Alternate Precursors in Biogenetic-Type Syntheses. IV.[1] The Selective Conversion of 2-Alkyl-1-(indol-3-ylmethyl)-1,2-dihydroisoquinolines into Either 2-Alkyl-3-(indol-3-ylmethyl)-3,4-dihydroisoquinolinium Salts or Indolopavine Derivatives

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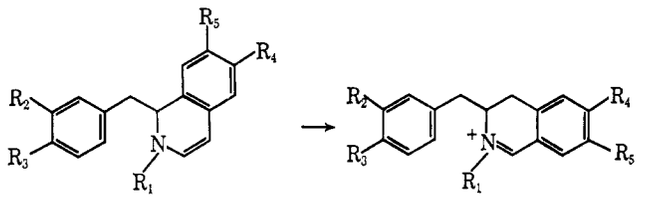
In contrast with what has been observed with **1**, the reaction of 2-alkyl-1-(indol-3-ylmethyl)-1,2-dihydroisoquinolines (**5**) with excess dilute acid results in the formation of indolopavine derivatives (**7**). The rearrangement of **5** to 2-alkyl-3-(indol-3-ylmethyl)-3,4-dihydroisoquinolinium salts (**6**) can be effected by using not more than 1 equiv of acid.

Knabe and coworkers[2] have described the rearrangement of 2-alkyl-1-benzyl-1,2-dihydroisoquinolines (**1**) to form 2-alkyl-3-benzyl-3,4-dihydroisoquinolinium salts (**2**). The conditions reported for effecting



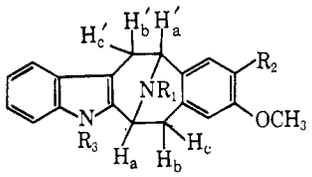
1 **2**

this transformation consisted of heating **1** with excess dilute acid and isolation of the product **2** as the corresponding 1-cyano-1,2,3,4-tetrahydro derivative. Extension of this procedure to 2-alkyl-1-(3-indolylmethyl)-1,2-dihydroisoquinolines (**5**) appeared to be a promising route to 2-alkyl-3-(indol-3-ylmethyl)-3,4-dihydroisoquinolinium salts (**6**) required as intermediates for our continuing study of the use of alternate precursors in biogenetic-type syntheses.

The starting materials for this investigation were 1-(indol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolines (**3a**[3] and **3c**[1]) (Chart I) which were aromatized by refluxing with palladium black in cymene to give **4a** and **4c**, respectively. Quaternization followed by lithium aluminum hydride reduction gave the required 1,2-dihydroisoquinolines (**5**) which were used without purification.

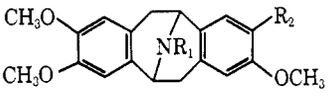
We have subjected **5** to the same conditions[2] employed with **1** and have found the reaction to take a completely different course. Instead of rearrangement of **5** to the corresponding 3-substituted derivative **6**, cyclization took place to give 6,7,12,13-tetrahydro-6,12-imino-5H-benz[5,6]cyclooct[1,2-*b*]indoles of structure **7a–d**.[4]

The conversion of **7a** and **7b** into the corresponding N_{ind}-methyl derivatives (**9a** and **9b**) was accomplished by the use of sodium amide and methyl iodide in liquid ammonia. Catalytic debenzylation of **7b**, **7d**, and **9b** gave the corresponding secondary amines, **9c**, **9d**, and **9e**. The 14-carbethoxy derivative, **9f**, was obtained by the reaction of **7a** with ethyl chloroformate and anhydrous sodium carbonate in dichloromethane. Treatment of **9f** with sodium hydride and ethyl chloroformate in dimethylformamide resulted in the formation of **9g**.



9a, $R_1 = R_3 = CH_3$; $R_2 = H$
b, $R_1 = C_6H_5CH_2$; $R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_2 = R_3 = H$
d, $R_1 = R_3 = H$; $R_2 = OCH_3$
e, $R_1 = R_2 = H$; $R_3 = CH_3$
f, $R_1 = CO_2C_2H_5$; $R_2 = R_3 = H$
g, $R_1 = R_3 = CO_2C_2H_5$; $R_2 = H$

The structural assignment of these compounds follows from elemental analyses, negative Ehrlich test, and examination of the nmr spectra as typified by that of **7b**. The bridgehead hydrogens, H_a and H_a' (see structure **9**), appear as two doublets (J = 6 cps) at 4.29 and 4.10 ppm, respectively, H_c and H_c' as two overlapping doublets (J = 17 cps) at 2.70 and 2.65 ppm, respectively, and H_b and H_b' as a multiplet between 3.67 and 3.25 ppm. This can be related to the reported spectra of **10a** and **10b** which were interpreted as rep-



10a, $R_1 = H$; $R_2 = OCH_3$
b, $R_1 = CH_3$; $R_2 = OCH_3$
c, $R_1 = CH_3$; $R_2 = H$

resenting a system in which the bridgehead hydrogens are coupled appreciably with only one of the two ad-

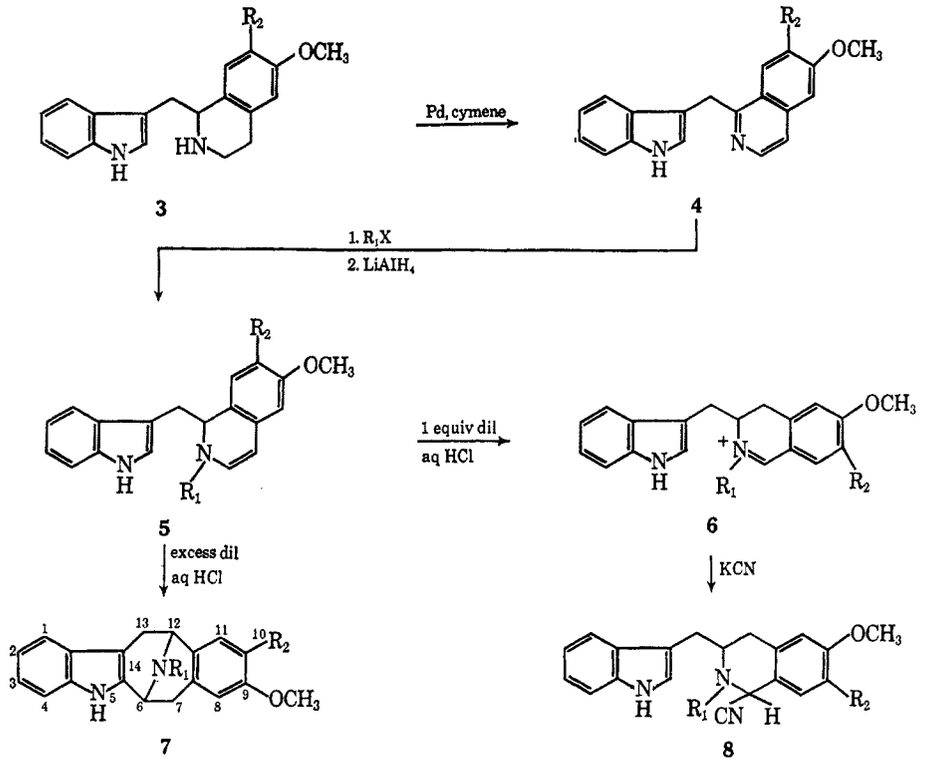
(1) Paper III: G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 1663 (1968).

(2) J. Knabe, J. Kubitz, and N. Ruppenthal, *Angew. Chem. Intern. Ed. Eng.*, **2**, 689 (1963); J. Knabe and J. Kubitz, *Arch. Pharm.*, **297**, 129 (1964); J. Knabe and N. Ruppenthal, *ibid.*, **297**, 141, 268 (1964); **299**, 159 (1966); J. Knabe and K. Detering, *ibid.*, **300**, 97 (1967). See also S. F. Dyke and M. Sainsbury, *Tetrahedron Lett.*, 1545 (1964); *Tetrahedron*, **21**, 1907 (1965).

(3) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).

(4) While the mechanism of formation of **7** has not been studied, it is apparent that these compounds could arise through direct cyclization at the unsubstituted indole 2 position of **5** or by preliminary attack at the 3 position. In the latter case, the resulting 3,3-spiroindolenine would be expected to rearrange preferentially to **7** because of the influence of the nitrogen. See A. H. Jackson and A. E. Smith, *Tetrahedron*, **24**, 403 (1968); A. H. Jackson and P. Smith, *ibid.*, **24**, 3227 (1968); B. Belleau, *Chem. Ind.* (London), 229 (1955).

CHART I



3 4 5 6 7 8

a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = C_6H_5CH_2$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = OCH_3$
d, $R_1 = C_6H_5CH_2$; $R_2 = OCH_3$

jacent hydrogens (*i.e.*, H_a coupled with H_b but not with H_c).[5-7]

Further evidence for the bridged structure is given by comparison of the nmr spectra of **9f** and **9g**. The bridgehead hydrogen signals of **9f** occur together as an apparent triplet at 5.45 ppm. With **9g**, the H_a' signal remains as a doublet at 5.42 ppm but that due to H_a separates as a doublet at 6.23 ppm.

These compounds may be considered as indolopavine derivatives since they are structurally related to **10a**, which has been known for many years as pavine.[8,9] The demonstration[5,10] that argemonine, isolated[11] from Argemone species, is identical with (−)-N-methylpavine (**10b**) has been followed by the discovery that other alkaloids also possess the pavine skeleton.[12] While no naturally occurring indolopavine derivatives have been reported, alstophylline and other related Alstonia alkaloids have been shown to have the same indolo-bridged structure with ring E being heterocyclic rather than homocyclic.[13] Since the argemonine class of alkaloids are believed to arise[14] through a reaction which is analogous to that employed in our indolopavine synthesis, it is apparent that the latter represents another example of the use of a 1-(indol-3-ylmethyl)-isoquinoline derivative as an alternate precursor[3,15] in a biogenetic-type[16] synthesis of a missing alkaloid system.[17]

Further study has shown that the Knabe[2] rearrangement can indeed be realized in the indole series by carefully avoiding excess acid. Control of the amount of acid used was most conveniently achieved by titration for total alkali content of the filtered hydrolyzed lithium aluminum hydride reaction mixture. It was then heated with slightly less than 1 equiv of dilute aqueous hydrochloric acid. Compounds **5a** and **5c** were thus converted into **6a** and **6c**, respectively. The latter

(5) M. J. Martell, Jr., T. O. Soine, and L. B. Kier, *J. Amer. Chem. Soc.*, **85**, 1022 (1963); *J. Pharm. Sci.*, **56**, 973 (1967).

(6) A similar phenomenon in the bicyclo[2.2.1]heptane system has been studied by F. A. L. Anet [*Can. J. Chem.*, **39**, 789 (1961)].

(7) The spectrum of **7b** differs from those reported[5] for **9a** and **9b** in that the latter show H_a and H_c each as a single doublet. This is a consequence of the symmetrical structure of **9a** and **9b** which makes H_a equivalent to H_a' and H_c equivalent to H_c'. We have recorded the spectrum of the less symmetrical **10c** and have found H_c and H_c' to be clearly represented by two overlapping doublets (J = 17 cps) at 2.67 and 2.50 ppm. The bridgehead hydrogens, H_a and H_a', are not so readily distinguishable since they appear fused together as a fairly broad signal centered at 3.97 ppm.

(8) F. L. Pyman and W. C. Reynolds, *J. Chem. Soc.*, **97**, 1320 (1910).

(9) A. R. Battersby and R. Binks, *ibid.*, 2888 (1955).

(10) F. R. Stermitz, S-Y. Lwo, and G. Kallos, *J. Amer. Chem. Soc.*, **85**, 1551 (1963).

(11) T. O. Soine and O. Gisvold., *J. Amer. Pharm. Assn. Sci. Ed.*, **33**, 185 (1944); J. W. Schermerhorn and T. O. Soine, *ibid.*, **40**, 19 (1951).

(12) R. H. F. Manske, K. H. Shin, A. R. Battersby, and D. F. Shaw, *Can. J. Chem.*, **43**, 2183 (1965); R. H. F. Manske and K. H. Shin, *ibid.*, 44, 1259 (1966); F. R. Stermitz and J. N. Seiber, *Tetrahedron Lett.*, 1177 (1966).

(13) T. Kishi, M. Hesse, C. W. Gemenden, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, **48**, 1349 (1965); M. Hesse, F. Bodmer, C. W. Gemenden, B. S. Joshi, W. I. Taylor, and H. Schmid, *ibid.*, **49**, 1173 (1966); Z. M. Khan, M. Hesse, and H. Schmid, *ibid.*, **50**, 1002 (1967); C. E. Nordman and S. Kumra, *J. Amer. Chem. Soc.*, **87**, 2059 (1965).

(14) (a) F. R. Stermitz and J. N. Seiber, *J. Org. Chem.*, **31**, 2925 (1966); (b) A. C. Barker and A. R. Battersby, *J. Chem. Soc., C*, 1317 (1967).

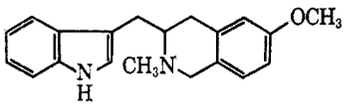
(15) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavet, Jr., *J. Org. Chem.*, **32**, 2551 (1967).

(16) E. E. van Tamelen, "Progress in the Chemistry of Organic Natural Products," Vol. 19, L. Zeckmeister, Ed., Springer-Verlag, Vienna, 1961, p 242.

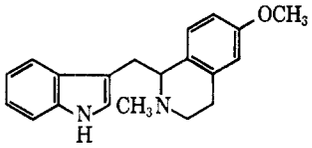
(17) A missing alkaloid system is defined as a ring system, considered derivable through biogenetic processes, which has not as yet been observed in natural products. It differs from a corresponding naturally occurring system through recognizable features such as isosterism and/or simple structural isomerism. The laboratory procedure for the cyclization of **1** (R_1 = CH_3, $R_2 = R_3 = R_4 = R_5 = OCH_3$) to N-methylpavine (**10b**) was described before naturally occurring argemonine was shown to have this structure.[5,10] Thus, N-methylpavine could have been considered to be representative of a "missing alkaloid system" when it was first synthesized.

were isolated as the corresponding cyano derivatives, **8a** and **8c**, in respective over-all yields[18] of 46 and 40%.

Evidence for the structure of **8a** was obtained by acid hydrolysis followed by sodium borohydride reduction to give **11**.[19] This was compared with and found to



11



12

be different from an authentic sample of its isomer **12**.[3] The nmr spectrum of **8a** and **8c** showed the proton geminal to the cyano group to be represented largely by a singlet at 4.75 ppm. However, a much smaller singlet was also present at 4.82 ppm, indicating the presence of a second diastereoisomer.[20]

The fact that there is greater competition between cyclization and rearrangement in the indole series (**5**) than in the benzene series (**1**) is undoubtedly related to the greater nucleophilicity of indole over that of alkoxy benzene. Compound **9b** has been obtained from **1** (R_1 = CH_3; R_2 = R_3 = R_4 = R_5 = OCH_3), but this required prolonged heating with a mixture of concentrated formic and phosphoric acids.[21]

The use of **11** as an intermediate in a biogenetic-type[3,15,16] synthesis of a novel bridged heterocyclic system will be described in a forthcoming publication.

Experimental Section[22]

1-(Indol-3-ylmethyl)-6-methoxyisoquinoline (4a).—A mixture of 125 g (0.43 mol) of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline (**3a**), 7.2 g of palladium black, and 2500 ml of *p*-cymene was refluxed under nitrogen with vigorous stirring for 20 hr. The contents were cooled to room temperature, and the mixture of palladium and crystalline product was filtered off. The product was dissolved away from the palladium with dichloromethane, and the filtered solution was distilled *in vacuo* to dryness, the last traces of dichloromethane being removed by distilling from some added Skellysolve C. The residue was triturated with petroleum ether (bp 30–60°) to give 100.8 g of product, mp 159–160°. Recrystallization from isopropyl ether gave an analytical sample: mp 163–164°; λ_{max} 224 mμ (ε 66,000), 232 (69,000), 272 (11,500), 280 (12,000), 291 sh (10,500).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.34; H, 5.52; N, 9.48.

The methiodide[23] had mp 247–249° dec.

Anal. Calcd for $C_{20}H_{19}IN_2O$: C, 55.83; H, 4.45; N, 6.51. Found: C, 55.53; H, 4.48; N, 6.62.

The benzyl bromide salt[23] had mp 219–222° dec.

1-(Indol-3-ylmethyl)-6,7-dimethoxyisoquinoline (4c).—With 80 g (0.24 mol) of **3c** the above procedure was employed with the exception that hot chloroform was used to separate the product from the palladium. Recrystallization of the crude product from methanol–dichloromethane gave 63 g of material: mp 241–243° dec; λ_{max} 216 mμ (ε 57,500), 237 (66,000), 268–274 (10,300), 290 sh (8220), 313 (4100), 326 (4800).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.56; H, 5.67; N, 9.02.

The methiodide[23] had mp 245–246° dec.

The benzyl bromide salt[23] had mp 217–218.5° dec.

1-(3,4-Dimethoxybenzyl)-6-methoxyisoquinoline.—The above procedure was employed with 20.7 g (0.066 mol) of 1-(3,4-dimethoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline.[24] In this case the product remained in solution and was thus filtered from the catalyst. The cymene filtrate was evaporated to a residue which solidified on trituration with petroleum ether (bp 30–60°). Recrystallization from dichloromethane–isopropyl ether gave 13 g of product, mp 85–87°. Further recrystallization gave an analytical sample: mp 88–89°; λ_{max} 233 mμ (ε 65,600), 281 (8400).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.91; H, 6.12; N, 4.65.

The methiodide[23] had mp 197–199° dec.

Reaction of 5c with (A) Excess and (B) 1 Equiv of Dilute Hydrochloric Acid.—A mixture of 20.7 g (0.045 mol) of the methiodide of **4c**, 5.1 g (0.135 mol) of lithium aluminum hydride, and 450 ml of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was hydrolyzed and filtered, and the filtrate was concentrated to a volume of 200 ml by the use of a rotary flash evaporator (maximum bath temperature 30°). Titration of a 1-ml aliquot indicated a total alkali content of 44.6 mequiv.

A.—Half of the tetrahydrofuran solution was treated with 450 ml of 0.5 *N* hydrochloric acid and stirred on a steam bath (temperature 95°) under nitrogen for 1 hr. The cooled reaction mixture was treated with 200 ml of 1 *N* sodium hydroxide (pH 5), made alkaline by the addition of excess sodium bicarbonate, and extracted with dichloromethane. *No precipitate* was obtained when a solution of 4.2 g of potassium cyanide in 10 ml of water was added to the aqueous layer. The dichloromethane was evaporated to dryness and the residue was triturated with 5 ml of methanol to give 5.5 g of 6,7,12,13-tetrahydro-9,10-dimethoxy-6,12-imino-5H-benzo[5,6]cyclooct[1,2-*b*]indole (**7c**), mp 225–227°. Recrystallization from dichloromethane–methanol gave an analytical sample: mp 227–228° dec; λ_{max} 225 mμ (ε 40,400), 282 (11,200), 291 (10,200).

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.37; H, 6.75; N, 8.17.

The hydrochloride salt, recrystallized from 2-butanone–ethanol, had mp 234–240° dec.

Anal. Calcd for $C_{21}H_{22}N_2O_2 \cdot HCl$: C, 68.01; H, 6.25; N, 7.55; Cl, 9.56. Found: C, 68.29; H, 6.37; N, 7.61; Cl, 9.72.

B.—To the second half of the tetrahydrofuran solution, described above, was added 215 ml of 0.1 *N* hydrochloric acid and 240 ml of water. The solution was stirred on a steam bath (temperature 95°) under nitrogen for 1 hr. The cooled reaction mixture was made alkaline with sodium bicarbonate and extracted with dichloromethane. Addition of a solution of 4.2 g of potassium cyanide in 10 ml of water to the aqueous layer resulted in precipitation of an oil which crystallized on scratching. This was collected and dissolved in dichloromethane. The solution was washed with water, dried, and evaporated to give 3.5 g of crystalline 1-cyano-3-(indol-3-ylmethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**8c**), mp 147–149°. Recrystallization from dichloromethane–methanol gave an analyti-

(18) Yields were based on the quaternary salt of **4a** and **4c**, respectively.

(19) The preparation of the desmethoxy analog of **14** by a different method has been described by H. Bader and W. Oroshnik [*J. Amer. Chem. Soc.*, **81**, 163 (1954)].

(20) We have prepared the corresponding cyano derivative of **2** (R_1 = CH_3, R_2 = R_3 = R_4 = OCH_3, R_5 = H). As in the case of **8a** and **8c**, the nmr showed the presence of a small singlet at 4.88 ppm accompanying the much larger singlet at 4.78 ppm.

(21) We have employed the same procedure for the preparation of **10c**. See the Experimental Section.

(22) Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DKI spectrophotometer and a Baird Model 455 double-beam instrument. The former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The pmr spectra were determined in $CDCl_3$ with the Varian A-60 spectrometer using Me_4Si as an internal standard. Compounds were checked for homogeneity using thin layer chromatography on alumina with varying proportions of *n*-heptane and 2-butanone as the eluent. Chromatograms were developed with iodine. The drying agent used throughout was sodium sulfate.

(23) These quaternary salts were precipitated in near-quantitative yield when an acetone solution of the base was refluxed with excess methyl iodide (3 hr) or benzyl bromide (20 hr). Since considerable decomposition occurred during attempted recrystallization, they were used without further purification.

(24) R. A. Robinson, U. S. Patent 2,683,146 (July 6, 1954); *Chem. Abstr.*, **49**, 9045*d* (1955).

cal sample: mp 149–150°; λ_{max} 220 mμ (ε 40,500), 250 (15,000), 279 (8800), 289 (8800), 310 (6700), 360 (5750).

Anal. Calcd for $C_{22}H_{23}N_3O_2$: C, 73.10; H, 6.41; N, 11.63. Found: C, 73.21; H, 6.69; N, 11.73.

General Preparative Method for the Synthesis of 14-Methyl- or 14-Benzylindolopavine Derivatives, 7a, 7b, 7c, and 7d.—A mixture of 0.4 mol of the methiodide or benzyl bromide salt of either **4a** or **4c**, 30.3 g (0.8 mol) of lithium aluminum hydride, and 4000 ml of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was hydrolyzed and filtered. To the filtrate was added 2730 ml of 1 *N* hydrochloric acid, and the tetrahydrofuran was distilled off. After the addition of 1500 ml of methanol and 1360 ml more 1 *N* hydrochloric acid, the mixture was refluxed under nitrogen for 1 hr and the methanol was removed by distillation. The resulting aqueous solution was made basic with ammonium hydroxide and extracted with dichloromethane. Purification was carried out as described for the individual compounds. Yields are based on quaternary salt of **4a** or **4c**.

Compound 7a.—Concentration of the dichloromethane solution resulted in crystallization of **7a**, mp 269–270° dec, in 76% yield. Recrystallization of a portion from dichloromethane–methanol gave an analytical sample: mp 271–272° dec; λ_{max} 225 mμ (ε 40,400), 279 (9600), 290 sh (6400).

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.86; H, 6.66; N, 9.01.

The phosphate salt, recrystallized from water, had mp 195–205° dec.

Anal. Calcd for $C_{20}H_{20}N_2O \cdot H_3PO_4 \cdot 0.5H_2O$: C, 58.39; H, 5.88; N, 6.81; P, 7.53. Found: C, 58.64; H, 5.99; N, 6.64; P, 7.43.

The methiodide salt, which crystallized on formation from acetone, had mp 273–275° dec.

Anal. Calcd for $C_{20}H_{20}N_2O \cdot CH_3I$: C, 56.51; H, 5.19; N, 6.28; I, 28.43. Found: C, 56.23; H, 5.24; N, 6.57; I, 28.23.

Compound 7b.—The dichloromethane solution was evaporated to dryness, and the residue was recrystallized from dichloromethane–ethanol to give **7b**, mp 231.5–232.5° dec, in 85% yield.

Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 81.93; H, 6.38; N, 7.22.

Compound 7c.—The dichloromethane solution was evaporated to dryness, and the residue was recrystallized from dichloromethane–ethanol to give **7c**, mp 227–228° dec, in 80% yield.

Compound 7d.—Evaporation of the dichloromethane solution gave a residue which was triturated with isopropyl ether to form amorphous **7d**, mp 140–150° dec, in 90% yield. Since this could only be recrystallized in very poor yield, it was used without further purification for the preparation of **11b**. An analytical sample, mp 140–145° dec, was obtained by recrystallization of a portion from isopropyl ether.

Anal. Calcd for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.83. Found: C, 78.79; H, 6.50; N, 6.96.

N_{ind} Methylation of Indolopavine Derivatives. Preparation of 9a and 9b.—To a solution of 5.85 g (0.15 mol) of sodium amide in 1500 ml of liquid ammonia was added a solution of 0.075 mol of **7a** or **7b** in 500 ml of tetrahydrofuran. The solution was stirred for 1 hr, 10.86 g (0.077 mol) of methyl iodide was added, and stirring was continued for an additional hour. The ammonia was evaporated off, the tetrahydrofuran was removed using a rotary flash evaporator, and the residue was partitioned between dichloromethane and water. The dried dichloromethane solution was evaporated to a residue. Purification was carried out as described below.

Compound 9a.—An ethereal solution of the residue was treated with excess hydrogen chloride. The precipitated hydrochloride salt was triturated with 2-butanone and then recrystallized from ethanol to give the crystalline hydrochloride, mp 265.5–166.5° dec, in 67% yield.

Anal. Calcd for $C_{21}H_{22}N_2O \cdot HCl$: C, 71.08; H, 6.53; N, 7.89; Cl, 9.99. Found: C, 70.99; H, 6.54; N, 7.69; Cl, 10.13.

Basification of an aqueous solution of the hydrochloride, extraction with dichloromethane, and evaporation of the solvent resulted in quantitative recovery of the amorphous base which could not be recrystallized. A filtered petroleum ether solution of the base was evaporated; the residue, after drying *in vacuo* at 80°, melted at 85–90° and showed a single spot on thin layer chromatography.

Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 78.95; H, 7.07; N, 8.61.

Refluxing an acetone solution of the base with methyl iodide resulted in precipitation of the methiodide, mp 306–307° dec.

Anal. Calcd for $C_{21}H_{22}N_2O \cdot CH_3I$: C, 57.40; H, 5.47; N, 6.09. Found: C, 57.47; H, 5.49; N, 6.27.

Compound 9b.—The residue was recrystallized from ethanol–dichloromethane to give the product, mp 173–174° dec, in 91% yield.

Anal. Calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 82.18; H, 6.70; N, 7.03.

Catalytic Debenzylation of 14-Benzylindolopavine Derivatives. Preparation of 9c, 9d, and 9e.—A solution of 0.03 mol of **7b**, **7d**,[25] or **10b** in 150 ml of glacial acetic acid was hydrogenated at an initial pressure of 50 psi, using 1.2 g of 5% palladium on carbon as the catalyst. The catalyst was filtered off, the filtrate was added to 400 ml of ice–water, and the solution was made basic with ammonium hydroxide. Purification was carried out as described below.

Compound 9c.—The resulting precipitate was collected and recrystallized from dichloromethane–methanol to give the product, mp 290–291° dec, in 93% yield.

Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.46; H, 6.13; N, 9.51.

The phosphate salt, recrystallized from water, had mp 231–234° dec.

Anal. Calcd for $C_{19}H_{18}N_2O \cdot H_3PO_4 \cdot 0.5H_2O$: C, 57.43; H, 5.57; N, 7.05; P, 7.80. Found: C, 57.23; H, 5.57; N, 6.85; P, 7.62.

Compound 9d.—The ammoniacal mixture was extracted with ether. Concentration of the ether solution gave a crystalline product, mp 251–252° dec, in 71% yield. Recrystallization from dichloromethane–methanol gave an analytical sample, mp 254–256° dec.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.70; H, 6.39; N, 8.64.

Compound 9e.—The ammoniacal mixture was extracted with dichloromethane, the solution was evaporated, and the residue was triturated with ethanol to give the product, mp 142–145° dec, in 92% yield. Recrystallization from ethanol gave an analytical sample, mp 146–147° dec.

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 79.21; H, 6.60; N, 9.25.

14-Carbethoxy-6,7,12,13-tetrahydro-9-methoxy-6,12-imino-5H-benzo[5,6]cyclooct[1,2-*b*]indole (9f).—A mixture of 6.1 g (0.02 mol) of **7a**, 60 ml of ethyl chloroformate, 12 g of anhydrous sodium carbonate, and 120 ml of dichloromethane was stirred at room temperature for 20 hr, filtered, and distilled *in vacuo* to an oily residue. Most of the remaining ethyl chloroformate was removed by repeating the procedure of dissolving the residue in chloroform and distilling *in vacuo*. A chloroform solution of the resulting oil was washed successively with 1 *N* hydrochloric acid and water. Evaporation of the dried solution gave a gummy residue which was triturated with several portions of petroleum ether and then with 20 ml of ethanol to give 5.1 g of crystalline product, mp 211–213°. Recrystallization gave an analytical sample: mp 213–215°; ν_{max} 3280 (m), 1660 (s), 1610 (m) cm^{-1}.

Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 73.14; H, 6.21; N, 8.01.

5,14-Dicarbethoxy-6,7,12,13-tetrahydro-9-methoxy-6,12-imino-5H-benzo[5,6]cyclooct[1,2-*b*]indole (9g).—To a slurry of 0.028 mol of sodium hydride in 125 ml of dimethylformamide was added 5.0 g (0.014 mol) of **12a** as a powder. The mixture was stirred at room temperature for 2 hr and then 3.25 g (0.03 mol) of ethyl chloroformate was added dropwise. The mixture was stirred at room temperature for 40 hr, 30 ml of 1 *N* sodium hydroxide was added, and stirring was continued for 10 min. It was poured into a mixture of 30 ml of 1 *N* sodium hydroxide and 800 ml of water, and the resulting white precipitate was collected, washed well with water, and dissolved in dichloromethane. The dried solution was evaporated to give a residue which was dissolved in benzene and chromatographed over 120 g of basic alumina. The first 200 ml of benzene eluate was discarded. The next 150 ml of benzene eluate was combined with the first 1500 ml of dichloromethane eluate. Evaporation gave 3.4 g of solid whose thin layer chromatogram showed a single spot. Trituration with isopropyl ether gave 2.9 g of crystalline product, mp 157–158°. Recrystallization from isopropyl ether gave an analytical sample: mp 159–161°; ν_{max} 1715 (s) and 1695 (s) cm^{-1}, no NH absorption.

(25) Crude amorphous **7d** was used.

Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.30; H, 6.08; N, 6.19.

5,6,11,12-Tetrahydro-2,3,8-trimethoxy-13-methyldibenzo[*a*,*e*]-cycloocten-5,11-imine (10c).—A mixture of 13.8 g (0.031 mol) of 1-(3,4-dimethoxybenzyl)-6-methoxyisoquinoline methiodide, 3.4 g of lithium aluminum hydride, and 300 ml of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was hydrolyzed and filtered, and the solvent was removed using a rotary flash evaporator (maximum temperature 30°). The residue was refluxed under nitrogen with a mixture of 55 ml of 90% formic acid and 22 ml of orthophosphoric acid for 25 hr. The cooled reaction mixture was diluted with 220 ml of water and washed with ether. The aqueous layer was made alkaline with 2 *N* sodium hydroxide and extracted with chloroform. Evaporation of the chloroform gave a residue which crystallized on trituration with petroleum ether (bp 30–60°) to yield 9.5 g of material, mp 110–115°. Recrystallization from ether gave 6.3 g of product, mp 122.5–123.5°.

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.98; H, 7.16; N, 4.49.

1-Cyano-3-(indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (8a).—A mixture of 87 g (0.2 mol) of the methiodide of **4a**, 15.2 g (0.4 mol) of lithium aluminum hydride, and 2000 ml of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was hydrolyzed and filtered. The filtrate was concentrated on a flash evaporator (maximum temperature was 30°) to a volume of 500 ml and a 1.0-ml sample was found, by titration, to contain 0.391 mequiv of base. To 498 ml (containing 0.1947 equiv of base) was added 1908 ml of 0.10 *N* hydrochloric acid followed by 2000 ml of water. The solution was heated under nitrogen on a steam bath (95°) for 1 hr and allowed to cool to room temperature. The clear yellow solution was decanted from some insoluble gum, made alkaline with sodium bicarbonate, and extracted with dichloromethane. The aqueous layer was treated with excess potassium cyanide, and the solid which precipitated on stirring and scratching was collected, washed well with water, and dissolved in dichloromethane. The dried solution was evaporated to a residue which was triturated with benzene to give 31 g of product, mp 152.5–154°. Recrystallization from benzene gave material: mp 153–154°; λ_{max} 220 mμ (ε 41,000), 282 (8800), 289 (8600), 328 (12,800).

Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.10; H, 6.39; N, 12.68. Found: C, 76.21; H, 6.49; N, 12.91.

3-(3-Indolylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (11).—A mixture of 1.65 g (0.005 mol) of **8a**, 20 ml of 1 *N* hydrochloric acid, and 50 ml of ethanol was refluxed for 1 hr. The resulting yellow solution was treated with 1 g (added in small portions) of sodium borohydride with cooling to maintain at room temperature. The mixture was stirred at room temperature for 20 hr, diluted with 300 ml of water, and extracted with dichloromethane. The organic layer was washed well with water, dried, and evaporated to give an oil which solidified on trituration with petroleum ether (bp 30–60°). Recrystallization from acetonitrile gave 1.1 g of product, mp 146–148°. Another recrystallization gave an analytical sample: mp 147–149°; λ_{max} 226 (ε 43,000), 280 (8000), 289 sh (6500). It was shown to be different from a sample of **12** (mp 128–129.5°)[3] by mixture melting point depression and by comparison of the infrared spectra.

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.63; H, 7.30; N, 9.01.

1-Cyano-3-(3,4-dimethoxybenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (Cyano Derivative of 2 Where R = CH_3; $R_2 = R_3 = R_4 = OCH_3$; $R_5 = H$).[20]—A mixture of 36 g (0.08 mol) of 1-(3,4-dimethoxybenzyl)-6-methoxyisoquinoline methiodide, 9.2 g of lithium aluminum hydride, and 1200 ml of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was hydrolyzed and filtered, and 800 ml of 0.5 *N* hydrochloric acid was added to the filtrate. The tetrahydrofuran was distilled off *in vacuo*, and the remaining aqueous solution was heated under nitrogen on a steam bath (temperature 95°) for 45 min. The cooled reaction mixture was made alkaline with sodium bicarbonate and washed with ether. The aqueous layer was treated with excess potassium cyanide, and the solid which precipitated was collected, washed well with water, and triturated with methanol to give 19 g of crystalline product, mp 146–148°. Recrystallization from ethanol gave an analytical sample, mp 148.5–149.5°.

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.80; N, 7.95. Found: C, 71.36; H, 6.86; N, 7.93.

Registry No.—**4a**, 16957-46-3; **4c**, 16957-47-4; **7a**, 16957-48-5; **7a** methiodide salt, 16957-49-6; **7a** phosphate salt, 16957-50-9; **7b**, 16957-51-0; **7c**, 16957-52-1; **7c** HCl, 16957-53-2; **7d**, 16957-54-3; **8a**, 16957-55-4; **8c**, 16957-56-5; **9a**, 16957-57-6; **9a** HCl, 16957-58-7; **9b**, 16957-59-8; **9c**, 16957-60-1; **9c** phosphate salt, 16957-61-2; **9d**, 16957-62-3; **9e**, 16957-63-4; **9f**, 16957-64-5; **9g**, 16957-65-6; **10c**, 16957-66-7; **11**, 16957-67-8; 1-(3,4-dimethoxybenzyl)-6-methoxyisoquinoline, 16957-68-9; 1-cyano-3-(3,4-dimethoxybenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 16957-69-0.

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