to room temperature, the amber solution was poured into 50 ml of water and extracted with ether. The ethereal extract was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure, affording 153 mg of an amber syrup. Chromatography over 10 g of acid-washed alumina and elution with hexane gave 52 mg (29%) of 2,4,6-cholestatriene (**9**), identical with that described previously. Elution with hexane–benzene (17:3) yielded 28 mg (15%) of 5α,6α-epoxy-2-cholestene (**5**) as a colorless syrup, identified by its infrared spectrum.

Solvolysis of 3β-Chloro-5α,6α-epoxycholestane (2c).—A solution of 3β-chloro-5α,6α-epoxycholestane (**2c**) (421 mg, 1 mmole) plus *p*-toluenesulfonic acid monohydrate (418 mg, 2 mmoles) and lithium chloride (420 mg, 10 mmoles) in 25 ml of DMF was kept under reflux for 2 hr. After cooling, the yellowish mixture was poured in 75 ml of water and extracted with ether. The ethereal extracts were washed with several portions of water, once with a saturated sodium chloride solution, then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to yield 320 mg of a yellowish syrup. Chromatography of this material over 20 g of alumina and elution with hexane afforded 183 mg (50%) of 2,4,6-cholestatriene (**9**), identical with that described previously. Elution with hexane–benzene (1:3) gave 46 mg (12%) of 4-chloesten-6-one (**7**), also identical with that described previously.

Solvolysis of 3α-Chloro-5α,6α-epoxycholestane (3c).—A solution of 3α-chloro-5α,6α-epoxycholestane (**3c**) (421 mg, 1 mmole) plus *p*-toluenesulfonic acid monohydrate (418 mg, 2 mmoles) and lithium chloride (420 mg 10 mmoles) in 50 ml of DMF was kept under reflux for 2.5 hr. The cooled product mixture was then treated in an identical manner with that described for the solvolysis of 3β-chloro-5α,6α-epoxycholestane (**2c** above) under these conditions, yielding 349 mg of a yellowish syrup whose infrared spectrum was superimposable upon that of the aforementioned product mixture. After standing for several days under ordinary laboratory conditions (*i.e.*, atmospheric oxygen), the residue was chromatographed over 20 g of alumina. Elution with hexane afforded 85 mg (23%) of 2,4,6-cholestatriene (**9**), identical with that reported previously. Elution with hexane–benzene (1:3) gave 40 mg (19%) of 4-cholesten-6-one (**7**), identified by its infrared spectrum.

2,4-Cholestadien-6α-ol (10).—A solution of 2,4-cholestadien-6-one[19] (96 mg, 0.25 mmole) in 15 ml of anhydrous ether was cooled in an ice bath under a nitrogen atmosphere, whereupon 2 ml of a 0.4 *M* ethereal solution of lithium aluminum hydride was added dropwise during several minutes. After an additional 15 min at ice-bath temperature, the mixture was allowed to warm to room temperature and the excess hydride was destroyed by addition of 6 drops of water followed by 10 drops of a 10% sodium hydroxide solution. Filtration through anhydrous sodium sulfate and removal of the ether under reduced pressure led to 96 mg of a colorless glass which could not be crystallized and decomposed in the presence of air and light. No carbonyl absorption was observed in the infrared; however, there were peaks at 2.79, 3.30, and 14.32 μ. The ultraviolet absorption, λ_{max}^{EtOH} 265 mμ, and a shoulder at 273 mμ disappeared upon addition of acid with the formation of a new peak, λ_{max}^{EtOH} 238 mμ.

Solvolysis of 2,4-Cholestadien-6α-ol (15) in DMF.—To a solution of freshly prepared 2,4-cholestadien-6α-ol (**15**) (295 mg, 0.8 mmole) in 20 ml of DMF was added *p*-toluenesulfonic acid monohydrate (155 mg, 0.5 mmole) and lithium chloride (150 mg, 3.6 mmoles). The resulting mixture was refluxed for 2.5 hr. After cooling to room temperature, the amber solution was poured into 50 ml of water and extracted with ether. The ether extract was washed with several portions of water, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield 239 mg of an amber syrup. Chromatography over 15 g of alumina and elution with hexane afforded 146 mg (51%) of 2,4,6-cholestatriene (**9**), whose physical and spectral properties were identical with those reported earlier.

Registry No.—**2a**, 1250-95-9; **2b**, 13095-29-9; **2c**, 13095-30-2; **3a**, 13095-31-3; **3b**, 2953-38-0; **3c**, 13095-33-5; **4a**, 570-96-7; **5**, 13095-35-7; **7**, 13095-36-8; **8**, 13095-37-9; **9**, 13095-38-0; **10**, 13095-39-1; dimethylformamide, 68-12-2.

Alternate Precursors in Biogenetic-Type Syntheses. I. The Synthesis of Cyclohex[*j*]indolo[2,3-*f*]morphan

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cis-Cyclohexindolomorphan was obtained by a Grewe-type synthesis. The *trans* isomer was obtained from 4a-chloro-2,3,4,4a,5,6,7,8-octahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline (**10**) by reduction, intramolecular halogen displacement, and a Plancher rearrangement. The chloro compound **10** arose from the Bischler–Napieralski cyclization of N-[2-(1-cyclohexenyl)ethyl]-N-methylindole-3-acetamide (**9**). Both isomers were degraded to 11-methylbenzo[*a*]carbazole.

The biogenetic-type synthesis of alkaloids, although originally explored by Robinson[1] in 1917, has only recently received widespread attention. The basic philosophy of this approach and some of the syntheses for which it has formed the basis has been the subject of a recent review.[2] A further extension of this work is the preparation of missing alkaloids by insertion of an alternate, biologically feasible precursor at some stage of an established biogenetic-type synthesis. For example, Schöpf[3] has replaced 3,4-dihydro-β-carboline by 6,7-dimethoxy-3,4-dihydroisoquinoline in the scheme for Ruteocarpin and obtained a dimethoxybenzene analog which has not yet been found in nature.

We became intrigued with the possibility of the substitution of tryptophan for one molecule of 3,4-dihydroxyphenylalanine in Robinson's[4] biogenetic scheme for morphine. However, a biogenetic-type synthesis involving the key oxidative coupling step has not yet been accomplished on a preparative basis.[5] Thus far, the closest approach[6] is the cyclization of a benzyloctahydroisoquinoline to tetrahydrodeoxycodeine by Grewe.[7] Therefore, initially, we decided to investigate the Grewe cyclization of the indolylmethyloctahydroisoquinoline **4** to **6**, the indole analog of tetrahydrodeoxycodeine.

(1) R. Robinson, *J. Chem. Soc.*, **111**, 876 (1917).

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

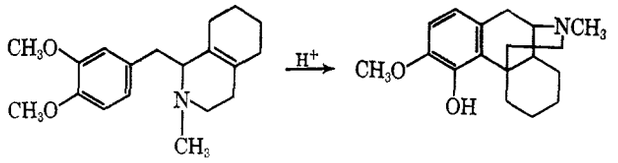
(3) C. Schöpf and H. Steuer, *Ann. Chem.*, **558**, 124 (1947).

(4) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931).

(5) Although D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas [*Proc. Chem. Soc.*, 203 (1963)] have accomplished the key oxidation step, the product could not be isolated, but instead was identified by isotopic dilution.

(6) Reference 2, p 259.

(7) R. Grewe, A. Mondon, and E. Nolte, *Ann. Chem.*, **564**, 161 (1949).



The condensation of indoleacetic acid with cyclohexenylethylamine gave the amide **1**. Cyclization of the amide with phosphorous oxychloride at room temperature produced the hexahydroisoquinoline **2**, which on reduction with sodium borohydride was converted to the octahydroisoquinoline **3**. The N-methyl derivative **4** was obtained by treatment of **3** with ethyl formate followed by reduction with lithium aluminum hydride. An alternate route to **4** was the quaternization of **2** with methyl iodide and subsequent reduction with sodium borohydride. The acid-catalyzed cyclization of **3** and **4** led to the cyclohexindolomorphans **5** and **6**, respectively. Methylation of **5** by the procedure described for **3** also produced **6**. Both **5** and **6** were assigned the *cis* (CD ring junction) stereochemistry since the Grewe cyclization has been shown to give predominately the normal series unless special catalysts are used.[8]

Although we have assumed that the Grewe cyclization would proceed in a manner analogous to the benzene series, there are other feasible products of the cyclization. For example, an unbridged pentacyclic compound could arise by reaction of the indole at the 8a end of the isoquinoline double bond. However, the presence of a doublet at 3.05 ppm (1 H, J = 18 cps) in the nmr spectrum of **6**, which is characteristic of the 10β-H of the bridged morphine system,[9] discredits this possibility. Another type of product would be a [3,2-*f*]-cyclohexindolomorphan (indole ring inverted) arising by an indirect route,[10] namely, reaction of the β position of the indole to give a spiroindolenine (*e.g.*, **12**) which could undergo the Plancher[11] rearrangement to either a [2,3-*f*]- or [3,2-*f*]cyclohexindolomorphan. To eliminate conclusively both of these possibilities, we have degraded **6** to a known ring system. Treatment of **6** with sodium hydride and dimethyl carbonate[12] gave the indole N-methylated derivative **7**, which was subjected to the Hofmann degradation, giving rise to **8**. Aromatization of **8** gave the known 11-methylbenzo[*a*]-carbazole (**16**) (see Scheme I).

The N-methylamide **9** was obtained from the condensation of indoleacetic acid with N-methylcyclohexenylethylamine. By cyclization of **9** with phosphorus oxychloride and subsequent reduction with sodium borohydride, we expected to have an alternate route to the N-methyloctahydroisoquinoline **4**. However, the product of the phosphorus oxychloride cyclization contained a nonionic chlorine atom. The chloro compound had ultraviolet absorption at 217 mμ (ϵ 31,000), 279 (6200), and 288 (5400) characteristic of indole, infrared absorption at 1655 cm^{-1} typical of a

(8) J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *J. Org. Chem.*, **28**, 2470 (1963).

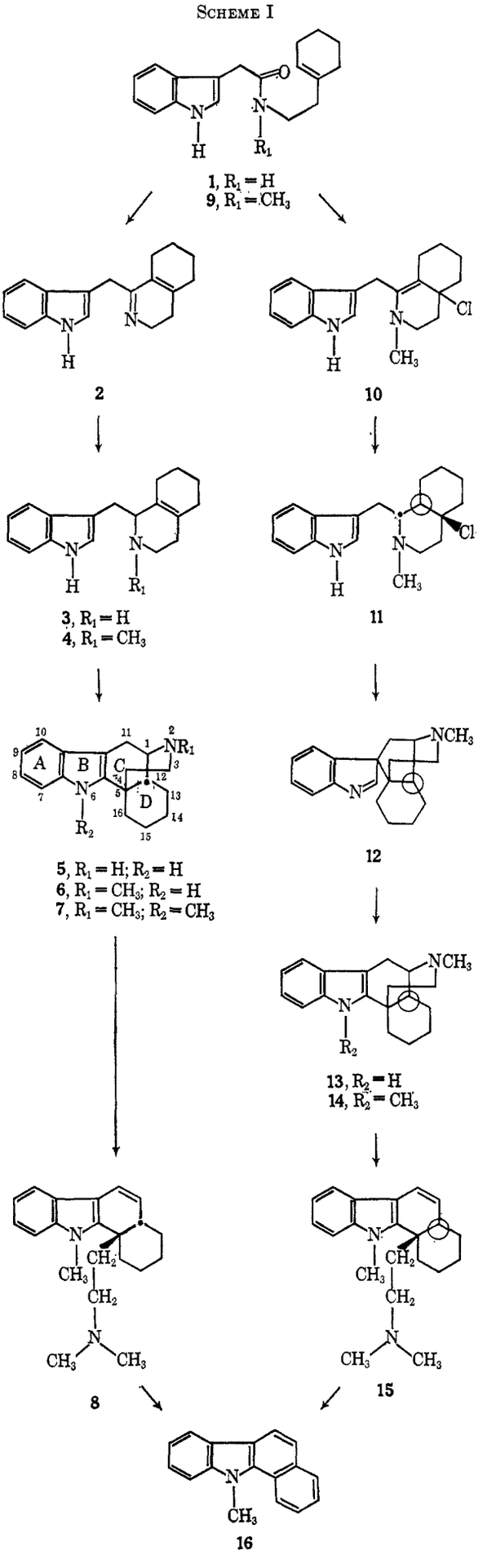
(9) S. Okuda, S. Yamaguchi, Y. Kawozoe, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 104 (1964).

(10) J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, **19**, 65 (1963).

(11) For a discussion of the Plancher rearrangement, see P. L. Julian, E. W. Meyer, and H. C. Printy in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 102.

(12) M. von Strandtmann, M. P. Cohen, and John Shavel, Jr., *J. Med. Chem.*, **8**, 200 (1965).

SCHEME I



vinylamine, and no signal in the olefinic region of the nmr spectrum. Apparently this compound is the result of 1,4 addition of hydrogen chloride[13] to the expected product and has the structure **10**. Reduction of **10** with sodium borohydride gave the dihydro derivative **11**. We now expected to be able to convert **11** to the octahydroisoquinoline **4** by dehydrohalogenation. However, when **11** was refluxed with methanolic potassium hydroxide, an oil was obtained. Chromatography of the oil gave a small amount of a crystalline compound (one isomer) and a larger amount of a noncrystalline material (mixture of isomers). Both gave analytical samples whose infrared spectra showed a peak at 1550 cm^{-1} (C=N) and no absorption at 3100–3600 cm^{-1} (NH). The ultraviolet spectrum displayed a broad plateau at 260 mμ (ϵ 4000). The spectral data suggest the indolenine[14] **12**. This structure would arise by removal of the hydrogen from the indole nitrogen, a shift of the anion to the indole 3 position, and intramolecular displacement of the halogen. If this is indeed the case, then treatment of **12** with acid should lead to one or more of the four possible cyclohexindolomorphans. When **12** was subjected to the Plancher rearrangement, a crystalline compound was obtained which was isomeric with **6**. There are three possibilities for the structure of this isomer: the *trans* isomer of **6**, the *cis*-[3,2-*f*] isomer, and the *trans*-[3,2-*f*] isomer. The first possibility can be distinguished from the second and third by degradation to a benzocarbazole. The *trans* isomer of **6** would give rise to 11-methylbenzo[*a*]carbazole (**16**) already obtained from the *cis* isomer, whereas the other [3,2-*f*] isomers would lead to 11-methylbenzo[*c*]carbazole.

When the unknown was degraded, the product was **16**, thus establishing the *trans*-[2,3-*f*] structure **13** for the unknown isomer and structures **14** and **15** for the degradation intermediates. Furthermore, reasoning backward, **12** must possess a *trans*-hydrindan ring system and, since **12** presumably arose by a SN2 mechanism, **11** must be the *trans-anti* isomer. To confirm our stereochemical assignments for the cyclohexindolomorphans, we have examined their rate of quarternization with methyl iodide. The half-life of the *cis* isomer was 1 hr, whereas the more hindered *trans* isomer was only 7% converted at that time.[15] These data are in agreement with previous work in the morphan series.[16]

Experimental Section

The melting points were determined using a Thomas–Hoover apparatus which had been calibrated against known standards. The infrared spectra were recorded with a Baird Model 455 instrument on chloroform solutions. The ultraviolet spectra were determined using a Beckman DKI spectrophotometer on 95% ethanol solutions. The nmr spectra were determined with a Varian Associates A-60 spectrometer on deuteriochloroform solutions.

N-[2-(1-Cyclohexenyl)ethyl]indole-3-acetamide (1). A. From Indoleacetic Acid.—A mixture of 175 g of indole-3-acetic acid and 138 g of cyclohexenylethylamine[17] was heated at 175° for 10 hr under a stream of nitrogen. The reaction mixture was dissolved in benzene. The benzene solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water and was dried over sodium sulfate. Dilution with Skellysolve B gave, on standing, 205 g (73%) of a crystalline solid, mp 88.5–89.5°.

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.51; H, 7.90; N, 9.89.

B. From Methyl Indoleacetate.—A mixture of 5.0 g of methyl indole-3-acetate and 3.25 g of cyclohexenylethylamine was heated at 100° for 48 hr in a flask equipped with an ascarite drying tube. Treatment of the reaction mixture as above gave 2.5 g (34%) of a crystalline solid, mp 88–89°. This sample was shown to be identical with that obtained in method A by the methods of mixture melting point and infrared analysis.

3,4,5,6,7,8-Hexahydro-1-(indol-3-ylmethyl)isoquinoline (2).—To 100 ml of phosphorus oxychloride in a round-bottomed flask equipped with a drying tube was added 28.2 g of N-[2-(1-cyclohexenyl)ethyl]indole-3-acetamide and the mixture was swirled occasionally until solution was obtained. The solution was allowed to stand at room temperature for 16 hr and then poured into 1 l. of ether. The precipitate was rubbed up to a gummy consistency and the supernatant was decanted. The dichlorophosphate was washed with an additional 500 ml of ether. Water (1 l.) was added and the mixture was heated at 45° for 30 min with occasional stirring. The resulting solution was cooled, filtered, made basic with 25% sodium hydroxide solution, and extracted with ether. The ethereal solution was washed with water and was dried over sodium sulfate. Removal of the solvent at 45° *in vacuo* gave 23.0 g of a gum.

Picrate.—An acidic aqueous solution of the base (from 2.82 g of amide) prepared as above was treated with aqueous picric acid giving 3.60 g (73%) of a yellow-red crystalline solid, mp 155–156.5° dec. Further recrystallization from ethanol gave an analytical sample, mp 156.5–158° dec.

Anal. Calcd for $C_{24}H_{23}N_5O_7$: C, 58.42; H, 4.70; N, 14.19. Found: C, 58.56; H, 4.89; N, 13.91.

1,2,3,4,5,6,7,8-Octahydro-1-(indol-3-ylmethyl)isoquinoline (3).—To a solution of crude 3,4,5,6,7,8-hexhydro-1-(indol-3-ylmethyl)isoquinoline dichlorophosphate (from 56.4 g of the amide as above) in 300 ml of ethanol was added 55 ml of 10% sodium hydroxide solution and 145 ml of water. The pH was adjusted to approximately 3 with 20% hydrochloric acid. Over a 30-min interval, 6.0 g of sodium borohydride was added while the temperature was held at 20–30°. After the addition had been completed, stirring was continued for 20 min. The pH was adjusted to below 2 with 20% hydrochloric acid and the solution was stirred for 10 min. The reaction mixture was made basic with 40% sodium hydroxide solution and was extracted with ether. Removal of the solvent and recrystallization from 200 ml of benzene gave 32.1 g (60%) of a crystalline solid, mp 157–158.5°. Further recrystallization from benzene gave an analytical sample, mp 160–161°.

Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33; N, 10.52. Found: C, 81.20; H, 8.51; N, 10.64.

1,2,3,4,5,6,7,8-Octahydro-1-(indole-3-ylmethyl)-2-methylisoquinoline (4). A. From 3,4,5,6,7,8-Hexahydro-1-(indol-3-ylmethyl)isoquinoline.—In a flask equipped with a drying tube a solution of 40 g of methyl iodide in 150 ml of acetone at 0° was added to 3,4,5,6,7,8-hexahydro-1-(indol-3-ylmethyl)isoquinoline (prepared from 28.2 g of amide as above) in 40 ml of acetone at 0°. The solution was allowed to stand at room temperature for 16 hr. Removal of the solvent at 45° *in vacuo* gave a gum which was dissolved in 250 ml of ethanol. Ethanol (50 ml) was removed *in vacuo* on the steam bath. The volume was adjusted to 1 l. and 25 g of sodium borohydride was added at 25–30° during a 90-min interval. Stirring was continued for 2 hr. The solvent was removed *in vacuo* on the steam bath. The residue was treated with 1250 ml of 2.5% sodium hydroxide solution and was extracted with ether. The ethereal solution was washed with water and was dried over sodium sulfate. Removal of the solvent gave 14.0 g of a solid which was chromatographed on alumina. Elution with ether gave 8.6 g of a solid which on recrystallization from Skellysolve B gave 7.0 g (22%) of a crystalline solid, mp 148.5–149.5°. Further recrystallization gave an analytical sample, mp 147.5–148.5°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.40; H, 8.81; N, 9.83.

B. From 1,2,3,4,5,6,7,8-Octahydro-1-(indol-3-ylmethyl)isoquinoline.—A solution of 90 mg of 1,2,3,4,5,6,7,8-octahydro-1-(indol-3-ylmethyl)isoquinoline in 10 ml of ethyl formate was

(13) For an example of 1,2 addition of hydrogen chloride to a Schiff base, see ref 14.

(14) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 1558 (1951).

(15) F. S. Hom, personal communication, 1966.

(16) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(17) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).

refluxed overnight. The excess ester was removed *in vacuo*. The residue was dissolved in 50 ml of ether and 1.0 g of lithium aluminum hydride was added. After stirring for 18 hr, the excess hydride was decomposed by the cautious addition of water. A 50% sodium hydroxide solution was added dropwise until the precipitate coagulated and the ether was decanted. Removal of the solvent gave 50 mg of a solid which on recrystallization from Skellysolve B gave 19 mg (19%) of a white crystalline solid, mp 149–150°. This sample was shown to be identical with that obtained in method A by the methods of mixture melting point and infrared analysis.

***cis*-Cyclohex[*j*]indolo[2,3-*f*]morphan (5).**—A solution of 30.0 g of 1,2,3,4,5,6,7,8-octahydro-1-(indol-3-ylmethyl)isoquinoline in 1500 ml of 48% hydrobromic acid was refluxed for 30 hr. The reaction mixture was made basic with 1 l. of 40% sodium hydroxide solution and was extracted with 500-ml and 250-ml portions of chloroform. The chloroform layer was washed with 125 ml of water, dried over sodium sulfate, and the solvent was removed. The residue was chromatographed on alumina. Elution with 10% methanol in ether gave, after recrystallization from benzene, 9.0 g (30%) of a crystalline solid, mp 210–213°. Further recrystallization gave an analytical sample, mp 215–216°.

Anal. Calcd for $C_{18}N_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.39; H, 8.31; N, 10.55.

***cis*-2-Methylcyclohex[*j*]indolo[2,3-*f*]morphan (6). A. From 1,2,3,4,5,6,7,8-Octahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline.**—A solution of 14.0 g of 1,2,3,4,5,6,7,8-octahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline in 140 ml of 85% phosphoric acid was heated at 150° in a nitrogen atmosphere for 16 hr. The reaction mixture was poured into ice water, made basic with 20% sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride layer was dried over sodium sulfate and the solvent was removed. Chromatography of the residue (13.3 g) on alumina gave on elution with dichloromethane 7.0 g of a solid. Recrystallization from Skellysolve B afforded 4.1 g (29%) of a white crystalline solid, mp 145–146°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.12; H, 8.74; N, 9.76.

B. From *cis*-Cyclohex[*j*]indolo[2,3-*f*]morphan.—Subjection of 0.25 g of *cis*-cyclohex[*j*]indolo[2,3-*f*]morphan to procedure B for compound **4** gave 0.12 g (46%) of a crystalline solid, mp 140–142°. Recrystallization from Skellysolve B gave a crystalline solid, mp 144–145°. This sample was shown to be identical with that obtained by method A by the methods of mixture melting point and infrared analysis.

***cis*-2,6-Dimethylcyclohex[*j*]indolo[2,3-*f*]morphan (7).**—A mixture of 2.0 g of *cis*-2-methylcyclohex[*j*]indolo[2,3-*f*]morphan, 2.0 g of a 55% sodium hydride dispersion in mineral oil, 20 ml of dimethyl carbonate, and 300 ml of tetrahydrofuran was refluxed for 18 hr. The reaction mixture was poured into 1 l. of cold water, made acidic with 20% hydrochloric acid, and extracted twice with two 250-ml portions of ether which were discarded. The aqueous layer was made basic with 10% sodium hydroxide solution and was extracted with two 250-ml portions of ether. The combined ether layers were washed with water, dried over sodium sulfate, and the solvent was removed. There remained 2.0 g (97%) of an oil.

The **hydrobromide** formed in ether and crystallized from ethyl acetate as a solid, mp 224–227°. Further recrystallization from ethanol gave an analytical sample, mp 231–233°.

Anal. Calcd for $C_{20}H_{27}N_2Br$: C, 63.99; H, 7.25; N, 7.46; Br, 21.29. Found: C, 64.06; H, 7.47; N, 7.18; Br, 21.25.

The **methiodide** formed in a 30% solution of methyl iodide in ethanol, mp 262.5–263°.

Anal. Calcd for $C_{21}H_{29}N_2I$: C, 57.80; H, 6.70; N, 6.42; I, 29.08. Found: C, 57.67; H, 6.74; N, 6.48; I, 29.10.

***cis*-11b-(2-Dimethylaminoethyl)-1,2,3,4,4a,11b-hexahydro-11-methyl-11H-benzo[*a*]carbazole (8).**—A mixture of 3.8 g of *cis*-2,6-dimethylcyclohex[*j*]indolo[2,3-*f*]morphan methiodide, 32 ml of 40% sodium hydroxide solution, and 80 ml of ethanol was refluxed for 16 hr. The reaction mixture was poured into water and was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. There remained 2.0 g (89%) of an oil. Distillation thru a short-pass still gave an analytical sample, bp 200° (block temperature, 0.05 mm).

Anal. Calcd for $C_{21}H_{28}N_2$: C, 81.77; H, 9.15; N, 9.08. Found: C, 82.03; H, 9.28; N, 9.29.

N-[2-(1-Cyclohexenyl)ethyl]-N-methylindole-3-acetamide (9). A. From Indole-3-acetic Acid.—A mixture of 139 g of N-methylcyclohexenylethylamine[18] and 175 g of indole-3-acetic acid was heated at 175° for 44 hr under a stream of nitrogen. The reaction mixture was dissolved in chloroform. The chloroform solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water, dried over sodium sulfate, and the solvent was removed. Recrystallization from benzene gave 97.5 g (46%) of a crystalline solid, mp 124–125°.

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.28; H, 8.21; N, 9.57.

B. From Methyl Indole-3-acetate.—A mixture of 5.0 g of methyl indole-3-acetate and 3.6 g of N-methylcyclohexenylethylamine was heated at 130° for 44 hr in a flask equipped with an ascarite drying tube. Treatment of the reaction mixture as above gave 1.3 g (17%) of a crystalline solid, mp 124–126°. This sample was shown to be identical with that obtained in method A by the methods of mixture melting point and infrared analysis.

4a-Chloro-2,3,4,4a,5,6,7,8-octahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline (10).—A solution of 10.0 g of N-[2-(1-cyclohexenyl)ethyl]-N-methylindole-3-acetamide in 40 ml of phosphorous oxychloride was allowed to stand for 20 hr. The reaction mixture was poured into ether with stirring. The ether was decanted and the precipitate stirred with 500 ml of water at 45° for 30 min. After filtration the solution was made basic with 10% sodium hydroxide solution and was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue on trituration with 50 ml of methanol gave 2.3 g (20%) of a crystalline solid. Recrystallization from benzene–Skelly solve B gave an analytical sample, mp 129–133°.

Anal. Calcd for $C_{19}H_{23}N_2Cl$: C, 72.49; H, 7.35; N, 8.90; Cl, 11.26. Found: C, 72.58; H, 7.62; N, 8.64; Cl, 11.34.

4a-Chlorodecahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline (11).—A solution of 76.8 g of N-[2-(1-cyclohexenyl)ethyl]-N-methylindole-3-acetamide in 300 ml of phosphorous oxychloride was allowed to stand for 20 hr. The reaction mixture was poured into 3 l. of ether with stirring. The ether was decanted and the precipitate washed with an additional 1 l. of ether. The residue was dissolved in 450 ml of ethanol and was neutralized with 280 ml of 10% sodium hydroxide solution. The pH was adjusted to 3 with 20% hydrochloric acid and 15 g of sodium borohydride was added over a 40-min interval while the temperature was held at 20–30°. The pH was adjusted to 2 and 750 ml of water was added. The solution was made basic with 10% sodium hydroxide solution and was extracted with 750-, 500-, and 500-ml portions of dichloromethane. The combined dichloromethane layers were washed with 500 ml of water, dried over sodium sulfate, and concentrated to 150 ml. On standing, there was deposited 40.0 g (49%) of a crystalline solid, mp 158–160°. Recrystallization from benzene gave an analytical sample, mp 159–160°.

Anal. Calcd for $C_{19}H_{25}N_2Cl$: C, 72.03; H, 7.95; N, 8.84; Cl, 11.18. Found: C, 71.73; H, 8.04; N, 8.56; Cl, 11.29.

4,5,6,7-Tetrahydro-10-methylspiro[(3aH-3,7a)iminoethanoindan-1,3′-indole] (12).—A mixture of 3.0 g of 4a-chlorodecahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline, 2.2 g of potassium hydroxide, and 22 ml of methanol was refluxed for 20 hr. The reaction mixture was poured into water and was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. There remained 2.4 g (90%) of an oil which was chromatographed on alumina. Elution with 20% benzene in ether gave 0.30 g (10%) of a solid, mp 79–89°. Recrystallization from Skellysolve B gave an analytical sample of isomer A, mp 101–102°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.38; H, 8.67; N, 10.14.

Elution with 40% benzene in ether gave 1.46 g (49%) of an oil. Distillation through a short-pass still gave an analytical sample, bp 190° (block temperature, 0.07 mm).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.18; H, 8.70; N, 9.77.

***trans*-2-Methylcyclohex[*j*]indolo[2,3-*f*]morphan Hydrochloride (13).**—A solution of crude 4,5,6,7-tetrahydro-10-methylspiro[(3aH-3,7a)iminoethanoindan-1,3′-indole] (prepared from 36 g of 4a-chlorodecahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline as above) in 210 ml of a 5% solution of hydrogen chloride in ethanol was refluxed for 5 min. On cooling, there was deposited

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24.3 g (68%) of a crystalline solid, mp 340° dec. Recrystallization from ethanol gave an analytical sample, mp 335° dec.

Anal. Calcd for $C_{19}H_{25}N_2Cl$: C, 72.02; H, 7.95; N, 8.84. Found: C, 71.81; H, 8.20; N, 9.09.

The **free base** was obtained by stirring the hydrochloride with a mixture of 300 ml of saturated sodium bicarbonate solution and 300 ml of chloroform. The chloroform layer was dried over sodium sulfate and the solvent was removed. Recrystallization from Skellysolve B gave a crystalline solid, mp 138–139°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.15; H, 8.67; N, 10.03.

trans-**2,6-Dimethylcyclohex[*j*]indolo[2,3-*f*]morphan (14).**—The same procedure as for the *cis* isomer gave 13.6 g (97%) of an oil.

The **hydrobromide** formed in ether and crystallized from ethanol–ethyl acetate as a solid, mp 237–238.5°.

Anal. Calcd for $C_{20}H_{27}N_2Br$: C, 64.00; H, 7.28; N, 7.46; Br, 21.29. Found: C, 63.92; H, 7.28; N, 7.69; Br, 21.33.

The **methiodide** formed in a 30% solution of methyl iodide in ethanol. Recrystallization from ethanol gave an analytical sample, mp 236.5–237.5°.

Anal. Calcd for $C_{21}H_{29}N_2I$: C, 57.80; H, 6.70; N, 6.42; I, 29.08. Found: C, 58.02; H, 6.94; N, 6.28; I, 29.07.

trans-**11b-(2-Dimethylaminoethyl)-1,2,3,4,4a,11b-hexahydro-11-methyl-11H-benzo[*a*]carbazole (15).**—The same procedure as that for the *cis* isomer gave 8.5 g (99%) of a crystalline solid, mp 107–108°. Recrystallization from ether gave an analytical sample, mp 107.5–108.5°.

Anal. Calcd for $C_{21}H_{28}N_2$: C, 81.77; H, 9.15; N, 9.08. Found: C, 82.01; H, 9.13; N, 9.11.

11-Methylbenzo[*a*]carbazole (16). A. From *cis*-11b-(2-Dimethylaminoethyl)-1,2,3,4,4a,11b-hexahydro-11-methyl-11H-benzo[*a*]carbazole.—A mixture of 1.64 g of *cis*-11b-(2-dimethylaminoethyl)-1,2,3,4,4a,11b-hexahydro-11-methyl-11H-benzo[*a*]carbazole and 1.64 g of 5% palladium on carbon in a test tube was immersed in a bath at 250°, the temperature raised to 310° over a 10-min interval, and then held there for 20 min. The reaction mixture was treated with 15 ml of chloroform and filtered. After removal of the solvent, there remained 0.53 g (35%) of a solid. Recrystallization from ethanol–benzene to constant melting point gave a crystalline solid, mp 169–170° (lit.[19] mp 168°).

From *trans*-11b-(2-Dimethylaminoethyl)-1,2,3,4,4a,11b-hexahydro-11-methyl-11H-benzo[*a*]carbazole.—The same procedure as that for the *cis* isomer gave 0.16 g (65%) of a solid. Recrystallization from ethanol to constant melting point gave a crystalline solid, mp 169–170°. The samples from method A and B were shown to be identical by the methods of mixture melting point and infrared analysis.

Registry No.—**1**, 13135-15-4; **2**, 13135-16-5; **2** picrate, 13135-17-6; **3**, 13127-45-2; **4**, 13135-18-7; **5**, 13169-22-7; **6**, 13118-57-5; **7**, 13135-19-8; **7** hydrobromide, 13135-20-1; **7** methiodide, 13281-79-3; **8**, 13127-47-4; **9**, 13135-21-2; **10**, 7670-45-3; **11**, 13135-22-3; **12**, 13127-49-6; **13**, 7763-45-3; **13** hydrochloride, 7718-29-8; **14** hydrobromide, 13135-24-5; **14** methiodide, 13135-25-6; **15**, 13135-26-7; **16**, 13127-50-9.

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Alternate Precursors in Biogenetic-Type Syntheses. II.[1] The Synthesis of Cyclohex[*j*]indolo [2,3-*f*]morphan-15-one

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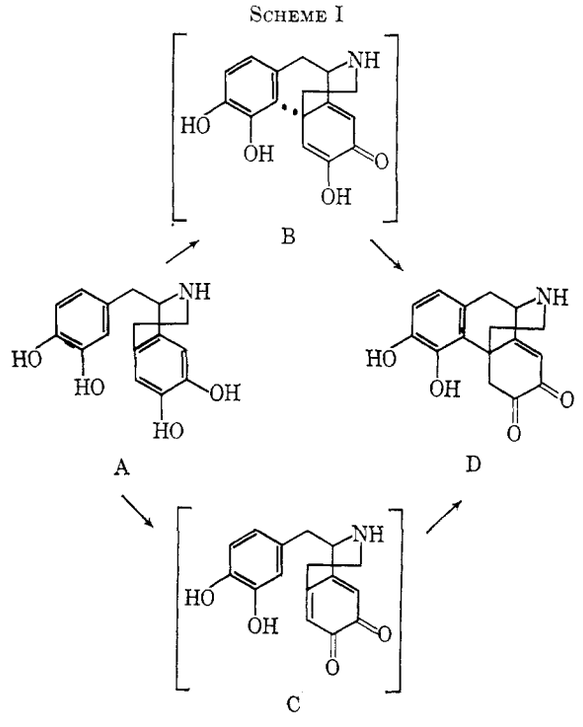
The C_6 oxygen function of morphine was introduced into the cyclohex[*j*]indolo[2,3-*f*]morphan ring system.

In our previous publication[1] we reported a biogenetic-type synthesis of the indole analog of tetrahydrodeoxycodeine. We now wish to describe the synthesis of a compound containing the C_6 oxygen atom of codeine *via* a cyclization which more closely resembles the biogenetic pathway of the morphine alkaloids.

The biogenesis of morphine has long been conceded to occur *via* an oxidative cyclization of a 1,2,3,4-tetrahydroisoquinoline, such as A in Scheme I, as originally proposed by Robinson and Gulland.[2] However, the intimate details of this step remain a mystery. The most popular concept has been that of radical coupling[3] *via* B. Another possibility is the oxidation to the quinone C followed by 1,4-addition to give D. We have selected the α,β-unsaturated ketone **7** as an approximation of the quinone C for the purpose of this work.

The amide **1** was prepared by the thermal condensation of indole-3-acetic acid and *m*-methoxyphenethylamine. Bichler–Napieralski cyclization of the amide

SCHEME I



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