Alternate Precursors in Biogenetic-Type Syntheses VI (1), An Indole Analogue of the Aporphines. An Indole Analogue of the Dibenzopyrrocolines

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In earlier papers of this series, we discussed the possible fate of the indole analogue of norlaudanosoline **A**. In this publication, we have turned our attention to the other possible indole analogue **B**. Oxidation of **B** to the quinone **C** affords two alternatives for cyclization. Closure onto the basic nitrogen would give an indole analogue of the dibenzopyrrocoline alkaloids (2) **D**, whereas attack on the indole nitrogen would afford an indole analogue of the aporphine alkaloids (3) **E**. We have selected the α,β-unsaturated ketone **10** as an approximation of the quinone **C** for the purpose of this work.

The amide **1** was obtained on heating tryptamine and *p*-methoxyphenylacetic acid. Bischler-Napieralski cyclization of the amide afforded the dihydro-β-carboline **2**. Borohydride converted **2** to the tetrahydro-β-carboline **3**. Reduction of **3** with sodium in ammonia gave the Birch product **4**. If the Birch product is subjected to acid, hydrolysis of the enol ether and conjugation of the double bond should occur to give **8** which could cyclize onto either nitrogen. To simplify the matter we have selectively blocked the nitrogen atoms to force the reaction along only one path. The indole nitrogen of the Birch product was methylated with dimethyl carbonate and sodium hydride to give **5** which was treated with acid to afford the α,β-unsaturated ketone **9**. Under these conditions **9** cyclized onto the basic nitrogen giving rise

CHART I

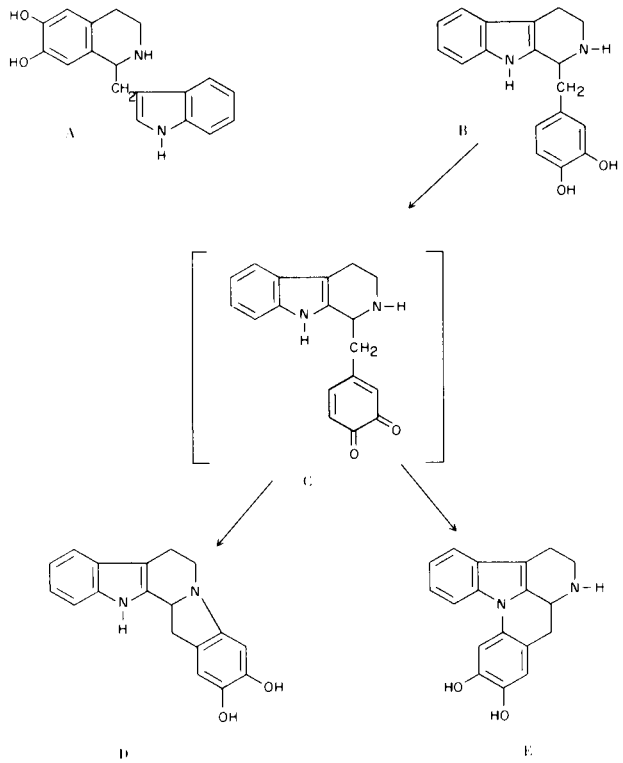
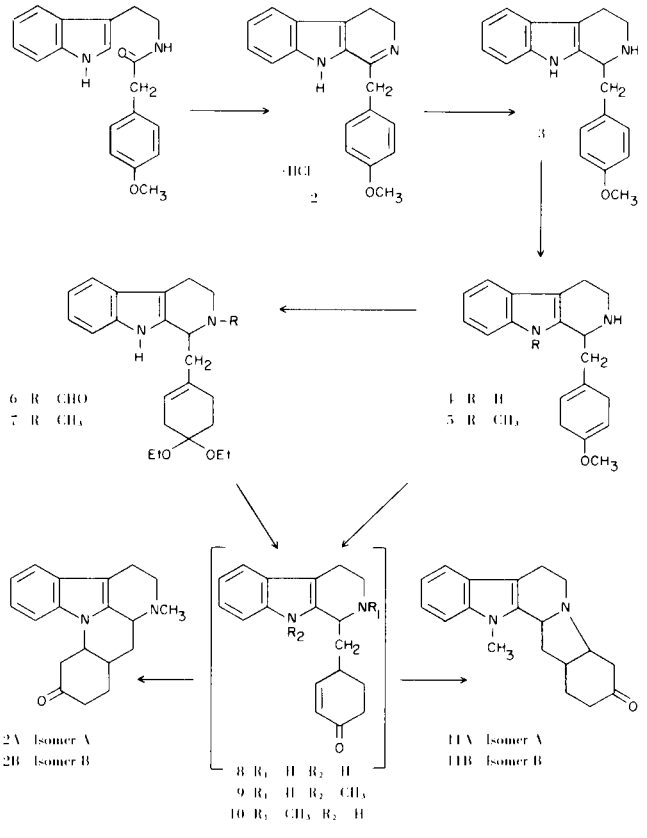


CHART II



to two stereoisomers of an indole analogue of the dibenzopyrrocolines (**IIA** and **IIB**).

Alternately, the basic nitrogen of the Birch product was methylated by formylation with ethyl formate in ethanol followed by reduction with lithium aluminum hydride. During formylation, the enol ether was converted to the diethoxy ketal thus giving rise to **6** and subsequently **7**. As previously, acid treatment of **7** led to the α,β-unsaturated ketone **10** which spontaneously cyclized to two stereoisomers of an indole analogue of the aporphines (**12A** and **12B**).

EXPERIMENTAL (4)

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

N-(2-Indol-3-ylethyl)-2-(*p*-methoxyphenyl)acetamide (**1**).

A mixture of 49.8 g. of *p*-methoxyphenylacetic acid and 48 g. of tryptamine was heated at 180-185° for 6 hours. Crystallization of the reaction mixture from 2.5 l. of ethyl acetate gave 77 g. (84%) of a crystalline solid, m.p. 151.5-152.5°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.75; H, 6.30; N, 9.33.

4,9-Dihydro-1-(*p*-methoxybenzyl)-3*H*-pyrido[3,4-*b*]indole Hydrochloride (**2**).

A solution of 83 g. of *N*-(2-indol-3-ylethyl)-2-(*p*-methoxyphenyl)acetamide in 425 ml. of phosphorus oxychloride was heated at 70° for 6 hours. The reaction mixture was poured into 3 l. of ether. The precipitate on crystallization from 400 ml. of ethanol gave 52 g. (59%) of a solid m.p. 238-239°. Further recrystallization gave an analytical sample, m.p. 235-235.5°.

Anal. Calcd. for $C_{19}H_{18}N_2O$·HCl: C, 69.83; H, 5.86; N, 8.57; Cl, 10.85. Found: C, 69.72; H, 6.08; N, 8.32; Cl, 10.66.

2,3,4,9-Tetrahydro-1-(*p*-methoxybenzyl)-1*H*-pyrido[3,4-*b*]indole (**3**).

To a solution of 41 g. of 4,9-dihydro-1-(*p*-methoxybenzyl)-3*H*-pyrido[3,4-*b*]indole hydrochloride in 200 ml. of water and 200 ml. of methanol was added 4.0 g. of sodium borohydride while the temperature was held below 40°. After the addition had been completed stirring was continued for an additional 10 minutes. The reaction mixture was diluted with 800 ml. of water, made basic with 100 ml. of 10% sodium hydroxide solution, and was extracted with methylene chloride. The methylene chloride layer was washed with water, dried over sodium sulfate, and the solvent was removed. Crystallization of the residue from benzene-Skelly solve B gave 27 g. (72%) of a solid, m.p. 110-112°. Further recrystallization gave an analytical sample, m.p. 111-112°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.06; H, 6.89; N, 9.59.

The *hydrochloride* formed in methanol as a crystalline solid, m.p. 256-258°. Further recrystallization gave an analytical sample, m.p. 257-258°.

Anal. Calcd. for $C_{19}H_{20}N_2O$·HCl: C, 69.40; H, 6.44; N, 8.52; Cl, 10.78. Found: C, 69.70; H, 6.56; N, 8.68; Cl, 10.73.

2,3,4,9-Tetrahydro-1-[(4-methoxy-1,4-cyclohexadien-1-yl)methyl]-1*H*-pyrido[3,4-*b*]indole (**4**).

To a solution of 17.0 g. of 2,3,4,9-tetrahydro-1-(*p*-methoxybenzyl)-1*H*-pyrido[3,4-*b*]indole in 400 ml. of tetrahydrofuran 800 ml. of ammonia was added. Over a 2 hour interval 8 g. of sodium and 34 ml. of *t*-butyl alcohol were added alternately in six equal portions and then stirring was continued for an additional 3 hours. The remaining sodium was destroyed by the addition of 2 ml. of methanol and the solvents removed. The residue was treated with 400 ml. of hot benzene, the solution filtered, and the solvent was removed. Crystallization of the residue from 50 ml. of ethyl acetate gave 6.1 g. (35%) of a solid, m.p. 137-137.5°. Another recrystallization gave an analytical sample, m.p. 137.5-138°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.51; H, 7.49; N, 9.36.

2,3,4,9-Tetrahydro-1-[(4-methoxy-1,4-cyclohexadienyl)methyl]-9-methyl-1*H*-pyrido[3,4-*b*]indole (**5**).

A mixture of 3.0 g. of 2,3,4,9-tetrahydro-1-[(4-methoxy-1,4-cyclohexadien-1-yl)methyl]-1*H*-pyrido[3,4-*b*]indole, 6 g. of sodium hydride, 36 ml. of dimethyl carbonate, and 200 ml. of tetrahydrofuran was refluxed for 20 hours. The reaction mixture was poured into 600 ml. of water and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue, after trituration with Skelly solve B, afforded 0.87 g. (30%) of a crystalline solid m.p. 128-132°. Recrystallization from Skelly solve B gave an analytical sample, m.p. 131.5-133.5°.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.99; H, 7.75; N, 8.96.

1-[(4,4-Diethoxy-1-cyclohexen-1-yl)methyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-2-carboxaldehyde (**6**).

A mixture of 3.0 g. of 2,3,4,9-tetrahydro-1-[(4-methoxy-1,4-cyclohexadien-1-yl)methyl]-1*H*-pyrido[3,4-*b*]indole, 75 ml. of ethyl formate and 300 ml. of ethanol was refluxed for 48 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue chromatographed on alumina. Elution with ether gave 2.4 g. of an oil. Crystallization from ether afforded 1.8 g. (54%) of a solid, m.p. 153.5-154.5°. Recrystallization from ethanol gave an analytical sample, m.p. 156-157°.

Anal. Calcd. for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.41; H, 7.91; N, 7.44.

1-[(4,4-Diethoxy-1-cyclohexen-1-yl)methyl]-2,3,4,9-tetrahydro-2-methyl-1*H*-pyrido[3,4-*b*]indole (**7**).

To a slurry of 4.5 g. of lithium aluminum hydride in 300 ml. of tetrahydrofuran was added a solution of 11.5 g. of 1-[(4,4-diethoxy-1-cyclohexen-1-yl)methyl]-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole-2-carboxaldehyde in 250 ml. of tetrahydrofuran and the mixture stirred for 10 hours. The reaction mixture was decomposed with 40% sodium hydroxide, filtered, and the solvent was removed. Crystallization of the residue from isopropyl ether gave 5.0 g. (46%) of a solid, m.p. 94-99°. Another recrystallization gave an analytical sample, m.p. 98-99°.

Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.70; H, 8.78; N, 6.66.

1,4,4a,6,7,12b,13,13a-Octahydro-12-methyl-12*H*-diindolo[1,2-*a*:2′,3′-*c*]pyridin-3(2*H*)one (**11**).

A solution of 750 mg. of 2,3,4,9-tetrahydro-1-[(4-methoxy-1,4-cyclohexadienyl)methyl]-9-methyl-1*H*-pyrido[3,4-*b*]indole and 15 ml. of hydrochloric acid in 40 ml. of methanol was refluxed for 1 hour. The methanol was removed on the steam

bath. The solution was made basic with 10% sodium hydroxide solution and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was chromatographed on 20 g. of alumina. Elution with benzene afforded, after recrystallization from Skelly solve B, 69 mg. (10%) of isomer A, m.p. 197-199.5°. Recrystallization from acetone-isopropyl ether gave an analytical sample, m.p. 198.5-199.5°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.74; H, 7.70; N, 9.66.

Elution with methylene chloride afforded, after recrystallization from ether-isopropyl ether, 75 mg. (11%) of isomer B, m.p. 145-146°. Recrystallization from acetone-isopropyl ether gave an analytical sample, m.p. 143-143.5° and 146-148.5°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.49; H, 7.57; N, 9.36.

5,6,7,7a,8,8a,9,10,12,12a-Decahydro-7-methyl-11*H*-benz[*b*]indolo-[3,2,1-*ij*][1,5]naphthyridin-11-one (**12**).

A solution of 19 g. of 1-[(4,4-diethoxy-1-cyclohexen-1-yl)-methyl]-2,3,4,9-tetrahydro-2-methyl-1*H*-pyrido[3,4-*b*]indole and 150 ml. of hydrochloric acid in 300 ml. of methanol was refluxed for 2 hours. The methanol was removed *in vacuo* and 500 ml. of water was added. The solution was made basic with 40% sodium hydroxide solution and extracted with methylene chloride. The methylene chloride layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue (16 g.) was chromatographed on 600 g. of alumina. Elution with benzene-methylene chloride (1:1) gave, after crystallization from cyclohexane, 4.0 g. (26%) of isomer A, m.p. 137.5-138.5°. Further recrystallization gave an analytical sample, m.p. 138.5-139°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.76; H, 7.50; N, 9.52.

Elution with methylene chloride gave, after crystallization from ether, 0.26 g. (1%) of a solid, m.p. 172-173°. Recrystallization from benzene-Skelly solve B gave an analytical sample of isomer B, m.p. 196.5-197°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.50; H, 7.59; N, 9.69.

REFERENCES

(1) H. Zinnes, F. R. Zuleski and J. Shavel, Jr., *J. Org. Chem.*, 34, 3165 (1969).

(2) J. Ewing, G. K. Hughes, E. Ritchie and W. C. Taylor, *Nature*, 169, 618 (1952).

(3) M. Shamma and W. Slusarchyk, *Chem. Rev.*, 64, 59 (1964).

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