoin and methylaniline.[13,14]

These results make it necessary to assign to the analogous N-ethyl- and N-phenyl "epoxides" (IV[9] and V[8,10]) the corresponding indoxyl structures VII and VIII.

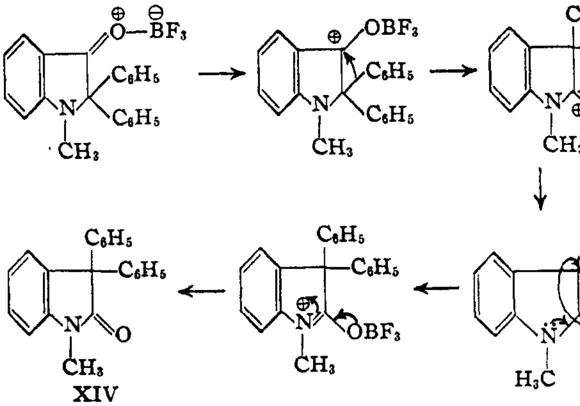
The following scheme presents an explanation for the concomitant formation of indoxyl and oxindole derivatives



XII XIIIa VI XIIIb XIV

the first product formed in the reaction of N-methylisatin with one mole of Grignard reagent is N-methyl-3-phenyldioxindole (XII).[15] In the case of isatin itself the dioxindole is the final product.[16] XII, however, can react with another mole of Grignard reagent to give the non-isolable glycol XIII, rearranged by excess Grignard reagent[17] or acid[9] to the indoxyl VI or to the oxindole XIV. These rearrangements are reminiscent of the reactions of 9-acetyl-10,11-dihydroxyhexahydrocarbazole.[18]

The direct formation of the oxindole XVII from the indoxyl VI has now been effected rapidly and in excellent yield by the action of two reagents with Lewis acid character, *viz.*, by phenyl Grignard reagent and by boron trifluoride in ether solution. This change in both cases may involve the following intermediate steps (formulated with boron trifluoride).



XIV

A related sequence of steps was discussed recently in the reaction of *spiro*-cyclopentane-1,2-$\psi$-indoxyl [with methylmagnesium iodide leading to *spiro*-cyclopentane-1,3′-$\psi$-2-methylindole].[19] The intermediate epoxide structure, not postulated and sterically impossible in the latter case, may only possess the character of a *quasi* three-membered cyclic intermediate. This we believe to hold even more in the base-catalyzed indoxyl → oxindole conversion to be discussed now.

We were interested in testing an N-unsubstituted indoxyl for its behavior toward acid *and* base. 2,2-Dibenzyl-$\psi$-indoxyl (XV) was prepared by the benzylation of indigo white according to Madelung.[20,21] Boron trifluoride etherate reacted with XV to give a red complex similar to, but somewhat weaker in color than, the analogous complex with VI. This complex, on refluxing in ether, faded and rearranged. The rearrangement product, 3,3-dibenzyl-$\psi$-oxindole (XX), was identified by comparison with the same compound synthesized in a new and simple way by direct benzylation of oxindole.[22] The same compound was obtained by the two different pathways as

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(13) M. B. Richards, *J. Chem. Soc.*, **97**, 977 (1910).

(14) E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **80**, 33 (1946); *C. A.*, **41**, 3094 (1947).

(15) M. Kohn and A. Ostersetzer, *Monatsh.*, **34**, 1748 (1913).

(16) M. Kohn and A. Ostersetzer, *ibid.*, **31**, 747 (1910); **32**, 905 (1911).

(17) M. Kohn and A. Ostersetzer, *ibid.*, **32**, 793 (1913).

(18) (a) *Cf.* J. B. Patrick and B. Witkop, THIS JOURNAL, **72**, 633 (1950). (b) NOTE ADDED IN PROOF: The preparation of 9-acetyl-10,11-dihydroxyhexahydrocarbazole [*cf.* A. Ek, H. Kissman, J. B. Patrick and B. Witkop, *Experientia*, in press] by the procedure of Milas and Sussman [THIS JOURNAL, **58**, 1302 (1936)] as well as with osmium tetroxide [D. W. Ockenden and K. Schofield, *Nature*, **168**, 603 (1951)] leaves little doubt about the *cis*-configuration of this glycol, which fails, however, to give an acetonyl derivative [B. Witkop, THIS JOURNAL, **72**, 613 (1950)]. The non-isolable intermediary glycol XIII should have the *trans*-configuration in analogy to the formation of *trans*-7,8-diphenylacenaphthenediol-7,8 by the reaction of phenylmagnesium bromide on acenaphthenequinone [W. E. Bachmann and E. J. Chu, *ibid.*, **58**, 1118 (1936); P. D. Bartlett and R. F. Brown *ibid.*, **62**, 2927 (1940)]. The presence of the nitrogen in XIII makes positions 2 and 3 of the glycol susceptible to easy inversion, a process which probably precedes the subsequent (acid-catalyzed) pinacol rearrangement of the cis-glycol XIII.

(19) B. Witkop and J. B. Patrick, *ibid.*, **73**, 1558 (1951).

(20) W. Madelung, *Ber.*, **57**, 241 (1924); *cf.* J. E. Thesen, *Z. physiol. Chem.*, **23**, 25 (1897).

(21) The interesting reactions encountered in the benzylation of leuco indigo leading to cleavage of the indigo molecule will be discussed in a later paper.

(22) The formation of N-benzyloxindole would be expected in this reaction in analogy to Baeyer's synthesis of (liquid) N-ethyl-oxindole (A. Baeyer and W. Comstock, *Ber.*, **16**, 1705 (1883)); A. Michaelis, *ibid.*, **30**, 2814 (1897), obtained the compound crystalline by another method.

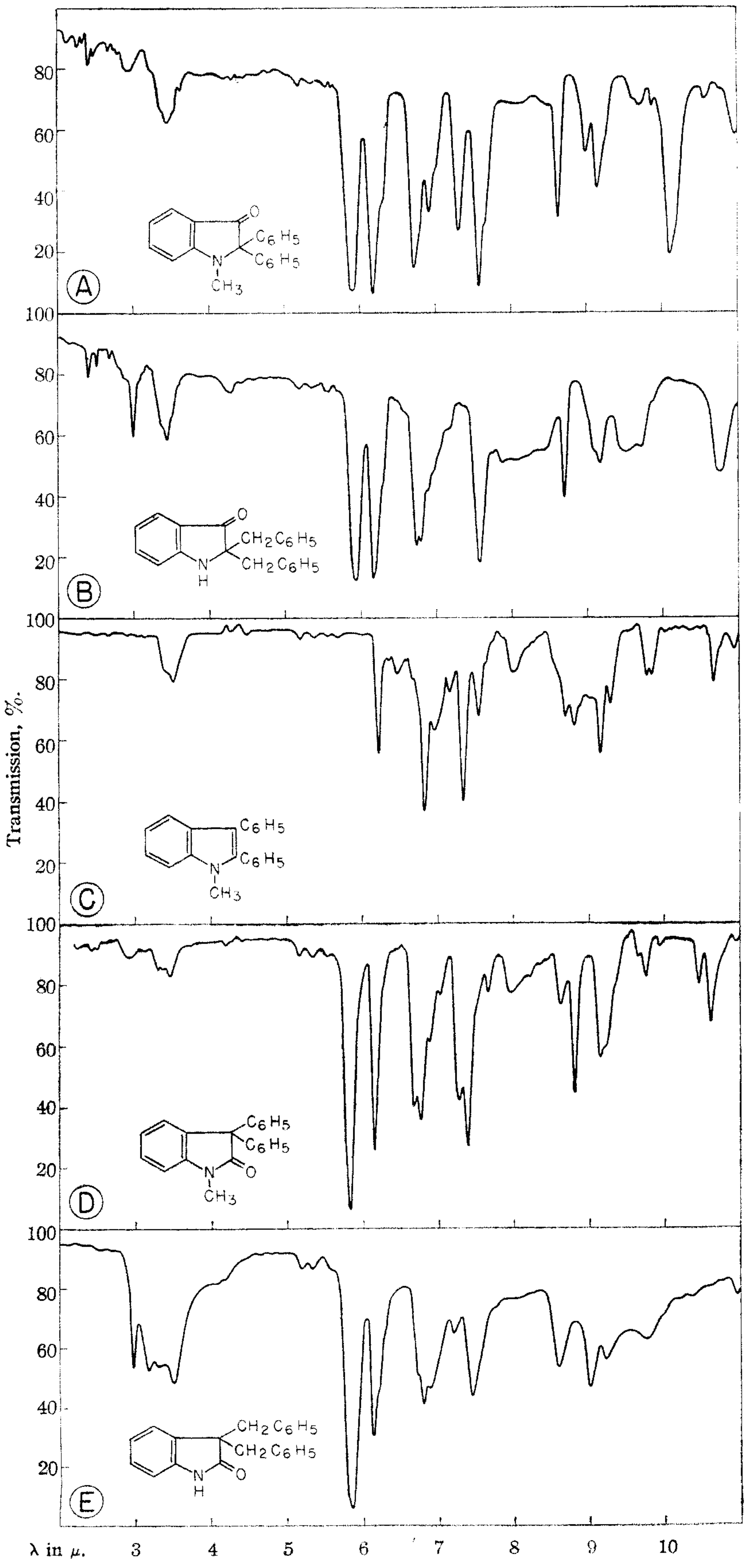


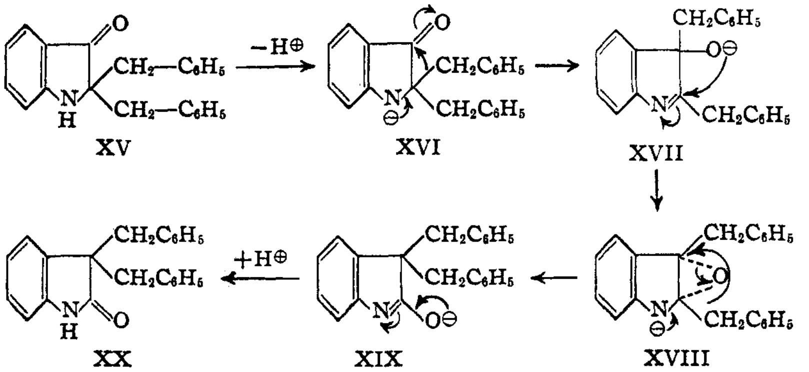
Fig. 2.—Infrared spectra in chloroform.

TABLE I

| Indoxyl compound | Hydrogenolysis, % of amine | Reduction, % of alkamine | Rearrangement, % of indole | Rearranging agent | Migrating group |
|---|---|---|---|---|---|
| 2,2-Bis-[3′-indyl]-ψ-indoxyl[12] | . . | . . | 70 | $LiAlH_4$ | 3-Indyl |
| 2-Methyl-2,3′-[2′-methylindyl]-ψ-indoxyl[12] | 30 | . . | 45 | $LiAlH_4$ | 3-Methyl-ketyl |
| *spiro*-[Cyclopentane-1,2′-ψ-indoxyl][11] | 40 | 55 | Quantitative | Acetic, picric, mineral acids | Ring expansion (5- to 6-memb.) |
| 2,2-Diphenyl-1-methyl-ψ-indoxyl (VI) | . . | 95 | Quantitative | HCl in ether | Phenyl |
| Isoquinamine[6] | . . | 90 | Forms new ring with acid | | . . . |

evidenced by a mixed melting point determination, and its composition and spectra (Figs. 1, 2E) showed it to be 3,3-dibenzyloxindole (XX).[23]

While the N-methylindoxyl VI does not give an insoluble Grignard complex and is not changed by sodium in isoamyl alcohol, the N-unsubstituted dibenzylindoxyl (XV) forms an orange-red precipitate with methylmagnesium iodide and shows a deepening of color with KOH in amyl alcohol as the result of the formation of the anion XVI. After refluxing for eight hours the oxindole (XX) can be isolated from the reaction mixture. The changes taking place under these conditions may be pictured in the following way



As mentioned above, the epoxide XVIII can only be a *quasi*-cyclic intermediate, since the *spiro*-cyclohexane-ψ-indoxyl (XXIV), presumably formed from the parent disubstituted phenylglycine (XXII),[24] underwent rearrangement under the conditions of alkali fusion to give the oxindole XXVI. In the case of the alkali fusion of the lower homologous anilinocyclopentanecarboxylic acid (XXI)[25] the first rearrangement of the intermediate indoxyl (XXIII)[26] would lead to an equivalent of 11-hydroxytetrahydrocarbazolenine, which under these extreme conditions forms the stablest compound possible, *viz.*, carbazole (XXV). Likewise, anilinoisobutyric acid[27] gave 3,3-dimethyloxindole.[28]

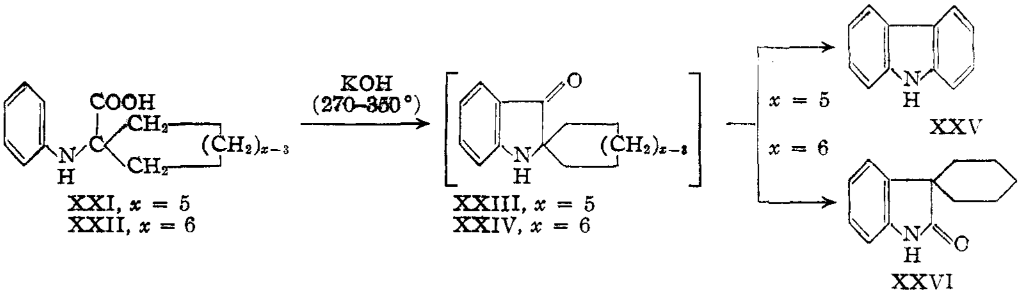
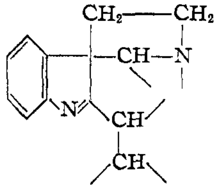


Table I correlates the ratios of the products resulting from reduction (alkamines), hydrogenolysis[29] (amines), and rearrangement (indoles) of the parent indoxyl derivatives studied so far. It appears that *gem*-disubstituted ψ-indoxyls with two bulky substituents next to the carbonyl group, such as two indyl- or phenyl groups or a quinuclidine and β-hydroxyethyl chain as in the case of isoquinamine, do not undergo hydrogenolysis; they form carbinols that can either be isolated or, if the migrating group possesses unusually high migrational aptitude, undergo rearrangement directly in the process of reduction.

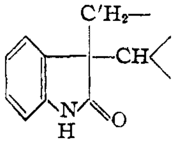
These twofold 1,2-shifts reported here and in the preceding paper[19] offer a potential route to useful intermediates approaching the characteristic *spiro*-structures (XXVII, XXVIII) present in the alkaloids strychnine and, presumably, gelsemine[30] and similar indole alkaloids presently under investigation.

## Experimental[31]

**2,2-Diphenyl-1-methyl-ψ-indoxyl (VI).**—Eight grams of 1-methylisatin, purified *via* the barium salt according to Kohn and Ostersetzer,[32] was dissolved in 50 ml. of benzene, and the warm solution was added through a steam-jacketed funnel in the course of 10 minutes to a solution of phenylmagnesium bromide from 6.1 g. of magnesium and 39.3 g. of bromobenzene in 150 ml. of ether and 100 ml. of benzene.



XXVII



XXVIII

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[23] H. Leuchs and H. Schulte-Overberg, *Ber.*, **64**, 1902 (1931).

[24] R. L. Betts, R. Muspratt and S. G. P. Plant, *J. Chem. Soc.*, 1310 (1927).

[25] S. G. P. Plant and J. A. Facer, *ibid.*, **127**, 2057 (1925).

[26] N. V. Sidgwick and S. G. P. Plant, *ibid.*, **127**, 209 (1925), report the formation of coördination complexes of *spiro*-[cyclopentane-1,2'-ψ-indoxyl] (XXIII) with alkali cations such as sodium, potassium and lithium. In the meantime it was shown [ref. 18 and THIS JOURNAL, **73**, 2188 (1951); ref. 28 and *J. Chem. Soc.*, 2127 (1950)] that the compound they dealt with was actually *spiro*-[cyclopentane-1,3'-ψ-oxindole]; their theoretical considerations based on the structural features of an indoxyl element, therefore, no longer hold. Based on the oxindole structure, one may consider formulations for the alkali coördination complexes similar to the ether-soluble and water-stable alkali complexes of certain enolones derived from precursors of methylreductic acid: G. Hesse and K. W. F. Böckmann, *Ann.*, **563**, 42 (1949).

[27] H. Bucherer and A. Grollé, *Ber.*, **39**, 991 (1906).

[28] S. G. P. Plant and R. Robinson, *Nature*, **165**, 36 (1950).

[29] *Cf.* L. H. Conover and D. S. Tarbell, THIS JOURNAL, **72**, 3586 (1950).

[30] Latest Literature: M. S. Gibson and R. Robinson, *Chemistry & Industry*, 93 (1951); and (added in proof) R. Goutarel, M.-M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta*, **34**, 1139 (1951).

[31] All melting points are corrected (Kofler block). The microanalyses were performed by Mr. S. M. Nagy and associates, Microchemical Laboratories, Massachusetts Institute of Technology.

[32] M. Kohn and A. Ostersetzer, *Monatsh.*, **37**, 25 (1916).

The *clear* brown (no color change) solution was refluxed for two hours, decomposed with 500 g. of ice and 20 ml. of concd. sulfuric acid and allowed to stand overnight. The gum which had separated solidified on rubbing and was filtered, washed with benzene and water and dried. The residue weighed 6.6 g. and consisted of a light brownish powder melting at 145–155°. This material, insoluble in benzene, became soluble after recrystallization from methanol or after chromatography on aluminum oxide. Repeated recrystallization from methanol gave pure yellow crystals, melting point 168–170°. Dilute solutions in polar solvents show an intense green fluorescence; in benzene the fluorescence is light blue. A one-gram sample was further purified by chromatographic adsorption on alumina from a petroleum ether–benzene (9:1) mixture following the standard procedure given by Reichstein and Shoppee.[33] Of the nine fractions thus obtained, fractions 2–7 had melting points above 170°; these were combined and recrystallized giving pure 2,2-diphenyl-1-methyl-ψ-indoxyl, subliming at 140°, m.p. 174–175°.

*Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72. Found: C, 83.98; H, 5.66.

**2,2-Diphenyl-3-hydroxy-1-methylindoline (IX).**—One gram of 2,2-diphenyl-1-methylindoxyl suspended in 40 ml. of ether was added to a suspension of 0.35 g. of lithium aluminum hydride in 25 ml. of ether. The yellow color and the fluorescence of the solution disappeared instantaneously. The mixture was allowed to stand overnight, decomposed with water and the ether layer separated after the addition of excess potassium sodium tartrate solution. The aqueous phase was extracted twice with ether, the combined extracts washed three times with water, dried over magnesium sulfate and evaporated to dryness in a stream of nitrogen leaving 0.96 g. of an almost colorless oil which could not be induced to crystallize. It was purified by chromatographic adsorption on alumina from petroleum ether–benzene solution (8:2); continued elution with the same solvent removed a trace of starting material; petroleum ether–benzene (1:1) and pure benzene eluted fractions which crystallized on scratching. A sample recrystallized from petroleum ether and a small amount of benzene had m.p. 124–126°.

*Anal.* Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35. Found: C, 83.49; H, 6.42.

**Hydrochloride.**—When less than the necessary amount of 2 *N* ethereal hydrochloric acid was added to a solution of 0.1 g. of the above compound (IX), in absolute ether the hydrochloride separated as a colorless crystalline powder which, after washing several times with absolute ether, showed a melting range from 85 to 105° (first softening, then sintering, then forming a slightly yellow bubbly melt). This hydrochloride is unstable and had to be analyzed immediately.

*Anal.* Calcd. for $C_{21}H_{19}NO \cdot HCl$: C, 74.12; H, 6.53; N, 4.12. Found: C, 73.84; H, 6.86; N, 4.01.

**2,3-Diphenyl-1-methylindole (XI).**—When the solution of the alkamine (IX) in ether was treated with an excess of ethereal hydrogen chloride, or when the above hydrochloride was allowed to evaporate from an alcoholic solution, fine needles were obtained which, after recrystallization from ethyl acetate–alcohol (1:1), melted at 137–138°. A mixture of (XI) with an authentic sample of 2,3-diphenyl-1-methylindole[13] showed no depression of melting point.

*Anal.* Calcd. for $C_{21}H_{17}N$: C, 89.01; H, 6.05. Found: C, 88.98; H, 6.01.

**Picrate.**—To a sample of the above indole dissolved in benzene was added a benzenic solution of picric acid and the resulting picrate was recrystallized from benzene to give fine brown-red needles, subliming at 140°, m.p. 160–161.5°. The mixed m.p. with an authentic sample[34] showed no depression.

**3,3-Diphenyl-1-methyl-ψ-oxindole (XIV). A. From 1-Methylisatin with Phenylmagnesium Bromide.**—The filtrate from the crystallization of the indoxyl-complex above was steam distilled to remove benzene and biphenyl, the residue was taken up in benzene, extracted with 2 *N* sodium hydroxide which removed appreciable amounts of dark colored (phenolic) material, washed with water, filtered and evaporated to dryness. The oily residue, 8.3 g., crystallized readily. Numerous recrystallizations from alcohol, benzene and ethyl acetate gave practically colorless material which still, however, fluoresced in solution. Chromatography of this material in petroleum ether–benzene (8:2) solution on alumina permitted the separation of a small amount of the indoxyl compound. The more strongly adsorbed oxindole was subsequently eluted with pure benzene. Recrystallization of the material from an ethyl alcohol–ethyl acetate mixture yielded perfectly colorless stubby needles of 3,3-diphenyl-1-methyloxindole, subliming at 145°, m.p. 176–177.5° (reported 171–171.5°; 175.5–176.5°).

The mixed melting point with the compound obtained by method B and C showed no depression.

**B. By Rearrangement of 2,2-Diphenyl-1-methyl-ψ-indoxyl with Phenylmagnesium Bromide.**—A solution of 1 g. of 2,2-diphenyl-1-methyl-ψ-indoxyl in 5 ml. of benzene was added to a solution of 1.04 g. of bromobenzene and 0.16 g. of magnesium in 5 ml. of ether. The clear light-tan mixture exhibited a slight fluorescence which disappeared in the course of four hours of refluxing. At the end of this period an excess of saturated ammonium chloride solution was added, the organic phase separated and washed repeatedly with water, dried over sodium sulfate and evaporated to dryness first in a stream of nitrogen and finally *in vacuo*. The residue, 0.82 g., of almost colorless crystals, was chromatographed on alumina.

| Fraction | Eluted with (ml.) | Weight, g. | Characterization | M.p., °C. |
|---|---|---|---|---|
| 1 | 20 benzene<br>80 pet. eth. | 0.025 | Colorless crystals | 55–69 |
| 2 | 20 benzene<br>80 pet. eth. | .03 | Oily colorless crystals | ....... |
| 3 | 30 benzene<br>70 pet. eth. | .004 | Yellow oil | ....... |
| 4 | 30 benzene<br>70 pet. eth. | .175 | Yellow crystals | 130–160 |
| 5 | 40 benzene<br>60 pet. eth. | .224 | Crystals with yellow tinge | 173–176 |
| 6 | 50 benzene<br>50 pet. eth. | .119 | Colorless crystals | 173–175.5 |
| 7 | 50 benzene<br>50 pet. eth. | .131 | Slightly yellow crystals | 161–166 |

Continued elution using finally ether gave only traces of yellow oils.

Fractions 5 and 6 were combined and recrystallized from a mixture of ethyl acetate and ethyl alcohol to give practically colorless prisms melting at 175.5–177° alone or mixed with authentic 3,3-diphenyl-1-methyloxindole.

**C. By Rearrangement of 2,2-Diphenyl-1-methyl-ψ-indoxyl with Boron Trifluoride.**—One-half gram of the indoxyl compound was refluxed with 10 ml. of freshly distilled boron trifluoride etherate for 10 minutes. The indoxyl initially went into solution with a strong *red* color which disappeared quickly on refluxing. The solution was poured into an excess of cold water, the ether was removed by warming on the steam-bath, and the remaining suspension of colorless crystals was cooled, filtered, washed with water, dried, and recrystallized from a mixture of ethyl alcohol and ethyl acetate, yielding 0.44 g. of colorless prisms and thick needles, subliming at 140° and melting alone and on admixture with 3,3-diphenyl-1-methyl-ψ-oxindole at 176–177.5°. The infrared spectra of the two compounds obtained by methods A and B were identical

*Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72. Found: C, 83.98; H, 5.74.

**3,3-Dibenzyl-ψ-oxindole (XX). A. By Rearrangement of 2,2-Dibenzyl-ψ-indoxyl (XV) with Boron Trifluoride.**—One-half gram of 2,2-dibenzyl-ψ-indoxyl, obtained by the benzylation of indigo white,[20] dissolved readily in 10 ml. of boron trifluoride etherate with *yellow* color and fluorescence. The solution turned black on refluxing, but the fluorescence persisted even after 45 minutes of refluxing. The reaction mixture was then cooled, poured into excess water and extracted repeatedly with ether. The ether extracts were washed with water, sodium bicarbonate solution and water again, dried over sodium sulfate and evaporated to dryness in a stream of nitrogen, leaving 0.47 g. of a brownish-red oil.

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(33) T. Reichstein and C. W. Shoppee, *Dis. Faraday Soc.*, 305 (1949).

(34) A. Bischler and P. Fireman, *Ber.*, **26**, 1345 (1893).

The oil was taken up in 10 ml. of benzene and 40 ml. of benzin was added. The supernatant intensely fluorescent liquid was poured onto a column containing 15 g. of aluminum oxide. The undissolved green precipitate was treated once more in the same fashion. Fractional elution of the column with a benzene–benzin mixture containing up to 50% benzene gave unchanged starting material. Further elution with benzene containing 10–20% of ether gave light pink crystalline material. The latter fractions were combined and sublimed at a bath temperature of 150–160° in a vacuum of 0.001 mm. The almost colorless sublimate, on recrystallization from benzene–benzin, gave well-shaped shining colorless rods subliming at 140° and melting, alone or mixed with synthetic 3,3-dibenzyl-ψ-oxindole, at 201–202°.

B. **By Rearrangement of 2,2-Dibenzyl-ψ-indoxyl with Sodium Isoamyl Oxide.**—A solution of 0.5 g. of 2,2-dibenzyl-ψ-indoxyl in 10 ml. of isoamyl alcohol was added to the cooled solution of 0.5 g. of sodium in 15 ml. of isoamyl alcohol. The mixture, which assumed a distinct *red* color, was refluxed for 8 hours under nitrogen. The resulting dark red solution was concentrated as much as possible on the steam-bath at 15 mm. The residue was taken up in ether, the ether extract was washed with water, dilute acid, sodium bicarbonate solution and then water again. After drying over sodium sulfate, benzene was added and the whole evaporated to dryness in a stream of nitrogen. The residue, on recrystallization from alcohol, yielded 0.1 g. of starting material. The mother liquor on concentration gave 0.4 g. of a red oil which was purified by chromatography similar to the procedure described above for the acid rearrangement. Starting material together with almost colorless non-fluorescent crystals was obtained by elution with benzene containing 4, 10 and 20% ether. Sublimation, followed by recrystallization from benzene–benzin yielded again colorless, shining rods, subliming at 140° and melting at 201–202°.

C. **By Benzylation of Oxindole.**—A solution of 1.3 g. of oxindole in 10 ml. of absolute alcohol was added to a solution of 0.23 g. of sodium in the same solvent. To this mixture was added 1.2 g. of benzyl bromide. This solution, on refluxing for 2.5 hours, deposited sodium bromide, turned light-red, and became neutral to moist litmus paper at the end of the refluxing period. The reaction mixture was concentrated in vacuum and poured into water. The resulting oil was extracted with benzene, the extract was washed with water, filtered and concentrated. The dried, slightly red solution was filtered through 5 g. of aluminum oxide which removed most of the color. The filtrate and washings were concentrated almost to dryness. Addition of benzene and scratching brought about crystallization. Recrystallization from ethyl acetate yielded 0.82 g. of well-shaped colorless shining rods subliming at 140° and melting at 202–203°, identical with the material obtained by methods A and B.

*Anal.* Calcd. for $C_{22}H_{19}NO$: C, 84.45; H, 6.12; N, 4.45. Found: C, 83.98; H, 6.08; N, 4.24.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

# Antitubercular Studies. I. N-Diphenylmethyl-4-alkylpiperidines[1,2]

BY PRICE TRUITT AND W. J. MIDDLETON

The preparations and properties of a number of N-diphenylmethyl-4-alkylpiperidines and N-(9-fluorenyl)-4-alkylpiperidines are described. None of the fluorenyl compounds showed appreciable antituberculous activity, *in vitro*, and the activity of the N-diphenylmethyl-4-alkylpiperidines was markedly affected by the nature of the 4-alkyl group.

The preparation of a number of N-diphenylmethyl-4-alkylpiperidines and N-(9-fluorenyl)-4-alkylpiperidines has been undertaken in order to study the correlation of antitubercular properties and the nature of the 4-alkylpiperidine moiety. These compounds are structurally related to other physiologically active diphenylmethyl derivatives, such as N,N-diethylaminodiphenylmethane.[3] According to a theory advanced by Burger, Graef and Bailey,[4] the activity of the tuberculostatic drug, 4,4′-diaminodiphenyl sulfone,[5] may be increased by introduction of other lipid solubilizing groups in place of the sulfone linkage. This has been borne out to some degree by the work of Kirkwood and Phillips[6] and Markees and Burger.[7] It seemed of interest to study a group of compounds with the 4-alkylpiperidine group attached to the methyl radical of diphenylmethane in order to determine the antituberculous activity of these derivatives. The similarity between the diphenylmethyl radical and the 9-fluorenyl radical made the inclusion of derivatives of the latter appear of interest.

The N-diphenylmethyl-4-alkylpiperidines were prepared by the catalytic hydrogenation of the N-diphenylmethyl-4-alkylpyridinium bromides. This approach represents the same general method used by Kröhnke and Fasold[8] in the synthesis of certain N-phenacylpiperidines. The 9-fluorenyl derivatives were prepared by the same procedures.

The initial condensation of the diphenylmethyl and 9-fluorenyl bromides with the 4-alkylpyridines was accompanied by the formation of colored products. The general nature of this type of material has been discussed in a paper by Pinck and Hilbert[9] and the colored products were discarded in the present investigation.

The condensation of diphenylmethyl bromide with 4-alkylpiperidines gave the desired products. However, the yields were very low, 8–10%, and too, this method entailed the prior tedious hydrogenation of the 4-alkylpyridines. In contrast, the hydrogenation of the quaternary salts proceeded readily at high or low pressure in the presence of reduced platinum oxide catalyst or palladium–charcoal catalyst. The rates of hydrogenation with the latter catalyst were slower but gave the same products. Raney nickel catalyst also gave the tertiary amines, but the yields were much

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(2) This paper represents part of a thesis submitted to the Graduate School by W. J. Middleton in partial fulfillment of the requirements for the M.S. Degree.

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