[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Cyclizative Condensations. II. 2-Methylindole with Methyl Ketones[1]

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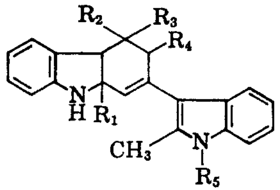
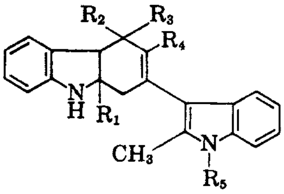
Monobases analogous to the 2:2 product from acetone (Ia) are formed by condensation of 2-methylindole with: (a) benzalacetone or its adduct with 2-methylindole (IIIa), leading to Ic; (b) methyl vinyl ketone or its adduct with 2-methylindole (IIIb), leading to Id; (c) 1-acetylcyclohexene, leading to the tetracyclic monobase V; and with (d) the adduct of indole and methyl vinyl ketone (IIIc), leading to Ie, which was aromatized to the carbazole VII. 1,2-Dimethylindole also condensed with the adduct of indole and methyl vinyl ketone (IIIc), leading to the monobase If. Attempted condensation of 2-methylindole with methyl isopropenyl ketone gave, not the monobase Ig, but 2,2′-dimethyl-3,3′-methylenebisindole (VIII), which was prepared independently from 2-methylindole and methyleneaminoacetonitrile. Condensation of 2-methylindole with methyl isobutyl ketone gave a monobasic 2:1 product of doubtful structure, possibly X, which forms an *N* (indoline)methyl derivative.

In Paper I[2] of this series the monobasic cyclizative condensation product from 2-methylindole with acetone, phorone, mesityl oxide, or with the 1:1 adduct of 2-methylindole and mesityl oxide, was shown to have structure Ia or IIa, the position of the olefinic double bond being uncertain. Two similar isomeric monobases (possibly Ib or IIb) were isolated from the corresponding condensation with methyl ethyl ketone.



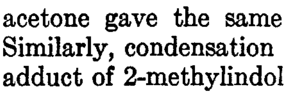
I



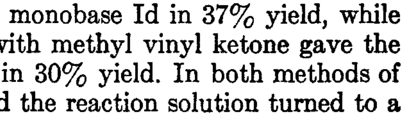
II

Ia or IIa. $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, $R_4 = H$, $R_5 = H$
Ib or IIb. $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = C_2H_5$, $R_4 = CH_3$, $R_5 = H$
Ic or IIc. $R_1 = CH_3$, $R_2 = C_6H_5$, $R_3 = H$, $R_4 = H$, $R_5 = H$
Id or IId. $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = H$, $R_5 = H$
Ie or IIe. $R_1 = H$, $R_2 = H$, $R_3 = H$, $R_4 = H$, $R_5 = H$
If or IIf. $R_1 = H$, $R_2 = H$, $R_3 = H$, $R_4 = H$, $R_5 = CH_3$
Ig or IIg. $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = CH_3$, $R_5 = H$

Condensation of 2-methylindole in ethanolic hydrochloric acid with 1:1 adducts of 2-methylindole and α,β-unsaturated methyl ketones to form monobasic cyclization products analogous to Ia has proved to be quite a general reaction. Condensation of 2-methylindole with the adduct of 2-methylindole and benzalacetone (IIIa) gave the corresponding monobase (Ic) in 34% yield, while the direct reaction of 2-methylindole with benzalacetone gave the same monobase in 31% yield. Similarly, condensation of 2-methylindole with the adduct of 2-methylindole and methyl vinyl ketone (IIIb)[3] gave the monobase Id in 37% yield, while direct reaction with methyl vinyl ketone gave the same monobase in 30% yield. In both methods of preparation of Id the reaction solution turned to a dark violet color, assumed to be due to the cyanine dye autoxidation product (IV), which has been reported previously as the product of this reaction.[4] Our success in isolating the monobase before it underwent autoxidation in the acidic reaction solution is attributed to the fact that its hydrochloride precipitated and was insulated from the air by a violet coating of the cyanine dye hydrochloride. The hydrochloride of the monobase (Id), which can be washed white with ether and a little ethanol, turns violet on the surface in contact with air. Ethanol solutions of the hydrochloride, not initially violet, turn violet and deepen in color with time. This is attributed to reversible ring opening



III



IV

IIIa. $R_1 = CH_3$, $R_2 = C_6H_5$
IIIb. $R_1 = CH_3$, $R_2 = H$
IIIc. $R_1 = H$, $R_2 = H$

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[1] It is a pleasure to acknowledge support of most of this research from the following sources: The du Pont Co. (M.R.V., Sept. 1957–Sept. 1958) through a Grant-in-Aid to the Department of Chemistry; through Research Grant CY-4073 from the National Cancer Institute, U. S. Public Health Service (M.R.V., R.A.L., C. G. Richards, and H. S. Desai, Oct. 1958–Dec. 1960); and from the National Science Foundation Undergraduate Research Participation Program (R.A.L., June–Aug. 1960); (a) M.R.V., postdoctoral fellow, Sept. 1957–Dec. 1958; (b) R.A.L., undergraduate research assistant, Sept. 1959–June 1960; undergraduate research participant, June–Aug. 1960; (c) C. G. Richards, postdoctoral fellow, Jan. 1959–June 1960; (d) H. S. Desai, postdoctoral fellow, Sept.–Dec. 1960. This work was presented in part as Paper 174 before the Organic Division at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 16, 1960, Abstracts, p. 92P.

[2] W. E. Noland, M. R. Venkiteswaran, and C. G. Richards, *J. Org. Chem.*, **26**, 4241 (1961).

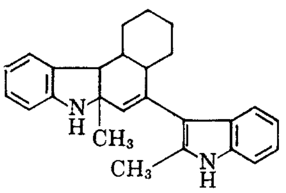
[3] J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957).

[4] A. Treibs and E. Herrmann, *Ann.*, **592**, 1 (1955).

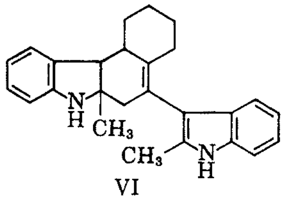
to a vinylindole (analogous to a tautomer of structure X in Paper I), which then undergoes air oxidation to the cyanine dye hydrochloride (IV), previously reported.[4]

The 1:1 adduct (IIIa) of 2-methylindole and benzalacetone, first obtained in 27% yield after an equimolar mixture of the reactants had been set aside for five months,[5] was obtained in 43% yield when dry hydrogen chloride gas was passed for six minutes into an equimolar solution of the reactants in dry ether.

The opportunity to build up polycyclic systems is illustrated by the direct condensation of 2-methylindole and 1-acetylcyclohexene to form the tetracyclic monobase V (or VI) in 23% yield.

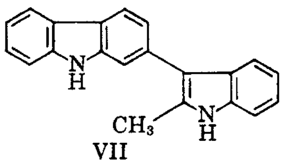


V



VI

Condensation of 2-methylindole with the 1:1 adduct of indole and methyl vinyl ketone (IIIc)[3,4] gave the monobase (Ie) in 34% yield. The monobase, which, unlike those previously described, contains no quaternary carbon atoms, was aromatized in 83% yield by the action of chloranil in refluxing xylene. The product is assigned the structure 2-(2-methyl-3-indolyl)carbazole (VII). The conjugated ultraviolet spectrum has maxima at 237 (log ε 4.74) and 320 mμ (log ε 4.36). Formation of a carbazole provides support for the structure (Ie or IIe) assigned to the monobase and tends to support the analogous structures assigned to other monobases (Ia–f, V). 1,2-Dimethylindole has also been condensed with the 1:1 adduct of indole and methyl vinyl ketone (IIIc), giving the monobase If in 52% yield.

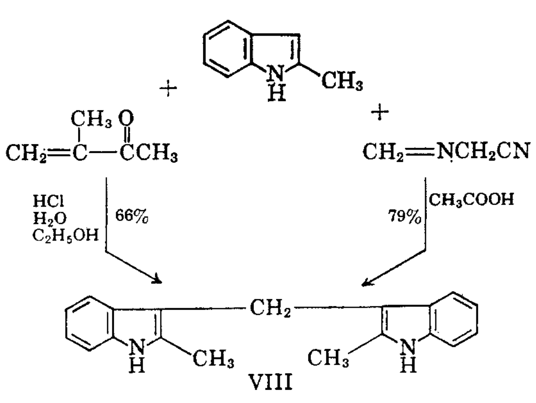


VII

With all the new monobasic condensation products described above (Ic–f, V), the presence of a single, basic secondary nitrogen atom has been established by acetylation to the corresponding monoacetyl derivatives. The monobases and their acetyl derivatives have the ultraviolet absorption maxima or inflections normally associated with an intact indole nucleus (as in IIIa, VIII), and an additional maximum or inflection in the 245–263 mμ region, normally associated with an indoline (2,3-dihydroindole) or 1-acylindoline nucleus.[6] The structures of the monobases (Ic–f, V) are assigned on the basis of their ultraviolet and infrared spectra (see Experimental), and by analogy with the structure established for the 2-methylindole-acetone monobasic condensation product (Ia),[2] reinforced by the fact that a monobase (Ie) having no angular methyl group was successfully aromatized to a carbazole (VII). As with the monobase Ia and its methylated derivatives, all the new monobases have a weak olefinic infrared absorption band, in the 1638–1659-cm.$^{-1}$ region. As with Ia, the position of the olefinic double bond is uncertain, and it may occupy either of the alternative positions in I or II, and in V or VI. In each case, only a single isomer was isolated from the reaction. For the sake of brevity, only the designations I or V (rather than II or VI) have, in general, been used throughout this paper.

The mechanism of formation of the monobases (Ic–f, V) is assumed to involve (1) if a 1:1 adduct is not used directly as a reactant, the acid-catalyzed Michael-type addition of 2-methylindole to the α,β-unsaturated ketone to form a 1:1 adduct (analogous to IIIa–b); and (2) acid-catalyzed condensation of the indole with the 1:1 adduct to form a tautomeric equilibrium mixture of vinylindoles, the terminal methylene member of which (analogous to structure X in Paper I) undergoes acid-catalyzed cyclization to the monobase.

Attempted condensation of 2-methylindole with methyl isopropenyl ketone gave, not the monobase Ig, but the formaldehyde condensation product,[7] 2,2'-dimethyl-3,3'-methylenebisindole (VIII), in 66% yield, which was prepared independently in 79% yield from the facile condensation in glacial acetic acid of 2-methylindole with another methylene(formaldehyde)-precursor, methyleneaminoacetonitrile. These results indicate that methyl isopropenyl ketone hydrolyzes more rapidly to formaldehyde (and methyl ethyl ketone) than it adds 2-methylindole to give the 1:1 adduct necessary for formation of the monobase Ig.



VIII

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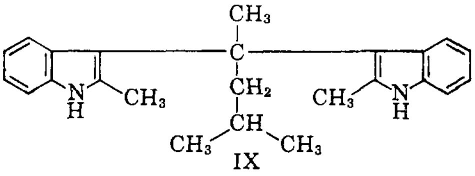
[5] Ronald F. Lange, Ph.D. thesis, University of Minnesota, June 1958, pp. 77–78, 80–81.

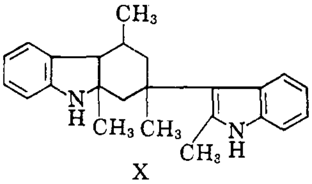
[6] W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960).

[7] E. Voisenet, *Bull. soc. chim. France*, [4] **5**, 736 (1909).

Condensation of 2-methylindole with methyl isobutyl ketone took a different course from the condensations with acetone and methyl ethyl ketone. The colorless product, formed in 11% yield, corresponds in composition to a 2:1 condensation product of 2-methylindole and methyl isobutyl ketone. The facts that the product forms a monohydrochloride and has an indoline band at 246 mμ in the ultraviolet spectrum rule out the possibility that it is the bisindole IX. The ultraviolet spectrum is like that of monobases of types I and V, but there is no olefinic double bond band in the infrared spectrum. The compound formed neither a benzylidene derivative nor a dihydro derivative from catalytic hydrogenation, and was recovered unchanged in 88 and 78% yields, respectively. It appeared to decompose on attempted acetylation. It forms an N-(indoline)methyl derivative in almost quantitative yield, which contains a single NH band in the infrared spectrum. While the structure of the monobase remains very much in doubt, a sequence of acid-catalyzed steps is suggested as a reasonable possibility, starting from the vinylindole 1:1 condensation product (analogous to structure IX in Paper I), proceeding through two double bond migrations to a terminal methylene compound, which cyclizes to a monobasic tertiary carbonium ion and alkylates a molecule of 2-methylindole to form the monobase X.



IX



X

EXPERIMENTAL

The initials of co-authors or names of persons after the heading of each section show who did the experimental work. Melting points were determined on Kofler micro hot stages or on Fisher-Johns hot stages.

4-(2-Methyl-3-indolyl)-4-phenyl-2-butanone (IIIa). (A) *With hydrogen chloride in dry ether* (R.A.L.). Dry hydrogen chloride was passed, with stirring, into a solution of 2-methylindole (6.56 g., 0.050 mole) and benzalacetone (7.30 g., 0.050 mole) in dry ether (85 cc.) for 6 min. The light amber solution darkened as hydrogen chloride was passed in and after 2 min. turned orange, with appearance of a precipitate. Then almost immediately a dark sticky residue appeared. Within a few minutes after the end of the reaction the solution and precipitate turned dark purple. Water was added, and the mixture neutralized with sodium bicarbonate and extracted with ether. A white interfacial precipitate (2.41 g.), m.p. 160–170°, was filtered off. The ether extract was dried over anhydrous potassium carbonate and evaporated. The residual dark red oil, which solidified after several days (11.17 g.), m.p. 65–83°, was recrystallized three times from ethanol, yielding white crystals (5.92 g., 0.0214 mole, 43%), m.p. 113–113.5°, mixed melting point with the sample from the uncatalyzed reaction, 114–118° (undepressed). The infrared spectra of the two samples in Nujol were identical.

The white interfacial precipitate was dissolved in ethanol and ether was added. The solution turned bright red and attempts to recover a crystalline solid were unsuccessful.

An attempt to prepare the adduct from equimolar portions of the reactants (0.015 mole each) in refluxing acetic acid (20 cc., 4 hr.) gave only an oil.[8]

(B) *Uncatalyzed reaction* (with Ronald F. Lange[5]). A mixture of 2-methylindole (6.55 g., 0.050 mole) and benzalacetone (7.30 g., 0.050 mole) was warmed on a steam bath just long enough to dissolve all the 2-methylindole. The pale yellowish orange oil was kept at room temperature. After several weeks it turned brown and became increasingly viscous with time, and after 5 months it finally partially crystallized. The mass was triturated with cold methanol (20 cc.) and the brown solid filtered (3.69 g., 0.0133 mole, 27%), m.p. 58–70°. Dilution of the filtrate with water gave a dark brown oil which did not crystallize on long standing. The brown solid was recrystallized six times from ethanol, yielding tiny white needles, m.p. 119.5–120.5°; λ_{max} in 95% ethanol, 225 mμ (log ε 4.49), 283 (3.85), 290 (3.81); ν_{NH} 3480 in chloroform, 3370 in Nujol, $\nu_{C=O}$ 1707 in chloroform, 1705 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{19}N_{19}NO$ (277.34): C, 82.28; H, 6.91; N, 5.05. Found: C, 82.46; H, 7.06; N, 5.29.

9a-Methyl-2-(2-methyl-3-indolyl)-4-phenyl-3,4,4a,9a-tetrahydrocarbazole (Ic) (M.R.V.). (A) *From benzalacetone.* A solution of 2-methylindole (2.62 g., 0.020 mole), benzalacetone (1.5 g., 0.010 mole), and concentrated hydrochloric acid (2.5 g.) in 95% ethanol (15 cc.) was kept at room temperature for 4 hr. Addition of the acid produced a deep red color in the solution, and a white precipitate soon began to form. The precipitate (1.61 g.) was filtered, washed with ether, dried, suspended in ethanol (250 cc.), and neutralized with ethanolic sodium hydroxide solution. When the original precipitate had completely dissolved, the solution was diluted with water, giving a white precipitate (1.21 g., 0.00310 mole, 31%). Four recrystallizations from ethanol-water yielded white rectangular prisms, m.p. 192–193°; λ_{max} in 95% ethanol, 227 mμ (log ε 4.54), 263–280 [broad plateau, with maxima at 263 (4.06), 267 (4.06), 274 (4.05), 280 (4.05)], 290 (3.99); ν_{NH} 3310, 3240, $\nu_{C=C}$ 1645 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{28}H_{26}N_2$ (390.50): C, 86.11; H, 6.71; N, 7.17. Found: C, 85.97; H, 6.99; N, 7.02.

(B) *From 4-(2-methyl-3-indolyl)-4-phenyl-2-butanone.* A solution of 4-(2-methyl-3-indolyl)-4-phenyl-2-butanone (3.15 g., 0.0114 mole), 2-methylindole (1.31 g., 0.010 mole), and concentrated hydrochloric acid (2.0 g.) in 95% ethanol (15 cc.) was kept at room temperature for 4 hr. until a white solid precipitated from the red solution. The solid was filtered, washed with a little ethanol and ether, dissolved in ethanol, neutralized with ethanolic sodium hydroxide solution, and the ethanol solution diluted with water. The resulting white precipitate was filtered and crystallized from ethanol-water, yielding white rectangular prisms (1.32 g., 0.00338 mole, 34%), m.p. 190–191°, mixed melting point with the sample prepared from benzalacetone, 190–192° (undepressed).

Monoacetyl derivative of Ic (R.A.L.). The compound was obtained in 88% yield from the monobase and acetic anhydride; small white needles from ethanol-water, m.p. 207–208°; λ_{max} in 95% ethanol, 228 mμ inflection (log ε 4.57), 262 (4.35), 280 inflection (4.21), 289 inflection (4.13); ν_{NH} 3340, $\nu_{C=C}$ 1641 inflection, $\nu_{C=O}$ 1632 cm.$^{-1}$ in Nujol.

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(8) Donald N. Robinson, Ph.D. thesis, University of Minnesota, March 1959, p. 98.

Anal. Calcd. for $C_{30}H_{28}N_2O$ (432.54): C, 83.30; H, 6.53; N, 6.48. Found: C, 83.43; H, 6.71; N, 6.25.

9a-Methyl-2-(2-methyl-3-indolyl)-3,4,4a,9a-tetrahydrocarbazole (Id) (M.R.V.). (A) *From methyl vinyl ketone.* Concentrated hydrochloric acid (2.0 g.) was added to a mixture of 2-methylindole (2.62 g., 0.020 mole) and methyl vinyl ketone (0.77 g., 0.0110 mole) in 95% ethanol (12 cc.), causing an exothermic reaction. The mixture turned violet and soon started depositing a violet-coated precipitate. The mixture was diluted with ether (50 cc.) and kept for 0.5 hr. until more crystalline precipitate separated. The crystals were filtered, washed with ether, and promptly dissolved in ethanol and neutralized with ethanolic sodium hydroxide solution, causing the deep pink solution to turn yellow. Dilution with a large volume of water produced a pale brown precipitate. The mixture was cooled at 0° and the precipitate filtered and crystallized from ethanol-water, with charcoal, giving whitish crystals, (0.95 g., 0.0030 mole, 30%). Three recrystallizations from ethanol-water yielded white crystals, m.p. 217–220°; λ_{max} in 95% ethanol, 228 mμ (log ϵ 4.49), 256 inflection (4.05), 279 inflection (4.00), 290 (3.95); ν_{NH} 3330, 3270, $\nu_{C=C}$ 1638 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{22}H_{22}N_2$ (314.41): C, 84.04; H, 7.05;N, 8.91. Found: C, 84.16; H, 7.09; N, 8.80.

A sample of the white monobase dissolved in ethanol and treated with concentrated hydrochloric acid did not give an immediate violet color. On keeping the solution for some time, however, the violet color developed and deepened with time, probably due to autoxidation to the hydrochloride salt of the cyanine dye (IV), which has been described previously.[4] The crude precipitate of the monobase hydrochloride obtained in this experiment is violet coated, probably due to contamination by the cyanine dye hydrochloride, but the precipitate can be washed with ether and a little ethanol to a white hydrochloride, which turns violet, probably due to autoxidation to the cyanine dye hydrochloride (IV) on the solid surface exposed to air.

(B) *From 4-(2-methyl-3-indolyl)-2-butanone.* A mixture of 4-(2-methyl-3-indolyl)-2-butanone[3] (2.02 g., 0.010 mole), 2-methylindole (1.31 g., 0.010 mole), and concentrated hydrochloric acid (1.5 g.) in 95% ethanol (10 cc.) was kept at room temperature for 2 hr. while the color became intense violet and violet crystals accompanied by some sticky material precipitated. The supernatant solution was decanted from the precipitate and the precipitate washed with ether, suspended in ethanol (200 cc.), and heated to dissolve it. The resulting solution was neutralized with ethanolic sodium hydroxide solution and diluted with water, giving a pale brown precipitate. The precipitate was recrystallized from ethanol, with charcoal, and cooling in an ice-box yielded whitish crystals (1.18 g., 0.00375 mole, 37%), m.p. 218–220°, mixed melting point with the sample prepared from methyl vinyl ketone, 217–219° (undepressed).

Monoacetyl derivative of Id. The compound was obtained in 80% yield from the monobase and acetic anhydride; white crystals from acetone-water, m.p. 160–161° λ_{max} in 95% ethanol, 226 mμ (log ϵ 4.54), 258 (4.34), 279 inflection (4.17), 289 inflection (4.10); ν_{NH} 3320, $\nu_{C=O}$ 1640 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{24}H_{24}N_2O$ (356.45): C, 80.86; H, 6.79; N, 7.86. Found: C, 80.94; H, 6.93; N, 7.75.

6a-Methyl-5-(2-methyl-3-indolyl)-1,2,3,4,4a,6a,11a,11b-octahydro-7H-benzo [c] carbazole (V) (M.R.V., R.A.L.). A solution of 2-methylindole (2.62 g., 0.020 mole), 1-acetylcyclohexene (1.24 g., 0.010 mole), and concentrated hydrochloric acid (2.0 g.) in 95% ethanol (15 cc.) was kept at room temperature for 9 hr. The solution was neutralized with ethanolic sodium hydroxide solution, the precipitated sodium chloride filtered, and the filtrate cooled in an ice bath and kept overnight. (If no precipitate forms, the solution can be diluted with water to induce precipitation.) The whitish precipitate (0.95 g., 0.00229 mole, 23%), m.p. 121–123°, was filtered and recrystallized from ethanol, yielding the monoethanolate as granular white crystals, m.p. 122–124° (not sharp); λ_{max} in 95% ethanol, 227 mμ (log ϵ 4.53), 247 inflection (4.12), 283 (4.02), 290 (3.99); ν_{OH} 3650 in chloroform, ν_{NH} 3480, 3410 in chloroform, 3260 (broad, must include OH) in Nujol, $\nu_{C=C}$ 1659 in Nujol, ν_{C-O} 1050 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{26}H_{28}N_2 \cdot C_2H_5OH$ (414.57): C, 81.11; H, 8.27; N, 6.76 [Calcd. for $C_{26}H_{28}N_2 \cdot H_2O$ (386.52): C, 80.79; H, 7.82; N, 7.25]. Found: C, 80.57; H, 8.20; N, 6.92.

The monoethanolate (0.84 g.) was dissolved in hot methanol, water added to the point of turbidity, and the solution allowed to crystallize. The yellowish precipitate (0.70 g.), m.p. 213–216°, was recrystallized three times from methanol, yielding the unsolvated form as white crystals (0.56 g.), m.p. 217.5–218.5°; λ_{max} in 95% ethanol, 227 mμ (log ϵ 4.52), 245 inflection (4.12), 283 (4.01), 291 (3.98); ν_{NH} 3430, 3380, $\nu_{C=C}$ 1644 cm.$^{-1}$ in Nujol; the ultraviolet spectrum is the same, after allowing for the difference in molecular weight, as that of the ethanolate, but the infrared spectra in Nujol are quite different. The strong alcohol band at 1050 cm.$^{-1}$ in the spectrum of the ethanolate is absent in the infrared spectrum of the unsolvated form.

Anal. Calcd. for $C_{26}H_{28}N_2$ (368.50): C, 84.74; H, 7.66; N, 7.60. Found: C, 84.27; H, 7.96; N, 7.79.

Monoacetyl derivative of V (R.A.L.). The compound was obtained in 90% yield from the monobase and acetic anhydride; small white needles from ethanol-water, m.p. 252–254°; λ_{max} in 95% ethanol, 226 mμ inflection (log ϵ 4.55), 261 (4.33), 280 (4.18), 290 inflection (4.10); ν_{NH} 3310, $\nu_{C=O}$ 1626 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{28}H_{30}N_2O$ (410.54), C, 81.91; H, 7.37; N, 6.82. Found: C, 81.92; H, 7.36; N, 6.87.

2-(2-Methyl-3-indolyl)-3,4,4a,9a-tetrahydrocarbazole (Ie) (M.R.V.). A mixture of 4-(3-indolyl)-2-butanone[3,5] (1.87 g., 0.0100 mole), 2-methylindole (1.31 g., 0.010 mole), and concentrated hydrochloric acid (1.5 g.) in 95% ethanol (10 cc.) was kept at room temperature for 4 hr. The color of the solution became intense violet, followed by precipitation of some violet, sticky material. The solution was decanted, and the precipitate was washed with a little ethanol and then with ether. The precipitate was dissolved in ethanol, neutralized with ethanolic sodium hydroxide solution, and diluted with water, giving a pale brown precipitate. The precipitate was filtered, washed with cold aqueous ethanol, dried, and crystallized from ethanol, with charcoal, giving almost white crystals (1.02 g., 0.00340 mole, 34%), m.p. 175–177°. Three recrystallizations from ethanol yielded the white analytical sample, m.p. 179–182°; λ_{max} in 95% ethanol, 228 mμ (log ϵ 4.53), 261 (4.09), 279 inflection (4.06), 290 inflection (4.00); ν_{NH} 3340, 3240, $\nu_{C=C}$ 1647 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{20}N_2$ (300.39): C, 83.96; H, 6.71; N, 9.33. Found: C, 84.04; H, 6.80; N, 9.22.

Monoacetyl derivative of Ie (with H. S. Desai,[1d] 1960). The compound, which was difficult to crystallize from the reaction mixture, was obtained, in 8% yield as the analytical sample, from the monobase and acetic anhydride; pale yellowish white crystals from ethanol, m.p. 148–150°; λ_{max} in 95% ethanol, 226 mμ (log ϵ 4.57), 258 (4.34), 278 inflection (4.19), 288 inflection (4.09); ν_{NH} 3260 in Nujol, 3220 in halocarbon oil, $\nu_{C=O}$ 1633 in Nujol, 1616 cm.$^{-1}$ in halocarbon oil.

Anal. Calcd. for $C_{23}H_{22}N_2O$ (342.42): C, 80.67; H, 6.48; N, 8.18. Found: C, 80.47; H, 6.54; N, 8.46.

2-(2-Methyl-3-indolyl)carbazole (VII) (with C. G. Richards,[1c] 1959). A solution of 2-(2-methyl-3-indolyl)-3-4,4a,9a-tetrahydrocarbazole (0.220 g., 0.000732 mole) and resublimed chloranil (0.360 g., 0.00146 mole) in ethanol (10 cc.) and xylene (30 cc.) was refluxed for 18 hr. The solution was poured into aqueous 2*N* sodium hydroxide solution, extracted with ether, the ether extract washed with aqueous 2*N* sodium hydroxide solution, and the solvents evaporated. The residual oil was crystallized from benzene–petroleum ether (b.p. 60–68°) giving a tan-tinted solid (0.180 g., 0.000607 mole, 83%), m.p. 188–193°. The solid was sublimed at 190–200° (0.002 mm.) and recrystallized six times from benzene–petroleum ether (b.p. 60–68°), yielding 2-(2-methyl-3-indolyl)carbazole as a pale yellowish solid, m.p. 193–194°,

λ_{max} in 95% ethanol, 237 mμ (log ε 4.74), 256 inflection (4.48), 292 inflection (4.13), 320 (4.36), 328 inflection (4.32); ν_{NH} 3370 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{16}N_2$ (296.35): C, 85.11; H, 5.44; N, 9.45. Found: C, 85.39; H, 5.58; N, 9.49.

2-(1,2-Dimethyl-3-indolyl)-3,4,4a,9a-tetrahydrocarbazole (If) (R.A.L.). A solution of 4-(3-indolyl)-2-butanone[3,5] (1.87 g., 0.010 mole), 1,2-dimethylindole (1.45 g., 0.010 mole), and concentrated hydrochloric acid (2.0 g.) in 95% ethanol was kept at room temperature for 5 days. The black crystalline precipitate (3.12 g.), m.p. 155–165°, was dissolved in hot ethanol and neutralized with ethanolic sodium hydroxide solution. The precipitated sodium chloride was filtered, and the filtrate evaporated to dryness. The residue was extracted with ether, the ether evaporated, and the sticky residue triturated with acetone, leaving behind an orange solid (1.65 g., 0.00524 mole, 52%), m.p. 140–145°. Three recrystallizations from acetone-water yielded white crystals, m.p. 146–147.5°; λ_{max} in 95% ethanol, 230 mμ (log ε 4.56), 256 inflection (4.09), 285 (4.04), 290 inflection (4.02); ν_{NH} 3360, $\nu_{C=C}$ 1651 cm^{-1}. in Nujol.

Anal. Calcd. for $C_{22}H_{22}N_2$ (314.41): C, 84.04; H, 7.05; N, 8.91. Found: C, 83.91; H, 7.00; N, 8.87.

Monoacetyl derivative of If. The compound was obtained in 88% yield from the monobase and acetic anhydride; small white crystals from ethanol-water, m.p. 189–190°; λ_{max} in 95% ethanol, 229 mμ (log ε 4.57), 255 (4.31), 278 inflection (4.13), 288 inflection (4.08); ν_{NH} none, $\nu_{C=O}$ 1645 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{24}H_{24}N_2O$ (356.45): C, 80.86; H, 6.79; N, 7.86. Found: C, 80.88; H, 7.13; N, 7.96.

2,2'-Dimethyl-3,3'-methylenebisindole (VIII) (M.R.V.). A. *From methyl isopropenyl ketone.* A solution of 2-methylindole (2.62 g., 0.020 mole), methyl isopropenyl ketone[9] (0.92 g., 0.0109 mole), and concentrated hydrochloric acid (2 g.) in 95% ethanol (15 cc.) was kept at room temperature for 3 hr. The violet coated crystals which deposited were collected in two crops from the intense violet solution. Washing with ether and then a little ethanol removed most of the violet oxidized coating, producing almost white crystals. The crystals were quite sensitive to air oxidation and tended to turn violet again easily. They were dissolved in ethanol (300 cc.) and neutralized with ethanolic sodium hydroxide solution, causing the violet color to become pale yellow. Dilution with water gave almost white crystals (1.8 g., 0.0066 mole, 66%), m.p. 224–228°. Four recrystallizations from ethanol yielded thick clusters of white rods, m.p. 235–238°, mixed melting point with the sample prepared from methyleneaminoacetonitrile, 235–241° (undepressed); reported[7] m.p. (softens 230°) 240°; ν_{NH} 3420, 3380 cm.$^{-1}$ in Nujol. The infrared spectrum in Nujol was very similar to that of the sample prepared from methyleneaminoacetonitrile.

Anal. Found: C, 83.50; H, 6.75; N, 10.15.

B. *From methyleneaminoacetonitrile.* A solution of 2-methylindole (2.62 g., 0.020 mole) and methyleneaminoacetonitrile (1.4 g., 0.021 mole) in glacial acetic acid (12 g.) was placed at room temperature. After 15 min. a white precipitate had formed. After 2 more hr. the precipitate was filtered off from the brown solution, washed with a little acetic acid, and crystallized from acetone-ethanol, giving white crystals (2.17 g., 0.0079 mole, 79%), m.p. 239–241°. Three recrystallizations from ethanol yielded the analytical sample, m.p. 238–243°; reported[7] m.p. (softens 230°) 240°; λ_{max} in 95% ethanol, 229 mμ (log ε 4.81), 283 (4.13), 291 (4.09); ν_{HN} 3410 inflection, 3380 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{19}H_{18}N_2$ (274.35): C, 83.17; H, 6.61; N, 10.21. Found: C, 83.39; H, 6.69; N, 10.45.

Condensation of 2-methylindole with methyl isobutyl ketone (compound X) (M.R.V., R.A.L.). A solution of 2-methylindole (5.25 g., 0.0400 mole), methyl isobutyl ketone (4.00 g., 0.0399 mole), and concentrated hydrochloric acid (3.0 g.) in 95% ethanol (20 cc.) was kept at room temperature for 4 days. The solution turned from yellow to red within several minutes. The *monohydrochloride of compound* X slowly crystallized. The whitish crystals (1.06 g., 0.00279 mole, 14%), m.p. 205–210°, were filtered and dried; ν_{NH} 3250, 2690, 2600, 2470 cm.$^{-1}$ in Nujol, $\nu_{C=C\ olefinic}$ none.

Anal. Calcd. for $C_{24}H_{29}N_2Cl$ (380.94): C, 75.66; H, 7.67; N, 7.35. Found: C, 74.40; H, 7.75; N, 7.39.

The same compound, m.p. 205–210°, was obtained by passing dry hydrogen chloride into an ether solution of compound X (0.20 g.) until a white precipitate (0.13 g., 59%) formed.

Anal. Found: C, 74.31; H, 8.23; N, 7.22.

The hydrochloride (1.06 g.) was dissolved in ethanol and neutralized with ethanolic sodium hydroxide solution. The precipitated sodium chloride was filtered off and much of the ethanol was evaporated, causing formation of a yellowish precipitate (0.73 g., 0.00212 mole, 11%), m.p. 144–146°. Three crystallizations from methanol or ethanol-water yielded compound X as white crystals (0.40 g.), m.p. 150–151°; λ_{max} in 95% ethanol, 225 mμ (log ε 4.64), 246 (4.02), 283 (3.94). 290 (3.93); ν_{NH} 3470 in carbon tetrachloride, 3360, 3240 cm.$^{-1}$ in Nujol, $\nu_{C=C\ olefinic}$ none.

Anal. Calcd. for $C_{24}H_{28}N_2$ (344.48): C, 83.67; H, 8.19; N, 8.13. Found: C, 83.36; H, 8.30; N, 8.38.

Compound X was also obtained from methanol, ethanol, or ethanol-water in another form, as small white needles, m.p. 185–187°. The lower-melting form changes in the solid state at room temperature after 3.5 months or longer to the higher-melting form: ν_{NH} 3380 cm.$^{-1}$ in Nujol. The infrared spectra of the two forms in Nujol are different.

Anal. Found: C, 83.89; H, 8.36; N, 8.18.

Attempted hydrogenation of compound X at 2 atm. in ethanol over Raney nickel catalyst at room temperature gave unchanged starting material in 78% yield. Similarly, an attempt to prepare a benzylidene derivative by warming compound X with an equimolar portion of benzaldehyde in ethanol solution on a steam bath for 10 min. gave unchanged starting material in 88% yield.

Three attempts to prepare a crystalline acetyl derivative by warming compound X in acetic anhydride solution on a steam bath for 10–20 min. gave only a dark reddish brown oil. On one occasion,[10] which could not be repeated on subsequent attempts, when compound X (0.185 g.) was kept with acetic anhydride (5 cc.) at room temperature for 14 hr., a small amount of product remained insoluble. Warming of the mixture at 98° in a water bath for 2 hr. produced complete solution. After being cooled and kept overnight at room temperature, the solution deposited pale pink rhombic crystals (0.032 g., 15%), m.p. 213–215°. Recrystallization from ethanol yielded the *monoacetyl derivative of compound* X[10] as colorless crystals, m.p. 230–231°; ν_{NH} 3160, $\nu_{C=O,\ C=C}$ 1618, 1590 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{26}H_{30}N_2O$ (386.52): C, 80.79; H, 7.82; N, 7.25. Found: C, 80.06; H, 7.65; N, 7.36.

N-(Indoline)methyl derivative of compound X (With H. S. Desai,[1d] 1961).[10] Anhydrous potassium carbonate (10 g.) was added to a solution of compound X (0.690 g., 0.00200 mole) in acetone (30 cc., distilled from potassium permanganate). Dimethyl sulfate (2 cc., 0.021 mole) was added, and the mixture was shaken and then refluxed for 7 hr. and kept overnight at room temperature. Evaporation of the acetone, dilution of the residue with water, and washing of the residual solid with water gave a solid (0.740 g., quantitative yield), m.p. 152–156°, having an infrared spectrum very similar to that of the analytical sample. Crystallization from ethanol gave lustrous crystals (0.320 g., 8.9 × 10^{-4} mole, 45%), m.p. 172–174°. Two recrystallizations from ethanol yielded the

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(9) Research sample kindly provided by Mr. J. E. Ball, Product Development Department, Chemical Division, Celanese Corp. of America, New York, N. Y.

(10) Section (with H. S. Desai) added to manuscript, May 1, 1961.

analytical sample as colorless lustrous crystals, m.p. 176–178°; λ_{max} in 95% ethanol, 223 mμ (log ϵ 4.55), 265 (4.25), 282 inflection (3.96), 289 (3.91), 311 (3.53); ν_{NH} 3360 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{25}H_{30}N_2$ (358.51): C, 83.75; H, 8.43; N, 7.81. Found: C, 83.61; H, 8.41; N, 7.69.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Cyclizative Condensations. III. Indole and 1-Methylindole with Methyl Ketones

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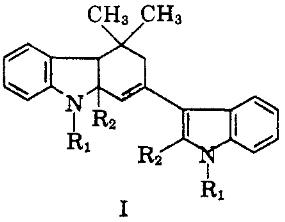
Condensation of indole with acetone in ethanolic hydrochloric acid gave five products, one of which was the easily autoxidizable monobase Ib. Acetylation and methylation of Ib was accompanied by loss of a molecule of hydrogen, giving the diacetyldehydro (IVa) and dimethyldehydro (IVb) derivatives. Condensation of 1-methylindole with acetone gave the same dimethyldehydro derivative (IVb), as well as the bisindole Va in larger yield, while condensation with mesityl oxide gave, depending upon the mole ratio, the 1:1 adduct VIb or the bisindole Va, along with 1-methylindole trimer. Reaction of indole with mesityl oxide gave the 1:1 adduct VIa. Heating of VIb at 140–150° gave a 2:1 condensation and rearrangement product (Vb or IX). Condensation of 1-methylindole with methyl isobutyl ketone gave a 2:2 product, probably XII or XIII, and a 1:2 product, possibly XIV or XV. Attempted cyclization of the 1:1 adduct of indole and methyl vinyl ketone gave two crystalline bimolecular condensation products, a neutral acyclic product (XVIII), and a basic cyclization product which is an indoline derivative, possibly XX.

In Paper I[2] of this series the structure of the monobasic 2:2 condensation product of 2-methylindole and acetone is shown to be Ia (or IIa); two similar cyclization products from 2-methylindole and methyl ethyl ketone are also described. In Paper II[3] cyclizative condensation of 2-methylindole with α,β-unsaturated methyl ketones and with their 1:1 adducts with indoles is shown to be quite general. In 1913 Scholtz[4] reported that the condensation of indole with acetone proceeded less smoothly than the corresponding reaction of 2-methylindole, but yielded, after the action of alkali on the orange-yellow monohydrochloride, a light yellow monobase, $C_{22}H_{22}N_2$, m.p. 170°, to which structure III was incorrectly assigned. We have confirmed the formation of a monobase having this empirical formula, melting point, and color.



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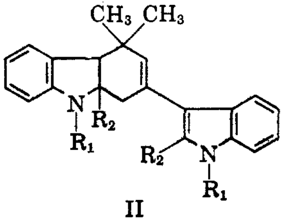
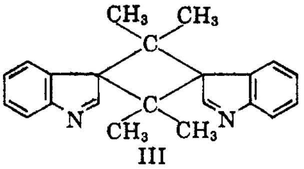


II

Ia or IIa. $R_1 = H$, $R_2 = CH_3$
Ib or IIb. $R_1 = H$, $R_2 = H$
Ic or IIc. $R_1 = CH_3$, $R_2 = H$



III

Condensation of indole with acetone was a very complex reaction, and gave, after chromatography of the products, five compounds, all of which may be products of cyclizative condensation:

(1) "Compound 1," white, m.p. 253–255°, the major product isolated in 9–24% yield, has the empirical formula $C_{25}H_{26}N_2$, corresponding to condensation of two indole and three acetone molecules, with loss of three molecules of water. The compound has a primarily indole type of ultraviolet spectrum, with an additional strong band at 234 mμ. The intensities of the absorption bands indicate that both indole nuclei are participating in the absorption (see Experimental). The two NH bands in the infrared spectrum suggest that both nitrogens of the indole nuclei remain unsubstituted. The compound is very sensitive to autoxidation and easily decomposes autoxidatively when recrystallization is attempted from hot solvents or when the compound is kept in solution for a considerable time. Under such conditions a crystalline autoxidation product, "compound 1 dioxide," $C_{25}H_{26}N_2O_2$,

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