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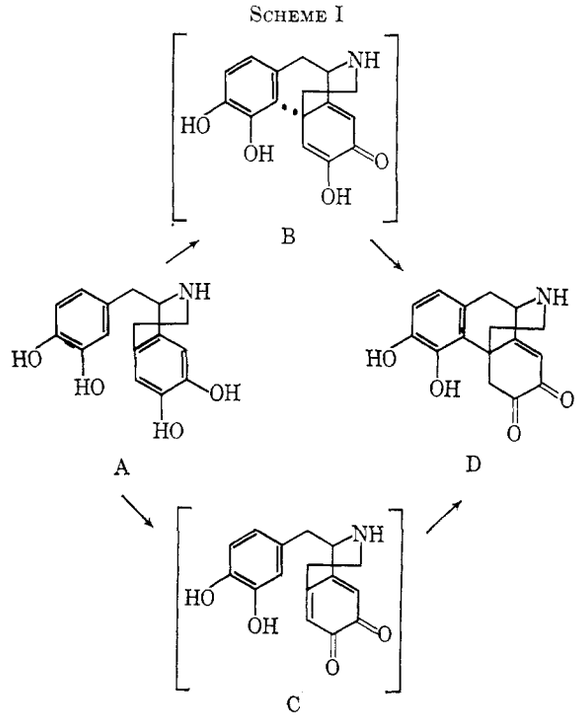
The C_6 oxygen function of morphine was introduced into the cyclohex[*j*]indolo[2,3-*f*]morphan ring system.

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

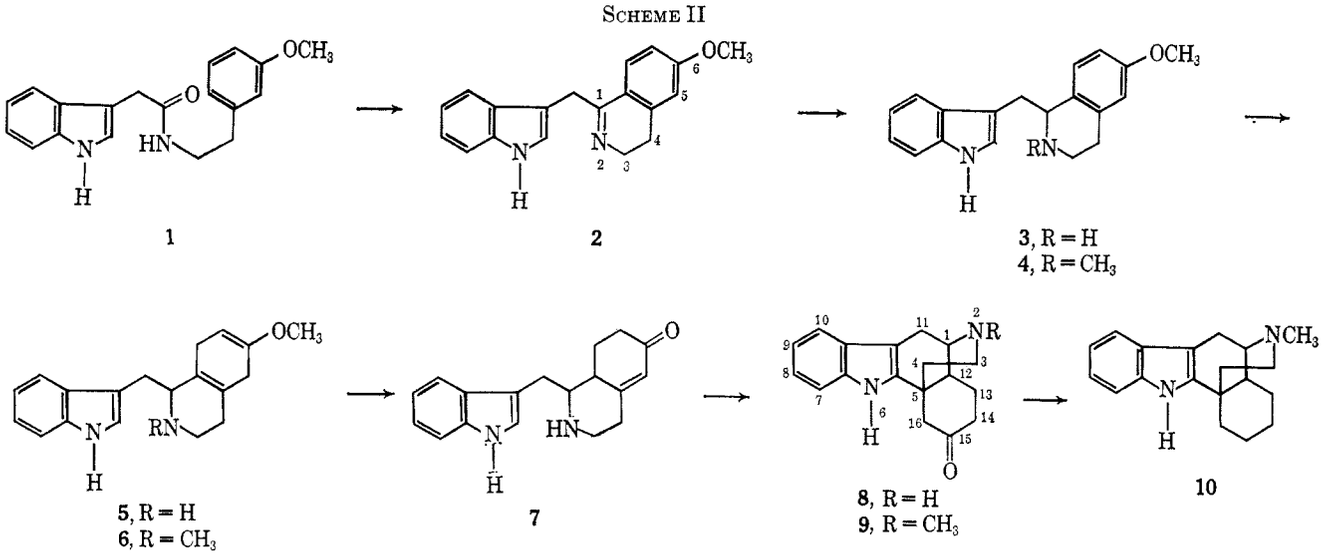


(1) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2551 (1967).

(2) J. M. Gulland and R. Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925).

(3) A. R. Battersby, *Proc. Chem. Soc.*, 189 (1963); G. W. Kirby, *Science*, **155**, 170 (1967).

SCHEME II



at room temperature produced the dihydroisoquinoline **2**, which was reduced with sodium borohydride to the tetrahydroisoquinoline **3**. Compound **3** was converted to the corresponding N-methyl derivative **4** by treatment with ethyl formate followed by lithium aluminum hydride reduction. Subjection of **3** and **4** to the conditions of the Birch reduction gave the hexahydroisoquinolines **5** and **6**, respectively. When the Birch product **6** was treated with 10% hydrochloric acid at room temperature for 20 hr, hydrolysis of the enol ether, conjugation of the double bond, and cyclization to *cis*-2-methylcyclohex[*j*]indolo[2,3-*f*]morphan-15-one (**9**) occurred in 13% yield. Refluxing for 1 hr increased the yield to 67%. Refluxing the Birch product **5** in 10% hydrochloric acid produced the indolomorphanone **8**. If **5** was treated with dilute oxalic acid at room temperature, it was possible to isolate the intermediate conjugated ketone **7**. Cyclohexindolomorphanone was shown to have the *cis* stereochemistry by conversion to *cis*-cyclohexindolomorphan (**10**) *via* the Wolf–Kishner reduction (see Scheme II).

Further applications of this general synthetic scheme, namely, the Birch reduction of methoxybenzene derivatives and the subsequent production of reactive precursors for cyclization to new ring systems, will be the subject of forthcoming publications.

Experimental Section

The melting points were determined using a Thomas–Hoover apparatus which had been calibrated against known standards.

N-(*m*-Methoxyphenethyl)indole-3-acetamide (1).—A mixture of 150 g of indole-3-acetic acid and 140 g of *m*-methoxyphenethylamine was heated for 20 hr at 175–180° under a stream of nitrogen. The reaction mixture was dissolved in 1200 ml of chloroform and washed with 5% hydrochloric acid, 5% sodium carbonate solution, and water. Removal of the solvent gave 220 g (83%) of a viscous gum. Distillation through a short-pass still gave an analytical sample, bp 250° (block temperature, 0.15 mm).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.59; N, 9.08. Found: C, 74.05; H, 6.53; N, 9.08.

3,4-Dihydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline (2).—To a solution of 81.3 g of N-(*m*-methoxyphenethyl)indole-3-acetamide in 400 ml of benzene was added 250 ml of phosphorus oxychloride and the resulting solution was refluxed for 3 hr. The reaction mixture was poured into 3 l. of ether. The resulting precipitate (62 g) was dissolved in ethanol, made basic with sodium hydroxide solution, and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate. Removal of the solvent gave 17.5 g (23%) of a crystalline solid, mp 150–152°. Recrystallization from benzene gave an analytical sample, mp 144–146°.

Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.30; H, 6.10; N, 9.42.

1,2,3,4-Tetrahydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline (3).—To 550 ml of phosphorus oxychloride was added 219 g of N-(*m*-methoxyphenylethyl)indole-3-acetamide. The mixture was swirled by hand until dissolution had been completed and then was allowed to stand at room temperature for 50 hr. The reaction mixture was poured into 3.5 l. of ether. The precipitate was dissolved in 1900 ml of ethanol and 300 ml of water was added. The solution was made basic with 10% sodium hydroxide solution, pH was adjusted to 3 with 20% hydrochloric acid, and 60 g of sodium borohydride was added portionwise while cooling with an ice bath such that the temperature remained at 20–30°. The pH was readjusted to 3 several times during the addition of the sodium borohydride. After the addition had been completed, the solution was acidified with hydrochloric acid, made basic with sodium hydroxide solution, and extracted with ether. The ether layer was washed with water and dried over sodium sulfate. Removal of the solvent gave 78 g (38%) of a crystalline solid, mp 162–164°. Recrystallization from benzene gave an analytical sample, mp 162–163.5°.

Anal. Calcd for $C_{19}H_{20}H_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.85; H, 6.80; N, 9.32.

1,2,3,4-Tetrahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline (4).—A mixture of 25 g of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline and 500 ml of ethyl formate was refluxed for 20 hr. The reaction mixture was filtered and the excess ethyl formate removed *in vacuo*. The residue was dissolved in 500 ml of tetrahydrofuran and 12.0 g of lithium aluminum hydride added slowly with cooling such that the temperature remained at 20–30°. After the addition had been completed, stirring was continued at room temperature for an additional 2 hr. The reaction mixture was decomposed by the cautious addition of water and 40% sodium hydroxide solution. The tetrahydrofuran layer was decanted, dried over sodium sulfate, and the solvent was removed. The residue, after crystallization from acetonitrile, gave 16.7 g (64%) of a crystalline solid, mp 125–127°. Further recrystallization gave an analytical sample, mp 128–129.5°.

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.52; H, 7.07; N, 8.86.

1,2,3,4,5,8-Hexahydro-(1-indol-3-ylmethyl)-6-methoxyisoquinoline (5).—To a solution of 4.0 g of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline in 150 ml of tetrahydrofuran was added 300 ml of ammonia. Then 4.0 g of sodium and 35 ml of *t*-butyl alcohol were added alternately in six equal portions over a 1-hr interval. One hour after this addition had been completed, 1.0 g of sodium was added and stirring was continued for 1 hr longer. The excess sodium was destroyed by the dropwise addition of methanol and the ammonia was allowed to evaporate. On pouring the reaction mixture into 700 ml of water, there was deposited 3.0 g (74%) of a crystalline solid, mp 155–157°. Re-

crystallization from benzene gave an analytical sample, mp 157–158°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.71; H, 7.51; N, 9.37.

1,2,3,4,5,8-Hexahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline (6).—To a solution of 12.0 g of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline in 200 ml of tetrahydrofuran was added 400 ml of ammonia. Then 5.0 g of sodium and 24 ml of *t*-butyl alcohol were added alternately in six equal protions. One hour after this addition had been completed, 0.5 g of sodium was added and stirring was continued for 1 hr longer. The excess sodium was destroyed by the dropwise addition of methanol and the ammonia was allowed to evaporate. On pouring the reaction mixture into 600 ml of cold water, there was deposited 8.0 g (66%) of a crystalline solid, mp 137–139°. Recrystallization from benzene gave an analytical sample, mp 141–142°.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.76; H, 7.92; N, 9.16.

1,2,3,4,8,8a-Hexahydro-1-(indol-3-ylmethyl)-6(7H)-isoquinolone (7).—A solution of 1.0 g of 1,2,3,4,5,8-hexahydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline in 100 ml of methanol was mixed with a solution of 1.33 g of oxalic acid in 20 ml of water and was allowed to stand at room temperature for 135 min. The reaction mixture was poured into 200 ml of ether. The ethereal solution was washed with 10% sodium carbonate solution and water and was dried over sodium sulfate, and the solvent was removed. The residue was chromatographed on neutral alumina. Elution with 2% methanol in ether gave, after recrystallization from benzene, 0.10 g (10%) of a crystalline solid: mp 203–204°; $\nu_{max}^{CHCl_3}$ 1668 (C=O, conjugated), 1620 (C=C, conjugated) cm^{-1}.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.32; H, 7.20; N, 9.91.

cis-**Cyclohex[*j*]indolo[2,3-*f*]morphan-15-one** (8).—A solution of 4.4 g of 1,2,3,4,5,8-hexahydro-(1-indol-3-ylmethyl)-6-methoxyisoquinoline and 45 ml of hydrochloric acid in 150 ml of methanol was refluxed for 1 hr. The reaction mixture was diluted with 45 ml of water and the methanol was stripped *in vacuo*. The solution was made basic with sodium hydroxide solution. Filtration gave a solid which, after recrystallization from ether, afforded 0.90 g (22%) of a crystalline solid, mp 201–201.5°.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.08; H, 7.23; N, 9.74.

cis-**2-Methylcyclohex[*j*]indolo[2,3-*f*]morphan-15-one** (9).—A solution of 5.0 g of 1,2,3,4,5,8-hexahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline and 45 ml of hydrochloric acid in 125 ml of methanol was refluxed for 1 hr. The reaction mixture was diluted with 70 ml of water and the methanol was stripped *in vacuo*. The solution was made basic with 40% sodium hydroxide solution. Filtration gave a solid which, after recrystallization from benzene, afforded 3.2 g (67%) of a solid, mp 236–237°. Further recrystallization gave an analytical sample, mp 236.5–237.5°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.52; N, 9.52. Found: C, 77.56; H, 7.71; N, 9.52.

cis-**2-Methylcyclohex[*j*]indolo[2,3-*f*]morphan** (10).—A solution of 2.0 g of *cis*-2-methylcyclohex[*j*]indolo[2,3-*f*]morphan-15-one, 1.6 g of sodium hydroxide, and 30 g of hydrazine hydrate in 80 ml of ethylene glycol was refluxed for 1 hr. The overhead then was removed until the temperature of the distillate reached 192°, after which heating was continued for 3 hr. On pouring the reaction mixture into 750 ml of water, there was deposited 1.1 g (58%) of a solid, mp 131–138°. Recrystallization from Skellysolve B gave a sample, mp 139–141°, which was shown to be identical with an authentic sample[1] by the methods of mixture melting point and infrared analysis.

Registry No.—**1**, 13118-18-8; **2**, 13118-19-9; **3**, 13118-20-2; **4**, 13118-53-1; **5**, 13118-54-2; **6**, 13118-55-3; **7**, 13118-56-4; **8**, 13131-50-5; **9**, 13143-77-6; **10**, 13118-57-5.

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Spectroscopic Studies of Aromatic Isoprenoids. Application of Nuclear Resonance to the Structural Differentiation of Tocopherols[1]

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A novel nuclear magnetic resonance (nmr) approach for definitively characterizing phenolic isoprenoids that belong to the vitamin E family is discussed and evaluated in the context of the nmr properties of a large number of binary systems containing as principal components several of these tocopherols. The method depends on experimentally developed anisotropy indices based on predictable orientation effects in some of the binary systems. These indices facilitate the assignment of chemical shifts that can be characteristically identified with specific ring positions in the system-modified tocopherols and these shifts can then be used for structural identification. The method, which is used in this study to identify specifically five tocopherols, appears to be suitable not only for other unsaturated tocopherols where heretofore ambiguous identifications were more likely, but for members of the coenzyme Q group (after straightforward conversions to their respective chromanols or chromenols), various other classes of phenols, aromatic amines, and aromatic mercaptans.

Recent reviews of the chemistry of tocopherols (vitamin E family)[2–4] have pointed to experimental difficulties in unequivocally differentiating unsaturated and certain of the less abundant saturated tocopherols isolable from natural sources, as well as synthetic analogs. Physical measurements cited in one of these reviews, in particular detailed nuclear magnetic resonance data,[2] appeared to hold out no promising applicability to this problem. In reexamining this in the larger context of structural elucidation of related ring systems, including substituted quinones capable of facile reduction to tocopherol-like prototypes, it appeared to us that the significant electron-acceptor properties of the phenolic group might possibly be-

(1) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

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