*Anal.* Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91; mol wt, 285.35. Found: C, 84.12; H, 5.25; N, 4.80; mol wt (chloroform), 300.

**2,6-Di-*t*-butyl-α,α-diphenyl-α-cyano-*p*-cresol (Vb).**—Sodium cyanide (980 mg, 20 mmoles) was added to a suspension of 3,5-di-*t*-butylfuchsone (1.85 g, 5 mmoles) in dimethyl sulfoxide (50 ml) which was agitated by a stream of nitrogen and kept in an oil bath at 75°. After 15 min a clear, light red solution had formed. Slow dilution with cold water yielded a colorless crystalline precipitate (mp 155°) which was recrystallized from hot methanol: yield, 1.81 g (91%); 156–157°.

*Anal.* Calcd for $C_{28}H_{31}NO$: C, 84.59; H, 7.86; N, 3.52; mol wt, 397.57. Found: C, 84.64; H, 7.82; N, 3.69; mol wt (benzene), 392.

**2,6-Diphenyl-α,α-diphenyl-α-cyano-*p*-cresol (Vc).**—Sodium cyanide (950 mg, 20 mmoles) was added to a suspension of 3,5-diphenylfuchsone (2.05 g, 5 mmoles) in dimethyl sulfoxide (50 ml) which was kept in an oil bath at 75°. After agitation with a stream of nitrogen, a clear light yellow solution had formed. The reaction mixture was poured into 300 ml of water and the white suspension was diluted with 50 ml of methanol. The resulting colorless precipitate was removed by filtration and recrystallized from boiling methanol: yield, 2.0 g (91%); mp 160–161°.

*Anal.* Calcd for $C_{32}H_{23}NO$: C, 87.84; H, 5.29; mol wt, 437.55. Found: C, 88.09; H, 5.34; mol wt (benzene), 440.

**3,5-Diphenyl-4-hydroxytriphenylcarbinol (VI).**—3,5-Diphenylfuchsone (1.025 g, 2.5 mmoles) was added to a mixture of sodium hydroxide (2.0 g), water (5 ml), and dimethyl sulfoxide (25 ml) which was kept in an oil bath at 90° and agitated by a stream of nitrogen. After 10 min the clear light yellow reaction mixture was poured into 500 ml of water. Filtration after 5 hr gave a colorless crystalline residue which was recrystallized from petroleum ether (bp 30–60°): yield, 500 mg (47%) of colorless to light yellow crystals; mp 141–142°.

*Anal.* Calcd for $C_{32}H_{24}O_2$: C, 86.89; H, 5.65; mol wt, 428.54. Found: C, 86.83; H, 5.64; mol wt (benzene), 414.

**2,6-Di-*t*-butyl-4-(α,α-diphenyl)pentylphenol (VIIa).**—*n*-Butyllithium (5.5 ml of a 1.6 *M* solution in hexane) was added under nitrogen to a solution of 3,5-di-*t*-butylfuchsone (1.85 g, 5 mmoles) in benzene (15 ml). The deep red reaction mixture was refluxed for 5 min. Evaporation of the solvent *in vacuo* and treatment the oily residue with 15 ml of aqueous methanol yielded light yellow crystals. The mixture was acidified with 2 ml of methanol containing 0.3 ml of concentrated hydrochloric acid and kept in the refrigerator for several hours. Filtration gave 1.4 g (65%) of light yellow crystals, mp 95–96°. Recrystallization by dissolving in a little ether and the addition of methanol raised the melting point to 97–98°.

*Anal.* Calcd for $C_{31}H_{40}O$: C, 86.86; H, 9.41; mol wt, 428.67. Found: C, 86.60; H, 9.24; mol wt (benzene), 414.

**2,6-Di-*t*-butyl-4-(α,α,β-triphenyl)ethylphenol (VIIb).**—Tetramethylethylenediamine (0.8 ml) was added to a solution of butyllithium (4 mmoles, in hexane) in toluene (30 ml). The orange reaction mixture was kept under nitrogen for 10 hr. Addition of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmoles) gave a deep red reaction mixture which was quenched after 5 min with 5 ml of methanol. Evaporation *in vacuo* yielded light yellow crystals (1.38 g), mp 163–164°. Recrystallization by dissolving in hot chloroform and the addition of methanol raised the melting point to 169–170°, yield, 1.25 g (90%).

*Anal.* Calcd for $C_{34}H_{38}O$: C, 88.26; H, 8.28; mol wt, 462.68. Found: C, 88.24; H, 8.55; mol wt (benzene), 450.

**3,5-Di-*t*-butyl-4-phenylmethoxytriphenylmethane (VIIIa).**—Phenyllithium (3.3 mmoles, in benzene–ether solution) was added under nitrogen to a solution of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmoles) in benzene (10 ml). The pale yellow reaction mixture was evaporated *in vacuo* after 3 min and the resulting yellow oil was dissolved in 25 ml of methanol. Dropwise addition of 2 ml of concentrated hydrochloric acid under rapid stirring gave a colorless crystalline precipitate (1.38 g), mp 150–153°. Recrystallization by dissolving in a few milliliters of ether and the addition of methanol gave colorless needle-shaped crystals: yield, 1.31 g (95%); mp 156–157°.

*Anal.* Calcd for $C_{34}H_{38}O$: C, 88.26; H, 8.28; mol wt, 462.60. Found: C, 88.51; H, 8.44; mol wt (benzene), 455.

**3,5-Di-*t*-butyl-4-phenylethoxytriphenylmethane (VIIIb).**—The phenyllithium addition to 3,5-di-*t*-butylfuchsone was carried out with the same amounts and in the same manner as described above. The oily product, however, was dissolved in 20 ml of ethanol. Addition of 40 ml of concentrated hyrochloric acid under stirring gave 1.32 g of colorless crystalline product, mp 150–152°. It was recrystallized by dissolving in ether and adding ethanol, giving 1.10 g (77%) of colorless crystals, mp 155–156°.

*Anal.* Calcd for $C_{35}H_{40}O$: C, 88.19; H, 8.46; mol wt, 476.71. Found: C, 87.98; H, 8.41; mol wt (benzene), 464.

**Registry No.**—IIIa, 13343-49-2; IIIb, 13343-50-5; IIIc, 13319-99-8; IIId, 13343-51-6; IIIe, 13343-52-7; IIIf, 13343-53-8; Va, 13343-54-9; Vb, 13343-55-0; Vc, 13343-56-1; VIIa, 13343-57-2; VIIb, 13343-58-3; VIIIa, 13343-59-4; VIIIb, 13343-60-7;

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## Azepinoindoles. III.[1a] 3,4,5,6-Tetrahydro-1H-azepino[4,3,2-*cd*]indoles

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As a continuation of our study of indole derivatives which might possess interesting activity in the central nervous system,[1b] we prepared a series of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indoles. The sodium hydroxide catalyzed condensation[2] of diethyl malonate with 4-nitrogramine (**1**)[3,4] gave the expected yellow adduct (**2**) (Scheme I). In our initial experiments catalytic reduction of **2** in ethanol with nickel, palladium, or platinum catalysts followed by chromatography of the crude product on neutral alumina (activity grade I)[5] with ether–chloroform mixtures gave the lactam (**3**) directly in 26–41% yield. It was later found, however, that the initial product of this reaction is the amine (**4**) which could be isolated as the hydrochloride in better than 90% yield. Pyrolysis of this hydrochloride at 200° under reduced pressure gave **3** in good yield. The structure of **3** was supported by spectral data. Its infrared spectrum ($\nu_{max}$ 3360, 3200, 1723, and 1655 $cm^{-1}$) was in good agreement with the proposed NH, ester, and amide fractions. The nmr spectrum[6a] had singlets at 656 and 613 cps for the protons on nitrogen, a broad multiplet at 429–393 cps for the aromatic protons, a triplet centered at 62 cps and a quartet centered at 241.5 cps (apparent $J$ = 7 cps) for the ethyl group of the ester, and an $AB_2$[7] pattern with peaks centered at about 226 and 193 cps ($J \cong 5$ cps) for the C-4 and C-3 protons, respectively.

Conversion of **3** to the amine (**5**) was accomplished without difficulty. Mild alkaline hydrolysis of the ester (**3**) gave the corresponding acid which without purification was transformed to lactam **6** by pyrolytic

(1) (a) Part II: J. B. Hester, Jr., *J. Org. Chem.*, **32**, 3804 (1967); (b) J. B. Hester, Jr., A. H. Tang, H. H. Keasling, and W. Veldkamp, *J. Med. Chem.*, in press.

(2) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Am. Chem. Soc.*, **67**, 38 (1945).

(3) J. B. Hester, *J. Org. Chem.*, **29**, 1158 (1964).

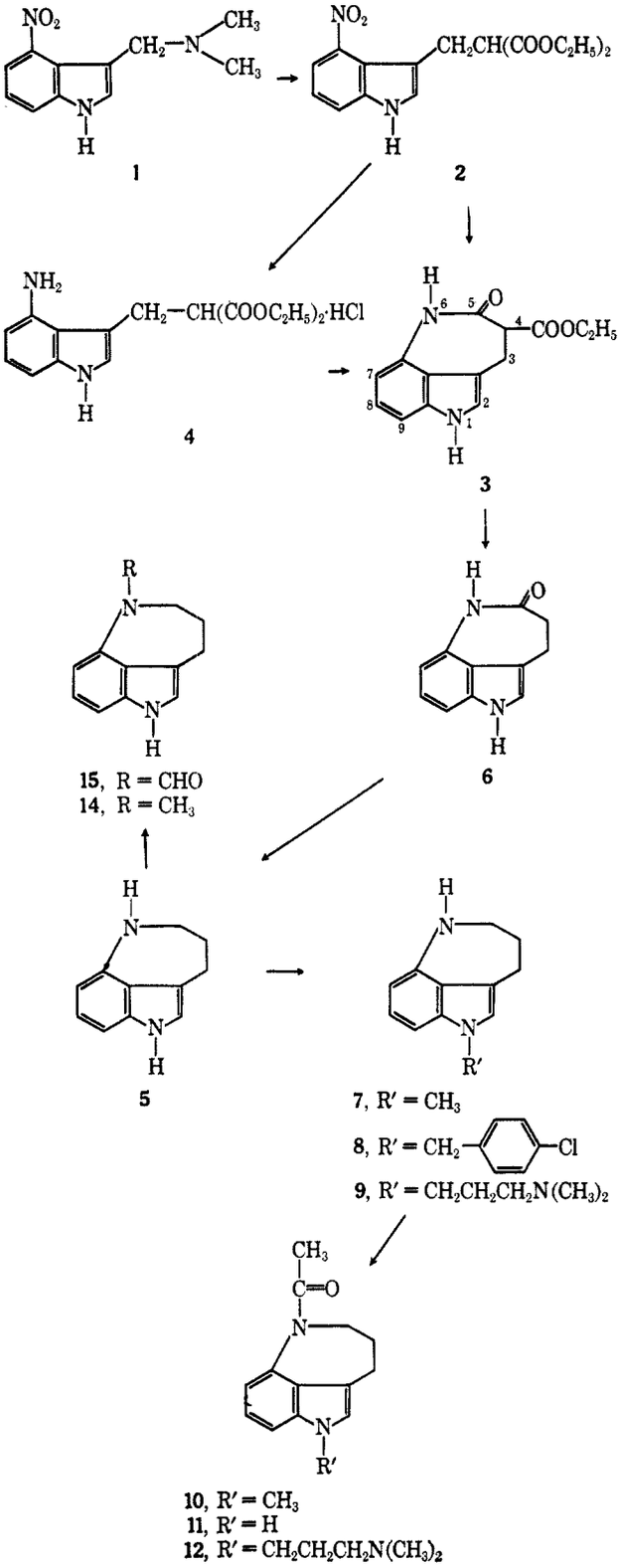
(4) G. Berti and A. DaSettimo, *Gazz. Chim. Ital.*, **90**, 525 (1960).

(5) H. Brockmann and H. Schodder, *Chem. Ber.*, **74**, 73 (1941).

(6) The nmr spectra were determined at 60 Mc in one of the following solvents: (a) deuteriodimethyl sulfoxide or (b) deuterium oxide. The peaks are reported in cycles per second downfield from tetramethylsilane.

(7) K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p 15.

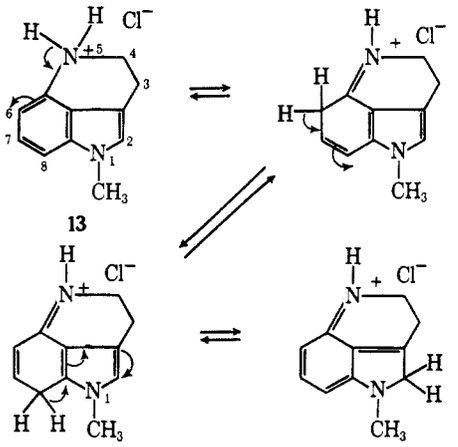
SCHEME I




decarboxylation. Lithium aluminum hydride reduction of **6** gave the amine (**5**) in good yield.

Selective alkylation of the indole nitrogen of **5** to give compounds **7**, **8**, and **9** was carried out using sodium hydride and the requisite alkyl halide.[3] Compound **7** was isolated as the N-6 acetamide (**10**) because of the apparent instability of its salts. The acetamides (**11**, **12**) of compounds **5** and **9**, respectively, were also prepared. An aspect of the nmr spectrum[6b] of the dihydrochloride salt of compound **9** is noteworthy. Instead of the complex multiplet normally observed for the four aromatic protons of this type of system (*vide supra*), this spectrum had a two-proton doublet with peaks at 446 and 441 cps. The exchangeable hydrogen peak at 290 cps was larger than expected which suggested that two of the aromatic protons were rapidly exchanging with the deuterium oxide solvent. Because of the insolubility of this compound in other nmr solvents, further study of this phenomenon was carried out with 1 - methyl - 1,3,4,5 - tetrahydropyrrolo[4,3,2 - *de*]quinoline hydrochloride (**13**).[3] In deuteriodimethyl sulfoxide, the nmr spectrum of **13** was normal, having a complex multiplet at 448–415 cps assigned to the four aromatic protons. In deuterium oxide, however, the aromatic protons were represented by a two-proton doublet with peaks at 438 and 424 cps. The exchangeable hydrogen peak at 279 cps accounted for the remaining aromatic protons. To explain this phenomenon, we suggest that salts of this type are in equilibrium with the tautomeric iminium ions (Scheme II). This explanation would predict the rapid equilibration of the C-6 and C-8 protons of **13** with deuterium oxide, leaving only the C-2 and C-7 proton absorption in the aromatic region of the spectrum. Slow equilibration of the C-2 proton might also be expected, but prolonged equilibration experiments have not been carried out to verify this proposal. Methylation of the basic nitrogen (N-6) of compound **5** to give **14** was accomplished in two steps by lithium aluminum hydride reduction of the formamide[3] (**15**).

SCHEME II




### Experimental Section[8]

**Diethyl (4-Nitroindol-3-ylmethyl)malonate (2).**—A vigorous stream of nitrogen was bubbled through a refluxing mixture of 100 g (0.457 mole) of 4-nitrogramine, 72 ml (0.474 mole) of diethyl malonate, 4 l. of dry benzene, and 5 g of powdered sodium hydroxide for 11.3 hr. The resulting dark mixture was allowed to stand for 18 hr at room temperature and was filtered. The solid was washed with ether and the combined filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to yield 98.5 g (64.5%) of diethyl (4-nitroindol-3-

(8) Melting points were taken in capillary tubes and are corrected. Unless otherwise indicated, ultraviolet spectra were determined in 95% ethanol using a Cary Model 14 spectrophotometer; infrared spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Darco G-60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington 99, Del. Celite is a filter aid manufactured by Johns-Manville, New York 16, N. Y. The alumina used for chromatography was obtained from M. Woelm, Eschwege, Germany, and the silica gel from E. Merck AG, Darmstadt, Germany.

ylmethyl)malonate, mp 109–111.5°. The analytical sample, mp 109–111°, was prepared by recrystallizing some of this material three times from ethyl acetate–Skellysolve B. The ultraviolet spectrum had $\lambda_{max}$ 212, 233, and 390 mμ (ε 37,000, 9300, and 4250, respectively) with an inflection at 336 mμ (ε 3150). The infrared spectrum showed NH 3335, C=O 1735, and $NO_2$ 1515, 1315 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.61; H, 5.38; N, 8.20.

**Diethyl (4-Aminoindol-3-ylmethyl)malonate Hydrochloride (4).**—A mixture of diethyl (4-nitroindol-3-ylmethyl)malonate (40.0 g, 0.120 mole), 10% palladium-on-carbon catalyst (8 g), and ethanol (1 l.) was hydrogenated in a Parr apparatus at an initial pressure of 27 psi for 2.5 hr. The catalyst was then removed by filtration through Celite and the filtrate was concentrated under reduced pressure. A suspension of the residue in water (100 ml) was acidified with 10% hydrochloric acid and the resulting crystalline salt was collected by filtration and dried under reduced pressure to give 37.6 g (91.5%) of diethyl (4-aminoindol-3-ylmethyl)malonate hydrochloride, mp 206–208° dec. The analytical sample, mp 217° dec, was prepared by recrystallizing some of this material from ethanol–Skellysolve B. The ultraviolet spectrum had $\lambda_{max}$ 224 and 278 mμ (ε 35,400 and 6720, respectively) with inflections at 286 and 298 mμ (ε 5950 and 4490, respectively). The infrared spectrum showed NH 3290 and C=O 1740 and 1710 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{21}ClN_2O_4$: C, 56.38; H, 6.21; Cl, 10.40; N, 8.22. Found: C, 56.66; H, 6.59; Cl, 10.23; N, 8.14.

**4-Carboethoxy-5-oxo-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]-indole (3).** A.—A mixture of the nitro diester (10 g, 29.9 mmoles), 10% palladium on charcoal (2 g), and 95% ethanol (300 ml) was hydrogenated in a Parr apparatus at an initial hydrogen pressure of 46 psi. After 15–30 min the reduction was complete and the catalyst was removed by filtration through Celite. The combined filtrate from five identical runs was concentrated *in vacuo*. Chromatography of the residue on 4 lb of Woelm neutral alumina (activity grade 1) with 50% ether–chloroform and 100% chloroform yielded a crystalline product which was recrystallized from ethanol to yield 15.8 g (41%) of 4-carboethoxy-5-oxo-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 211–213.5°. A sample of this material was crystallized three times from methanol for analysis, mp 211–213.5°. The ultraviolet spectrum had $\lambda_{max}$ 229 and 304 mμ (ε 34,300 and 10,850, respectively).

*Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.22; H, 5.75; N, 10.83.

B.—Diethyl (4-aminoindol-3-ylmethyl)malonate hydrochloride (1.00 g, 2.88 mmoles) was heated at 200–220° in an evacuated flask (18 mm). When the bubbling had become slow (about 10 min), the flask was cooled and the residue was crystallized from ethanol to give 0.355 g, mp 211–213°, and 0.183 g, mp 209.5–211° (72.5% yield) of 4-carboethoxy-5-oxo-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole. The mixture melting point with authentic material was undepressed.

**5-Oxo-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (6).**—A mixture of 4-carboethoxy-5-oxo-3,4,5,6-tetrahydro-1H-azepino-[4,3,2-*cd*]indole (16.7 g, 64.9 mmoles), 0.433 *N* aqueous potassium hydroxide (150 ml, 65 mmoles), and ethanol (850 ml) was refluxed under nitrogen for 6 hr and allowed to stand for 18 hr at room temperature. It was then concentrated to dryness *in vacuo*. An aqueous solution of the residue was cooled in an ice bath and acidified with hydrochloric acid. The solid which precipitated was collected by filtration, washed with water, and dried under reduced pressure at 30° to yield 15.7 g, mp 143–148° dec, of the crude acid. This was heated at about 170° in an evacuated flask (17 mm) for 30 min. During the reaction the solid acid slowly decarboxylated to yield a solid product. This was recrystallized from ethanol to yield 10.8 g (89.4%) of 5-oxo-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 213–214°. A sample of this material was recrystallized three times from ethanol for analysis, mp 214–216°. The ultraviolet spectrum had $\lambda_{max}$ 231 and 304 mμ (ε 37,050 and 10,850, respectively). The infrared spectrum showed NH 3220, 3100 and C=O 1645 $cm^{-1}$.

*Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.83; H, 5.32; N, 14.85.

**3,4,5,6-Tetrahydro-1H-azepino[4,3,2-*cd*]indole (5).**—To a stirred, ice-cold suspension of 7 g of lithium aluminum hydride in 700 ml of dry tetrahydrofuran was added, under nitrogen, 7 g (37.6 mmoles) of 5-oxo-3,4,5,6-tetrahydro-1H-azepino-[4,3,2-*cd*]indole. The resulting mixture was refluxed for 6 hr and allowed to stand at room temperature for 18 hr. It was then treated successively with 7 ml of water, 7 ml of aqueous 15% sodium hydroxide, and 21 ml of water. The inorganic precipitate was collected by vacuum filtration and washed with ether. Concentration of the combined filtrates yielded the product which was crystallized from ethyl acetate–Skellysolve B to give 3.41 g (52.7%) of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 119–121.5°. An ether solution of the base was decolorized with Darco G 60 and crystallized several times from ether for analysis, mp 119–120°. The ultraviolet spectrum had $\lambda_{max}$ 230 and 296 mμ (ε 31,750 and 8750, respectively) with inflections at 288 and 302 mμ (ε 8350 and 8600, respectively).

*Anal.* Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 77.11; H, 7.22; N, 16.43.

**6-Formyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (15).**—Formic acetic anhydride was prepared by allowing a mixture of 97% formic acid (3.98 ml) and acetic anhyride (9.45 ml) to stand at room temperature for 1 hr. To 10 ml of this reagent, cooled in an ice bath, was added 2.50 g (14.5 mmoles) of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole. The product rapidly crystallized from the solution. The resulting mixture was allowed to stand at room temperature for 24 hr. It was then poured into ice water. The solid was collected by filtration, washed with water, and dried under reduced pressure at 30° to yield 2.84 g of crude product, mp 190–192°. Recrystallization of this material from ethyl acetate yielded 2.67 g (92.2%) of 6-formyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 190.5–193°. The analytical sample, mp 192–193°, was prepared by recrystallizing some of this material three times from ethyl acetate. The ultraviolet spectrum had $\lambda_{max}$ 226 and 296 mμ (ε 37,550 and 9650, respectively) with an inflection at 288 mμ (ε 8700). The infrared spectrum showed NH 3280 and C=O 1640 $cm^{-1}$.

*Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.79; H, 6.19; N, 13.57.

**6-Methyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (14).**—To an ice-cold suspension of 2.5 g of lithium aluminum hydride in 260 ml of dry tetrahydrofuran was added 2.48 g (12.4 mmoles) of 6-formyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole. The resulting mixture was refluxed, under nitrogen, for 10 hr. It was then cooled in an ice bath and treated successively with 2.5 ml of water, 2.5 ml of 15% aqueous sodium hydroxide, and 7.5 ml of water. The resulting mixture was stirred in the ice bath for about 1 hr. The solid was collected by filtration and washed several times with ether. Concentration of the combined filtrate yielded the product which was dissolved in ether, decolorized with activated charcoal, and crystallized from ether–Skellysolve B to yield 2.05 g (88.7%) of 6-methyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 98–99.5°. The analytical sample, mp 98.5–100.5°, was prepared by recrystallizing some of this material from ether–Skellysolve B. The ultraviolet spectrum had $\lambda_{max}$ 229 and 305 mμ (ε 34,200 and 10,500, respectively) with an inflection at 290 mμ (ε 9250).

*Anal.* Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.70; H, 7.69; N, 14.92.

**6-Acetyl-1-methyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]-indole (10).**—To a stirred solution of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (3.0 g, 17.4 mmoles) in dry dimethylformamide (90 ml), under nitrogen, was added a 53.4% suspension of sodium hydride in mineral oil (1.02 g, 22.6 mmoles). The resulting mixture was stirred at room temperature for 1 hr, cooled in an ice bath, and treated, during 10 min, with methyl iodide (3.20 g, 22.6 mmoles). It was then allowed to warm up to room temperature and stand for 20 hr. The reaction mixture was poured into ice water (600 ml) and extracted with ether. The ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in acetic anhydride (30 ml) was allowed to stand at room temperature under nitrogen for 18 hr. It was then poured into water and the product was extracted with ether. The ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residual oil on silica gel (300 g) with ethyl acetate resulted in a solid which was crystallized from ethyl acetate–Skellysolve B to yield 2.0 g of 6-acetyl-1-methyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]-indole, mp 89–90°. The ultraviolet spectrum had $\lambda_{max}$ 231 and 303 mμ (ε 35,950 and 7850, respectively) with an inflection at 280 mμ (ε 5150).

*Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.63; H, 7.16; N, 12.35.

**1-(*p*-Chlorobenzyl)-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]-indole (8).**—To a stirred solution of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (3.0 g, 17.4 mmoles) in dry dimethylformamide (90 ml), under nitrogen, was added a 53.4% suspension of sodium hydride in mineral oil (1.02 g, 22.6 mmoles). The resulting mixture was stirred at room temperature for 1 hr, cooled in an ice bath, and treated during 10 min with 3.63 g (22.6 mmoles) of *p*-chlorobenzyl chloride. It was then allowed to warm up to room temperature and stand for 20 hr. The reaction mixture was poured into ice water (500 ml) and extracted with ether. The ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was decolorized with Darco G 60 and recrystallized several times from ethyl acetate–Skellysolve B to yield 2.0 g (39%) of 1-(*p*-chlorobenzyl)-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 116–117.5°. The ultraviolet spectrum had $\lambda_{max}$ 226 and 313 mμ (ε 32,050 and 9900, respectively) with inflections at 269, 278, and 290 mμ (ε 4200, 5700, and 7300, respectively).

*Anal.* Calcd for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; Cl, 11.95; N, 9.44. Found: C, 73.11; H, 5.80; Cl, 12.13; N, 9.74.

**1-[3-(Dimethylamino)propyl]3,4,5,6-tetrahydro-1H-azepino-[4,3,2-*cd*]indole Dihydrochloride (9).**—To a stirred solution of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (3.0 g, 17.4 mmoles) in dry dimethylformamide (90 ml), under nitrogen, was added a 53.4% suspension of sodium hydride in mineral oil (1.02 g, 22.6 mmoles). The resulting mixture was stirred at room temperature for 1 hr, cooled in an ice bath, and treated, during 10 min, with 4.86 ml (22.6 mmoles) of a 50% solution of 3-(dimethylamino)propyl chloride in toluene. It was then allowed to warm up to room temperature and stand for 20 hr. The reaction mixture was poured into ice water (600 ml) and extracted with ether. The ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in ether was acidified with ethereal hydrogen chloride. The resulting hydrochloride was recrystallized from methanol–Skellysolve B to yield 2.14 g (38.9%) of 1-[3-(dimethylamino)-propyl]-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole dihydrochloride, mp 268–269° dec. The analytical sample, mp 276° dec, was prepared by recrystallizing some of this material from methanol–Skellysolve B. The ultraviolet spectrum had $\lambda_{max}$ 233, 291, and 313 mμ (ε 29,400, 7200, and 8800, respectively) with an inflection at 214 mμ (ε 16,900).

*Anal.* Calcd for $C_{16}H_{23}N_3 \cdot 2HCl$: C, 58.18; H, 7.63; N, 12.72; Cl, 21.47. Found: C, 57.81; H, 7.33; N, 12.30; Cl, 20.26.

**6-Acetyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (11).**—A mixture of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (1.19 g, 6.88 mmoles) and acetic anhydride (15 ml) was allowed to stand under nitrogen, for 18 hr. It was then poured into water. The solid product was collected by filtration, washed with water, and dried under reduced pressure at 35°. A solution of this material in ethyl acetate was decolorized with Darco G-60 and crystallized to yield 1.06 g (72%) of 6-acetyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 196–197.5°. The analytical sample, mp 197–199°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum had $\lambda_{max}$ 228 and 294 mμ (ε 38,700 and 8450, respectively) with an inflection at 285 mμ (ε 7750).

*Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.73; H, 6.33; N, 13.14.

**6-Acetyl-1-[3-(dimethylamino)propyl]-3,4,5,6-tetrahydra-1H-azepino[4,3,2-*cd*]indole Hydrochloride (12).**—A suspension of 1-[3-(dimethylamino)propyl]-3,4,5,6-tetrahydro-1H-azepino-[4,3,2-*cd*]indole dihydrochloride (1.50 g, 4.74 mmoles) in dilute sodium hydroxide was stirred with ether. The resulting ether solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in acetic anhydride (20 ml) was allowed stand at room temperature for 18 hr. It was then poured into water. The aqueous solution was made alkaline with sodium hydroxide and the product was extracted with ether. The ether solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in ether was acidified with ethereal hydrogen chloride; the resulting hydrochloride was crystallized from ethanol–ether to yield 1.49 g of 6-acetyl-1-[3-(dimethylamino)propyl]-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole hydrochloride, mp 250–251°. The ultraviolet spectrum had $\lambda_{max}$ 231 and 301 mμ (ε 38,550 and 9150, respectively) with an inflection at 283 mμ (ε 6600).

*Anal.* Calcd for $C_{18}H_{25}N_3O \cdot HCl$: C, 64.36; H, 7.80; N, 12.51; Cl, 10.56. Found: C, 64.84; H, 8.12; N, 12.62; Cl, 10.24.

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## 4-Indol-3-yl-1-methylhexahydroazepines

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Our interest in the chemistry of 3-(1-methyl-2-pyrrolidinyl)indole[1] (1) led us to investigate the susceptibility of this graminelike compound to nucleophilic ring opening reactions. After several abortive attempts to condense 1 with potassium cyanide, we studied its sodium hydroxide catalyzed reaction with diethyl malonate, a reaction which proceeds well with gramine to give ethyl 2-carboethoxy-3-(indol-3-yl)propionate.[2] In theory, diethyl malonate could in this case serve both as a nucleophile and as an anion acceptor. Thus, displacement of the amine from C-2 of the pyrrolidine ring would yield a highly reactive anion which could be accepted by one of the ester groups to form a cyclic amide, driving the reaction to completion. In practice, reaction of 1 with diethyl malonate and powdered sodium hydroxide under forcing conditions (refluxing xylene for 2 days) yielded *trans*-3-carboethoxy-4-(indol-3-yl)-1-methylhexahydroazepin-2-one (2) which was isolated by chromatography in about 13% yield (Scheme I). Structure 2 was supported by its infrared ($\nu_{max}$ 3290, 1740, and 1627 $cm^{-1}$) and ultraviolet ($\lambda_{max}$ 220, 281.5, and 290 mμ) spectra which provide evidence for an NH, ester, and amide carbonyls, and the indole chromophore. The nmr spectrum[3a] had a singlet at 647 cps for the indole NH, a complex multiplet at 460–410 cps for the five additional indole protons, a doublet centered at 258 cps[4] ($J$ = 9.5 cps) assigned to the C-3 proton of the azepine ring, a quartet centered at 234 cps and a triplet centered at 56.5 cps (apparent $J$ = 7 cps) for the ethyl group of the ester, a sharp singlet at 175.5 cps for the N-methyl protons, and a broad absorption centered at about 104 cps for the C-5 and C-6 protons. The C-4 proton of the azepine ring (centered at 211 cps[4]) was partially obscured by the C-7 proton absorption at about 236–214 cps.

The stereochemical assignment for the indole and ester groups of 2 was obtained by a consideration of the

(1) G. A. Youngdale, *et al.*, *J. Med. Chem.*, **7**, 415 (1964).

(2) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Am. Chem. Soc.*, **67**, 38 (1945).

(3) The nmr spectra were determined at 60 Mc in one of the following solvents: (a) deuteriodimethyl sulfoxide or (b) deuteriodimethylformamide. The peaks are reported in cycles per second downfield from tetramethylsilane.

(4) Calculated, *cf.* R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 165, p 84.