Biindolyls. II. 2-(3-Indolyl)-3*H*-pseudoindol-3-ones from the Condensation of Isatin α-Chlorides with Indoles[1]

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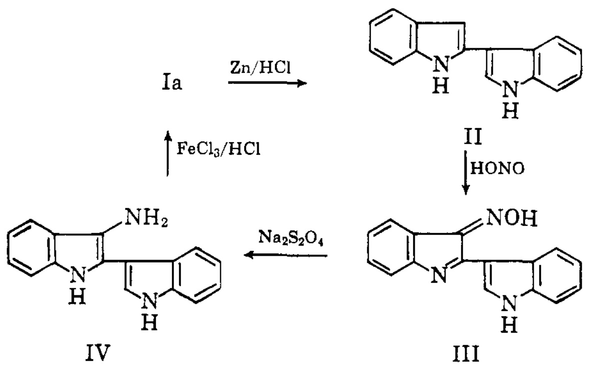
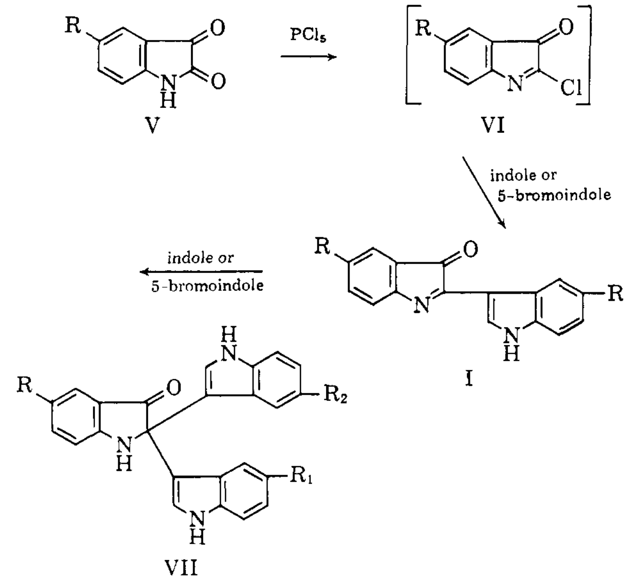
Condensation of isatin α-chlorides, prepared from isatin, 5-bromo-, and 5-nitroisatin, with indole or 5-bromoindole led to a series of 2-(3-indolyl)-3*H*-pseudoindol-3-ones (Ia–e) in yields of 36–74%. The parent member (Ia) of the series was identical with indoxyl red, prepared from 2,3′-biindolyl (II) *via* a series of previously known conversions (II, III, IV, Ia). The deep red indolones (Ia–d) were characterized by the facile addition of indole or 5-bromoindole across the imino bond to yield 2,2-bis(3-indolyl)indoxyl (VIIa) and several mono-, di-, and tribromo derivatives (VIIb–f). Zinc dust and hydrochloric acid in glacial acetic acid reduced Ia to II and Ib to 5′-bromo-2,3′-biindolyl (VIII); however, the poor yields (3–5%) contraindicated further preparative use of these reagents.

In continuation of our search[3] for more generalized methods for the synthesis of substituted 2,3′-biindolyls, our attention was drawn to a report[4] that indoxyl red (Ia), 2-(3-indolyl)-3*H*-pseudoindol-3-one, is quantitatively reduced by zinc and hydrochloric acid to 2,3′-biindolyl (II). Unfortunately, indoxyl red, the only known representative of this class, has heretofore been prepared most definitively *via* initial nitrosation of 2,3′-biindolyl (II) to indole red (III).[5] Subsequent reduction of this oxime with sodium dithionite gave 3-amino-2,3′-biindolyl (IV), which on oxidation with ferric chloride, and hydrolysis of the resulting imine, yielded indoxyl red (Ia).[6]





where:

	R	R$_1$	R$_2$
a.	H	H	H
b.	H	Br	H
c.	H	Br	Br
d.	Br	H	H
e.	Br	Br	H
f.	Br	Br	Br

where:

	R	R$_1$
a.	H	H
b.	H	Br
c.	Br	H
d.	Br	Br
e.	NO$_2$	Br

It has now been found that indoxyl red (Ia) and a number of bromo- and nitro-substituted congeners (Ib–e) may be easily obtained by reaction of isatin α-chlorides (VI. R = H, Br, NO$_2$) with indoles, as illustrated by the sequence: V, VI, I. The isatin α-chlorides were prepared by refluxing a suspension of the isatin (V. R = H, Br, NO$_2$) in benzene with an equimolar portion of phosphorus pentachloride, as previously reported for isatin[7] and various substituted isatins.[8] The isatin α-chlorides were not isolated, but were allowed to react *in situ* by addition of a benzene solution of indole (or 5-bromoindole) to the hot solutions. An immediate reaction occurred to produce a deep purple precipitate of pigment hydrochlorides, from which, after conversion to the free bases, the 2-(3-indolyl)-3*H*-pseudoindol-3-ones (Ia–e) were selectively extracted with benzene in yields of 36–74%. Indoxyl red (Ia) prepared in this manner was identical in all respects with an authentic sample prepared from 2,3′-biindolyl by Seidel's method[6] (sequence: II, III, IV, Ia) as described previously.

These deep red indolones (I) all showed characteristic visible absorption in the range 512–545 mμ, and were further characterized by their addition reactions[9] with indoles to form 2,2-bis(3-indolyl)indoxyls (VIIa–f). The tribromo compound (VIIf) was also prepared by oxidation of 5-bromoindole with hydrogen peroxide in acetic acid, after the method of Witkop and Patrick.[10] These adducts were prepared simply by heating the indolone (I) with an equimolar amount of either indole or 5-bromoindole in glacial acetic acid for a short time. In most cases the products began to crystallize almost

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[1] This investigation was supported in part by research grant C-4425 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

[2] Based on the M.S. thesis of D. S. Auld, Lehigh University, 1962.

[3] Part I of this series: T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).

[4] P. Seidel, *Ber.*, **77B**, 788 (1944).

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

[6] P. Seidel, *Ber.*, **77B**, 797 (1944).

[7] A. Baeyer, *ibid.*, **12**, 456 (1878).

[8] E. Kambli, *Helv. Chim. Acta*, **24**, 93 (1941); V. Q. Yen, N. G. Buu-Hoi, and N. D. Xuong, *J. Org. Chem.*, **23**, 1858 (1958).

[9] Seidel[6] has previously reported the addition of indole across the imino bond of indoxyl red (Ia) to form VIIa, which he called α,α-diindylisatin, and which is also produced by oxidation of indole with hydrogen peroxide in acetic acid.[10]

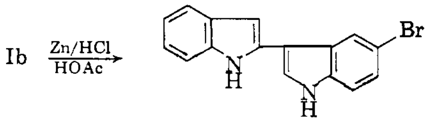
[10] B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951).

immediately from the hot mixture. The purified, canary yellow adducts (VII) showed a tendency to be thermally unstable above 200°, and because of this, exhibited somewhat erratic melting points, which appeared to be a function of the time of heating prior to melting (*cf.* experimental data for VIIf).

A particularly anomalous melting point behavior was observed in the case of 2-(5-bromo-3-indolyl)-2-(3-indolyl)indoxyl (VIIb), which was prepared both by addition of indole to Ib and by addition of 5-bromoindole to Ia. The freshly precipitated adduct (VIIb) melted with decomposition *ca.* 230–235°, but after recrystallization from aqueous ethanol had a melting point about 50° lower. Chromatographic purification gave an analytical sample of m.p. 184–186°. Witkop and Patrick[10] obtained compound VIIa in a low melting (m.p. 202–204°) and a high melting (m.p. 243–245.5°) modification, although in their example the higher melting form was the more stable.

Compound VIIe was also obtained by two alternate routes; namely, addition of indole to Id, and addition of 5-bromoindole to Ic. The identity of the adducts (VIIe) in this case, as well as in the example of the preceding paragraph, confirms the 2,2-bis(3-indolyl)indoxyl structure, since any mode of reaction other than addition of the β—C—H of the indole to the C=N bond of the 3*H*-pseudoindol-3-one, would have yielded non-identical adducts. Furthermore, the absorption spectra of all of the adducts (VIIa–f) were quite similar throughout the ultraviolet-visible region, and all showed a visible maximum (402–418 mμ) characteristic of the 2,2-disubstituted indoxyl structure.[10]

Several attempts to reproduce Seidel's reported[4] zinc dust reduction of indoxyl red (Ia) to 2,3′-biindolyl (II) gave a crude product in yields which did indeed appear to be nearly quantitative. However, this product was extremely crude (m.p. 100–150°) and on repeated recrystallization from xylene gave only a 3% yield of the desired product. A similar reduction of 2-(5-bromo-3-indolyl)-3*H*-pseudoindol-3-one (Ib) yielded only 5% of 5′-bromo-2,3′-biindolyl (VIII), which is the first known example of a 2,3′-biindolyl substituted only in the primed ring. The similarity of the ultraviolet absorption spectrum of VIII with the spectra of other known 2,3′-biindolyls[3] corroborated the structural assignment. Attempts to convert the remaining indolylindolones (Ic–e) to 2,3′-biindolyls were deferred, pending the investigation of more effective reducing agents.



VIII

Experimental

All melting points are corrected. Ultraviolet-visible spectra were determined in 95% ethanol on a Beckman DK-2A spectrophotometer; infrared spectra were run in potassium bromide at 1% weight concentration on a Perkin-Elmer Model 21 spectrophotometer.

2-(3-Indolyl)-3*H*-pseudoindol-3-one; "Indoxyl Red" (Ia) According to Seidel.[6]—2,3′-Biindolyl[11] was nitrosated as already described[5] to give a 67% yield of 2-(3-indolyl)-3*H*-pseudoindol-3-one oxime, indole red (III); m.p. 244.5–245.5° (lit.,[4,6] m.p. 245°); ultraviolet-visible spectrum: λ_{max}, mμ (log ε): 272 (4.55), 334 shoulder (3.73), 350 shoulder (3.60), 445 (3.84); infrared spectrum (cm.$^{-1}$): 3450 (O—H). Diacetyl derivative; m.p. 213.5–215° (lit.,[6] m.p. 214–215°); ultraviolet-visible spectrum: λ_{max}, mμ (log ε): 257 (4.17), 296 (3.72), 445 (3.29).

The indole red was converted (after Seidel,[6] *cf.* text) in 68% over-all yield to indoxyl red as black-red crystals which sintered indistinctly 195–197° dec. even after repeated recrystallization from 95% ethanol and from ethyl acetate (lit.,[6] m.p. 212°); ultraviolet-visible spectrum: λ_{max}, mμ (log ε): 275 (4.46), 346 shoulder (3.62), 522 (3.73); infrared spectrum (cm.$^{-1}$): 3205 (N—H), 1733 (C=O).

Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.02; H, 4.09; N, 11.38. Found: C, 78.10; H, 4.25; N, 11.35.

General Procedure for the Preparation of 2-(3-Indolyl)-3*H*-pseudoindol-3-ones (I) from Isatin α-Chlorides and Indoles.—A mixture of 0.050 mole of the appropriate isatin, 10.60 g. (0.051 mole) of phosphorus pentachloride, and 250 ml. of reagent grade benzene was refluxed until all of the reactants had dissolved and hydrogen chloride evolution had subsided (V. R = H, 2 hr.; R = Br, 3.5 hr.; R = NO_2, 6 hr.). The resulting deep red solution of the isatin α-chloride was cooled slightly below the boiling point and stirred vigorously while a solution of 0.050 mole of the appropriate indole in 50 ml. of benzene was added dropwise at a rate of 1 ml. per min. An exothermic reaction occurred, hydrogen chloride was evolved, and a deep maroon precipitate formed. The mixture was then stirred at reflux for an additional 2 hr. and filtered hot. The dark precipitate was washed on the filter with three 50-ml. portions of boiling benzene, then air dried. This product, which contained the hydrochlorides of the 2-(3-indolyl)-3*H*-pseudoindol-3-ones and another unidentified pigment, was then wetted with enough 95% ethanol to form a paste and neutralized by stirring with 150 ml. of 10% sodium bicarbonate solution for 1.5 hr. By the end of this time carbon dioxide evolution had ceased. The precipitated mixture of free bases was then collected by filtration, washed with water, oven dried at 110° for 2 hr., and finally extracted with 700 ml. of benzene in a Soxhlet extractor until the color of the extract around the cup had faded to a pale pink. The extraction cup retained the deeply colored (purple, maroon, or brown), benzene-insoluble by-products, whose structures have not been determined. The deep red benzene extract, which at this point contained some crystallized product, was evaporated to dryness to give the crude (yield basis) 2-(3-indolyl)-3*H*-pseudoindol-3-ones (Ia–e), which were purified for analysis by recrystallization from ethyl acetate. The compounds prepared by this procedure are described individually in the following paragraphs.

2-(3-Indolyl)-3*H*-pseudoindol-3-one (Ia) was prepared in 37% yield from isatin (*via* the α-chloride) and indole. The product formed deep red (almost black) crystals which sintered indistinctly at 197°. The ultraviolet-visible spectrum: λ_{max}, mμ (log ε): 274 (4.40), 338 shoulder (3.53), 522 (3.73), and infrared spectrum (cm.$^{-1}$): 3205 (N—H), 1733 (C=O) were identical with those of indoxyl red prepared by Seidel's method.

Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.02; H, 4.09; N, 11.38. Found: C, 78.30; H, 4.23; N, 11.33.

Acetyl derivative; m.p. 185.5–187.5° (lit.,[6] m.p. 185°); infrared absorption (cm.$^{-1}$): 1733 (C=O).

2-(5-Bromo-3-indolyl)-3*H*-pseudoindol-3-one (Ib), obtained in 41% yield from isatin (*via* the α-chloride) and 5-bromoindole,[12] formed large, brown, rectangular prisms, m.p. 224–226°; ultraviolet-visible spectrum: λ_{max}, mμ (log ε): 225 (4.39), 270 (4.32), 340 (3.50), 512 (3.56).

Anal. Calcd. for $C_{16}H_9BrN_2O$: C, 59.09; H, 2.79; N, 8.62; Br, 24.58. Found: C, 58.81; H, 2.87; N, 8.58; Br, 24.35.

5-Bromo-2-(3-indolyl)-3*H*-pseudoindol-3-one (Ic) was obtained in 74% yield from 5-bromoisatin[12] (*via* the α-chloride) and indole. The compound crystallized as a deep brown, glistening, microcrystalline powder, m.p. 193–194°; ultraviolet-visible spectrum: λ_{max}, mμ (log ε): 219 (4.42), 281 (4.45), 354 (3.62), 545 (3.78).

Anal. Calcd. for $C_{16}H_9BrN_2O$: C, 59.09; H, 2.79; N, 8.62. Found: C, 59.26; H, 3.13; N, 8.68.

5-Bromo-2-(5-bromo-3-indolyl)-3*H*-pseudoindol-3-one (Id), obtained in 53% yield from 5-bromoisatin (*via* the α-chloride)

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[11] Prepared as described in ref. 3 and recrystallized from xylene to give white crystals, m.p. 205–206.5° dec.

[12] 5-Bromoindole, 5-bromoisatin, and 5-nitroisatin were obtained from the Aldrich Chemical Co., Milwaukee, Wis.

and 5-bromoindole, formed dark brown crystals, m.p. 237–238°; ultraviolet-visible spectrum; $\lambda_{\max}$, mμ ($\log \epsilon$): 224 (4.52), 277 (4.48), 355 (3.64), 530 (3.70).

Anal. Calcd. for $C_{16}H_8Br_2N_2O$: C, 47.55; H, 2.00; N, 6.93. Found: C, 47.57; H, 2.30; N, 6.78.

2-(5-Bromo-3-indolyl)-5-nitro-3*H*-pseudoindol-3-one (Ie) was obtained in 36% yield from 5-nitroisatin[12] (*via* the α-chloride) and 5-bromoindole, as dark brown, glistening needles, m.p. 261–262°; ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 224 (4.62), 252 shoulder (4.19), 268 shoulder (3.99), 288 (3.93), 355 (4.14), 535 (3.15).

Anal. Calcd. for $C_{16}H_8BrN_3O_3$: C, 51.91; H, 2.18; N, 11.35. Found: C, 51.94; H, 2.34; N, 11.20.

2,2-Bis(3-indolyl)indoxyl (VIIa).—A solution of 0.65 g. (0.0026 mole) of Ia (from isatin α-chloride and indole) and 0.35 g. (0.0030 mole) of indole in 10 ml. of glacial acetic acid was warmed on the steam bath for 0.5 hr. during which yellow crystals separated from the brown solution. The mixture was allowed to stand for 24 hr. and the crude product collected by filtration, washed once with acetic acid, then with ether and air dried to give 0.91 g. (95% yield) of product, m.p. 232–234° dec. Recrystallization from methanol gave pure material, m.p. 241.5–243° dec.; ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 260 (4.19), 280 (4.16), 404(3.51), identical (mixed m.p. 242–244°) with a sample, m.p. 243.5–244.5°, prepared by oxidation of indole with hydrogen peroxide in acetic acid as described in the literature[10]; ultraviolet-visible spectrum reported by these authors: $\lambda_{\max}$, mμ ($\log \epsilon$): 260 (4.07), 280 (4.05), 404 (3.42).

2-(5-Bromo-3-indolyl)-2-(3-indolyl)indoxyl (VIIb). Method A.—A solution of 2.00 g. (0.00815 mole) of Ia and 1.59 g. (0.00815 mole) of 5-bromoindole in 25 ml. of glacial acetic acid was heated on the steam bath for 45 min., then allowed to stand at room temp. for 24 hr. The crude yellow solid, which was collected by filtration and dried at 50° overnight, weighed 1.90 g. (53% yield) and decomposed sharply at 231°. Recrystallization from aqueous ethanol caused a striking drop in melting point (186–200°). This material was dissolved in a minimum amount of acetone and applied to a 2.2 × 60 cm. column containing 200 g. of Fisher adsorption alumina (packed wet with ether), and eluted with ether. The third and fourth 100-ml. fractions contained most of the product, which separated from the eluate as yellow crystals, m.p. 180–185°; ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 260 (4.15), 284 (4.11), 292 (4.10), 402 (3.50).

Anal. Calcd. for $C_{24}H_{16}BrN_3O$: C, 65.17; H, 3.65; N, 9.50. Found: C, 65.32; H, 3.79; N, 9.54.

Method B. Reaction of 1.00 g. (0.00307 mole) of Ib with 0.36 g. (0.0031 mole) of indole in 10 ml. of acetic acid was effected as in method A. The crude product weighed 1.16 g. (86% yield) and melted at 235–237°. This material also exhibited a large decrease in melting point to 170–190° when crystallized from aqueous ethanol. Purification by a second recrystallization from ether-acetone gave canary yellow crystals, m.p. 184–186°, which showed no depression on admixture with a sample prepared by method A, and had $\lambda_{\max}$, mμ ($\log \epsilon$): 259 (4.19), 283 (4.14), 291 (4.12), 402 (3.52).

2,2-Bis(5-bromo-3-indolyl)indoxyl (VIIc).—A solution of 1.00 g. (0.00307 mole) of Ib and 0.61 g. (0.0031 mole) of 5-bromoindole in 15 ml. of glacial acetic acid was heated on the steam bath for 45 min. then allowed to stand at room temperature for 48 hr. The yellow solid which separated was collected by filtration, washed with cold acetic acid, then with 95% ethanol and dried at 110°. The yield was 1.20 g. (75%), m.p. 217–222°. Two recrystallizations from 70% ethanol gave canary yellow crystals, m.p. 233–234° dec., inserted at 220°; ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 229 (4.87), 260 shoulder (4.15), 290 (4.08), 406 (3.52).

Anal. Calcd. for $C_{24}H_{15}Br_2N_3O$: C, 55.30; H, 2.90; N, 8.06. Found: C, 55.04; H, 2.81; N, 7.96.

5-Bromo-2,2-bis(3-indolyl)indoxyl (VIId).—A solution of 1.00 g. (0.00307 mole) of Ic and 0.36 g. (0.0031 mole) of indole in 15 ml. of glacial acetic acid was warmed on the hot plate for 15 min., during which the color of the mixture changed from purple to brown, and yellow crystals began to form. After the mixture had stood for 14 hr. at room temperature (no further crystallization was apparent) the crystals were collected, washed with petroleum ether (b.p. 30–40°) and air dried. The yield was 1.30 g. (96%) of yellow solid, m.p. 260–260.5° dec., inserted at 190°. Recrystallization from 60% ethanol gave golden yellow crystals; m.p. 279–279.5° dec., inserted at 265°; ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 274 (4.32), 291 (4.25), 417 (3.49).

Anal. Calcd. for $C_{24}H_{16}BrN_3O$: C, 65.16; H, 3.65; N, 9.50. Found: C, 65.37; H, 3.94; N, 9.38.

5-Bromo-2-(5-bromo-3-indolyl)-2-(3-indolyl)indoxyl (VIIe). Method A.—A solution of 0.75 g. (0.0019 mole) of Id and 0.22 g. (0.0019 mole) of indole in 10 ml. of glacial acetic acid was heated nearly to boiling for 15 min. The solution turned brown and yellow crystals began to form. After the mixture had stood for 10 hr. at room temperature, 10 ml. of absolute ethanol was added to complete precipitation of the product, which was collected and dried at 110°. The yield of yellow-green solid was 0.57 g. (59%), m.p. 254–257°. Two recrystallizations from dilute ethanol gave pure material, m.p. 265–265.5° dec., inserted at 260°; ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 272 (4.28), 289 (4.14), 417 (3.47); infrared spectrum (cm.$^{-1}$): 3470 (N–H), 1708 (C=O), other strong bands at 1620, 1475, 885, 744.

Anal. Calcd. for $C_{24}H_{15}Br_2N_3O$: C, 55.30; H, 2.90; N, 8.06. Found: C, 55.25; H, 3.14; N, 8.07.

Method B.—In a similar manner 1.00 g. (0.00307 mole) of Ic and 0.70 g. (0.0031 mole) of 5-bromoindole yielded 0.60 g. (44%) of crude product, m.p. 259–259.5° dec., inserted at 250°, which after two recrystallizations from dilute ethanol had m.p. 273.5–274° dec., inserted at 269°. The ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 273 (4.30), 288 (4.16), 417 (3.52), and the infrared spectrum were identical with those observed for the compound prepared by method A.

5-Bromo-2,2-bis(5-bromo-3-indolyl)indoxyl (VIIf). Method A.—A solution of 6 ml. of 30% hydrogen peroxide in 8 ml. of glacial acetic acid was added to a solution of 5.00 g. of 5-bromoindole in 19 ml. of acetic acid. The initially yellow solution had darkened to a forest green color in 1 hr. After 3 hr., some crystals began to separate. After standing at ambient conditions for 24 hr., the mixture was filtered to give 3.40 g. of light green solid which melted indistinctly at 252–295°. After having stood another 48 hr., the filtrate deposited an additional 0.60 g. of crude product. The combined crude solids were boiled with 200 ml. of ether, filtered to remove 0.40 g. of blue solid (m.p. above 400°), concentrated to 30 ml., and applied to a 2.2 × 60 cm. column packed wet with 200 g. of Fisher adsorption alumina in ether. Development with ether separated the adsorbate into (from bottom to top) a thin blue band, a wide yellow band, and finally a small purple band. Elution with ether and evaporation of the combined yellow fractions gave an oil which crystallized from aqueous acetone to yield 1.90 g. (37%) of crude product, m.p. 273–274°. Recrystallization from aqueous ethanol (Norite) gave analytically pure material, the melting point of which showed a remarkable dependency on the time of heating prior to melting; m.p. 282.5–283° (inserted at 250°), 285–285.5° (inserted at 270°), 292–292.5° (inserted at 282°), all with decomposition. Ultraviolet-visible spectum: $\lambda_{\max}$, mμ ($\log \epsilon$): 229 (5.06), 272 (4.25), 291 (4.16), 418 (3.51); infrared spectrum (cm.$^{-1}$): 3470 (N—H), 1708 (C=O), other strong bands at 1618, 1470, 883, 800.

Anal. Calcd. for $C_{24}H_{14}Br_3N_3O$: C, 48.03; H, 2.35; N, 7.00. Found: C, 48.32; H, 2.43; N, 7.01.

Method B.—A solution of 0.75 g. (0.0020 mole) of Id and 0.38 g. (0.0020 mole) of 5-bromoindole in 10 ml. of glacial acetic acid was warmed on the hot plate for 10 min. Within 1 min. the solution had turned brown and after 2 min. crystals separated. The solution was allowed to cool to room temperature then refrigerated (10°) for 3 hr. The light yellow-green product was collected by filtration, washed with petroleum ether (b.p. 30–40°), and dried. The yield of crude product, m.p. 273.5–274° dec., inserted at 268°, was 0.95 g. (85%). The compound was recrystallized from aqueous ethanol to give yellow needles, m.p. 282° dec., inserted at 270°. The ultraviolet-visible spectrum: $\lambda_{\max}$, mμ ($\log \epsilon$): 228 (4.97), 270 (4.27), 288 (4.16), 416 (3.51), and the infrared spectrum were identical with those cited for the compound prepared by method A.

5′-Bromo-2,3′-biindolyl (VIII).—A mixture of 2.0 g. of Ib, 49 ml. of glacial acetic acid, 4.0 g. of zinc dust, and 3 ml. of concentrated hydrochloric acid was stirred and heated on the steam bath for 2.5 hr. An additional 2.0 g. of zinc dust, 15 ml. of acetic acid, and 2 ml. of concentrated hydrochloric acid were added and heating continued another 0.5 hr. The mixture was filtered hot to remove unreacted zinc and the filtrate was diluted with 125 ml. of water to give a mustard-yellow solid, which was collected by filtration and air dried. This crude product weighed 0.83 g. and melted at 120–210°. Recrystallization from xylene (Norite) gave 0.10 g. (5% yield) of tan crystals, m.p. 201–204°, which after sublimation at 190°/0.2 mm. gave white needles, m.p. 203.5–206° dec. Ultraviolet spectrum: λ_{max}, mμ (log ε): 246 (4.31), 312 (4.22).

Anal. Calcd. for $C_{16}H_{11}BrN_2$: C, 61.75; H, 3.56; N, 9.00. Found: C, 61.38; H, 3.83; N, 9.15.

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Reduction of Steroidal Enamines

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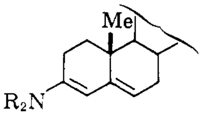
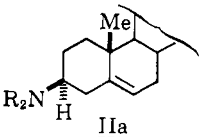
Further studies on the reduction of steroidal enamines with sodium borohydride and acetic acid have indicated that the mechanism involves initial protonation of the substrate followed by reduction of the immonium cation. Procedures are described for obtaining yields as high as 60% in the reduction of dienamines of type I and 70% in the case of simple enamines.

In connection with the total synthesis of racemic conessine,[1] we have studied further the previously reported[2] reduction of dienamines derived from α,β-unsaturated ketones. The present paper describes an improved procedure and also sheds some light on the mechanism of this type of reduction.



Ia
Ib

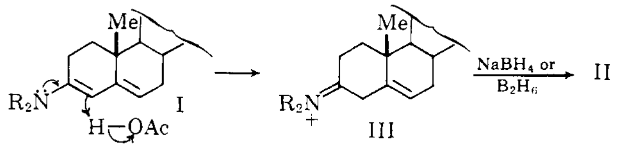


IIa
IIb

a = conessine series, R_2 = Me_2
b = cholestane series, R_2 = —$(CH_2)_4$—

Our first observation of significance was that there was no reaction between the dienamine Ia (3,4-dehydroconessine) and sodium borohydride until *after* acetic acid was added to the reaction mixture. This point was demonstrated by observing no change in the characteristic ultraviolet spectrum, λ_{max} 265 mμ (ε 13,500), until acetic acid was added. When the product was isolated immediately after this acid treatment, we were surprised to find that it was not conessine (IIa) but rather an intractable solid which appeared to be an amine–borane as evidenced by a strong band at 4.2 μ in the infrared spectrum.[3] Since conversion to conessine was effected in 28–36% yield by decomposition of this complex with acetic acid at 100° for one hour, we entertained the hypothesis that diborane, produced from sodium borohydride and acetic acid,[4] was the reducing species.[5]

To test the above hypothesis, the more readily available dienamine, 3-N-pyrrolidylcholestadiene-3,5 (Ib),[6] was used. Reduction with sodium borohydride and acetic acid in tetrahydrofuran, followed by decomposition of the intractable intermediate complex (λ_{max} 4.2 μ)[3] with acetic acid at 100°, afforded the highly crystalline 3β-N-pyrrolidylcholestene-5 (IIb), m.p. 165–175° (polymorphic), in 44% yield. It is particularly noteworthy that the yield was increased to 60% when diglyme was used as solvent; therefore this promises to be the method of choice for reducing such dienamines. This result is to be compared with the attempted reduction of the dienamine Ib with diborane. The maximum due to the dienamine in the ultraviolet spectrum decreased relatively slowly, indicating that direct hydroboration was likewise slow compared with the reduction in the presence of acetic acid described above. When acetic acid was added to the diborane–dienamine mixture, rapid reaction ensued to give an amine–borane with an infrared spectrum which was essentially identical (including the band at 4.2 μ) with that of the complex described above. Heating with acetic acid gave the amine IIb, m.p. 159–172°, but in only 32% yield. The low yield by the diborane reduction as compared with the borohydride procedure was confirmed by repeated experiments. In addition, a comparatively large fraction of the total product from the diborane reaction appeared to consist of a stable boron compound (alkyl borane?) which was not eluted from alumina in the chromatographic purification.[7] It is therefore concluded that the sodium borohydride–acetic acid reduction does not proceed by hydroboration of the free enamine.



In view of the foregoing considerations we prefer the reduction mechanism depicted in the accompanying flowsheet which involves a preferential (rate-controlled) protonation at C-4 of the dienamine I leading to an immonium cation III which is attacked rapidly by hydride (or diborane) at C-3 to give II. The results indicate that protonation at C-4 is kinetically favored over protonation at C-6 when acetic acid is used.[8]

For purposes of comparison amine IIb was independently prepared by solvolysis of cholesteryl *p*-tolu-

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(1) J. A. Marshall and W. S. Johnson, *J. Am. Chem. Soc.*, **84**, 1485 (1962).

(2) W. S. Johnson, V. J. Bauer, and R. W. Franck, *Tetrahedron Letters*, No. **2**, 72 (1962).

(3) *Cf.* M. F. Hawthorne, *Tetrahedron*, **17**, 117 (1962); H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960); E. C. Ashby, *ibid.*, **81**, 4791 (1959).

(4) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, **28**, 595 (1963).

(5) G. Stork and G. Birnambaum, *Tetrahedron Letters*, No. **10**, 313 (1961), have already suggested this possibility.

(6) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

(7) Poor material recovery (<50%) was realized from such chromatographic purifications when diborane was used in contrast with high material recoveries (80–90%) when sodium borohydride and acetic acid was the reducing agent.

(8) Apparently this selectivity is lost with stronger acids. *Cf.* G. Opitz and W. Merz, *Ann. Chem.*, **652**, 139 (1962), for a detailed study of this process in the reduction of enamines derived from crotonaldehyde.