A Non-Aromatic Ring D Analogue of the Dibenzopyrrocoline Alkaloids

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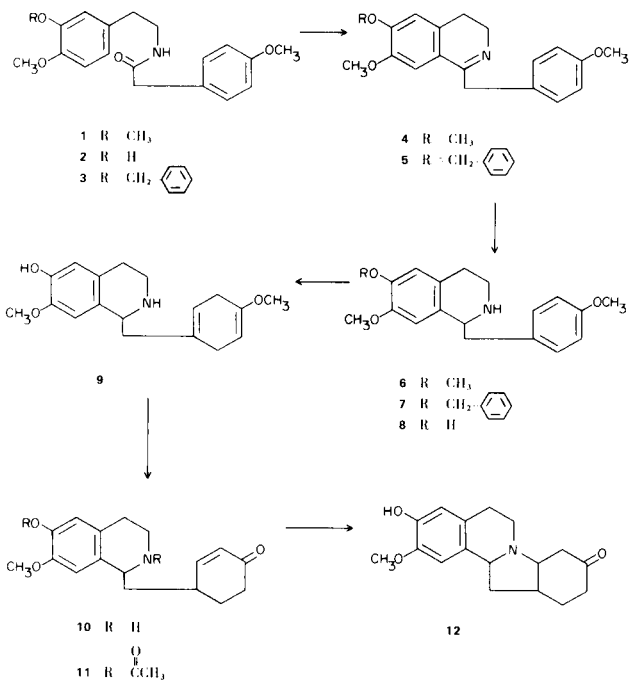
As part of a program (1) for the synthesis of alkaloid like compounds by the reduction of a monomethoxybenzene ring and subsequent cyclization of the thus formed α,β-unsaturated ketone precursor, we have turned our attention to a non-aromatic ring D analogue of the dibenzopyrrocoline alkaloids (2).

The condensation of homoveratrylamine and *p*-methoxyphenylacetic acid afforded the amide **1**. Bischler-Napieralski cyclization of the amide produced the dihydroisoquinoline **4** and reduction with sodium borohydride gave the tetrahydroisoquinoline **6**. Birch reduction of **6** produced the desired dihydroanisole system and cleaved the 6-methoxyl of the isoquinoline ring system to give **9**. To establish that it was the 6-methoxyl that had been cleaved, we carried out an unequivocal synthesis of **9**. The hydroxyamide **2** was obtained on heating 3-hydroxy-4-methoxyphenethylamine with *p*-methoxyphenylacetic acid and the hydroxyl function was protected by a benzyl group. The benzyl amide **3** was cyclized to the dihydroisoquinoline **5** and reduced to the tetrahydroisoquinoline **7**. The benzyl group was removed catalytically to give the hydroxyisoquinoline **8**. Birch reduction of **8** afforded the same hydroxy compound as previously obtained from **6**.



Heating **9** in concentrated hydrochloric acid for a short time afforded the α,β-unsaturated ketone **10**, isolated in the form of the crystalline diacetate **11**. Longer acid treatment of **9** afforded a non-aromatic ring D analogue of the dibenzopyrrocoline alkaloids **12**.

EXPERIMENTAL (3)

N-(3,4-Dimethoxyphenethyl)-2-(*p*-methoxyphenyl)acetamide (**1**).

A mixture of 54.5 g. of 3,4-dimethoxyphenethylamine and 50.0 g. of *p*-methoxyphenylacetic acid were heated at 190° for 2 hours. The reaction mixture was poured into 250 ml. of benzene. On standing there was deposited 87.0 g. of crystalline solid, m.p. 124-125°. Further recrystallization from benzene gave an analytical sample, m.p. 125-125.5°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.58; H, 7.06; N, 4.43.

N-(3-Hydroxy-4-methoxyphenethyl)-2-(*p*-methoxyphenyl)acetamide (**2**).

A mixture of 105 g. of 3-hydroxy-4-methoxyphenethylamine and 106 g. of 4-methoxyphenylacetic acid was heated at 190° for 1½ hours. Recrystallization of the residue from methanol-ether gave 131 g. (67%) of a solid, m.p. 113-119°. Further recrystallization gave an analytical sample, m.p. 117.5-118°.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.74; H, 6.71; N, 4.67.

N-(3-Benzyloxy-4-methoxy)-2-(*p*-methoxyphenyl)acetamide (**3**).

A solution of 45 g. of *N*-(3-hydroxy-4-methoxyphenethyl)-2-(*p*-methoxyphenyl)acetamide, 12 g. of sodium hydroxide, and 41 g. of benzyl bromide in 500 ml. of methanol was refluxed for 2 hours. Then a solution of 6.0 g. of sodium hydroxide in 10 ml. of water was added and refluxing was continued for an additional 3 hours. The reaction mixture was poured into 2.5 l. of water 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 a mixture of 100 ml. of ethyl acetate and 160 ml. of isopropyl ether gave 36.8 g. (64%), m.p. 115.5-119°. Recrystallization from isopropyl ether gave an analytical sample, m.p. 115.5-118°.

Anal. Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.32; H, 6.76; N, 3.66.

3,4-Dihydro-6,7-dimethoxy-1-(*p*-methoxybenzyl)isoquinoline Hydrochloride (**4**).

A solution of 80 g. of *N*-(3,4-dimethoxyphenethyl-2-(*p*-meth-

oxyphenyl)acetamide and 70 ml. of phosphorus oxychloride in 600 ml. of benzene was refluxed for 90 minutes. Filtration of the reaction mixture gave a solid which on recrystallization from ethanol gave 84 g. (99%) of a solid, m.p. 195.5-196.6°. Recrystallization from 1-butanol gave an analytical sample, m.p. 197-198°.

Anal. Calcd. for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.37; N, 4.03; Cl, 10.19. Found: C, 65.77; H, 6.31; N, 3.80; Cl, 10.22.

6-Benzyloxy-3,4-dihydro-7-methoxy-1-(*p*-methoxybenzyl)isoquinoline Hydrochloride ½ Hydrate (**5**).

A solution of 65 g. of *N*-(3-benzyloxy-4-methoxy)-2-(*p*-methoxyphenyl)acetamide and 70 ml. of phosphorus oxychloride in 500 ml. of benzene was refluxed for 2 hours. The reaction mixture was poured into 3 l. of ether. The precipitate was taken up in 300 ml. of hot ethanol and 900 ml. of water was added. On standing there was deposited 59.4 g. (87%) of a crystalline solid, m.p. 173-175°. Recrystallization from ethanol gave an analytical sample, m.p. 172-172.5°.

Anal. Calcd. for $C_{25}H_{27}ClNO_{3.5}$: C, 69.36; H, 6.29; O, 12.93; Cl, 8.19. Found: C, 69.65; H, 6.40; O, 12.89; Cl, 8.17.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(*p*-methoxybenzyl)isoquinoline Hydrobromide (**6**).

To a solution of 80 g. of 3,4-dihydro-6,7-dimethoxy-1-(*p*-methoxybenzyl)isoquinoline hydrochloride in 350 ml. of ethanol and 1500 ml. of water was added 15 g. of sodium borohydride while the temperature was held at 20-30°. After the addition had been completed stirring was continued for an additional 15 minutes. The *p*H was adjusted to 11 with 40% sodium hydroxide solution and the mixture was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was dissolved in ether and excess hydrogen bromide added. Trituration of the precipitate with isopropanol gave 45 g. (59%) of a solid, m.p. 214-215°. Recrystallization from ethanol gave an analytical sample, m.p. 215-215.5°.

Anal. Calcd. for $C_{19}H_{24}BrNO_3$: C, 57.88; H, 6.13; N, 3.55; Br, 20.27. Found: C, 57.68; H, 6.21; N, 3.46; Br, 20.33.

6-Benzyloxy-1,2,3,4-tetrahydro-7-methoxy-1-(*p*-methoxybenzyl)-isoquinoline (**7**).

To a solution of 59.4 g. of 6-benzyloxy-3,4-dihydro-7-methoxy-1-(*p*-methoxybenzyl)isoquinoline hydrochloride ½ hydrate in 1 l. of ethanol was added 10 g. of sodium borohydride and the solution was stirred for 2 hours. The reaction mixture was diluted with 1 l. of water, made basic with 40% 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 400 ml. of isopropyl ether gave 29 g. (59%) of a solid m.p. 90-91°. Further recrystallization gave an analytical sample, m.p. 90.5-91°.

Anal. Calcd. for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.11; H, 6.99; N, 3.87.

1,2,3,4-Tetrahydro-7-methoxy-1-(*p*-methoxybenzyl)-6-isoquinolinol Hydrochloride (**8**).

To a solution of 5.0 g. of 6-benzyloxy-1,2,3,4-tetrahydro-7-methoxy-1-(*p*-methoxybenzyl)-2-methylisoquinoline and 20 ml. of 2*N* hydrochloric acid in 125 ml. of ethanol was added to 1.5 g. of 5% palladium on carbon and the mixture was hydrogenated. The catalyst was removed by filtration and the solution was concentrated to 75 ml. On standing there was deposited 3.3 g. (75%) of a crystalline solid m.p. 238-238.5°. Recrystallization from ethanol gave an analytical sample m.p. 238.5-239°.

Anal. Calcd. for $C_{18}H_{22}ClNO_3$: C, 64.38; H, 6.60; N, 4.17; Cl, 10.56. Found: C, 64.45; H, 6.63; N, 4.34; Cl, 10.61.

The *free base* was obtained on shaking the salt with methylene chloride and sodium bicarbonate solution and removing the solvent from the organic layer as a crystalline solid m.p. 178-179°. Recrystallization from ethanol gave an analytical sample m.p. 179.5-180°.

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.12; H, 6.90; N, 4.85.

1-[(4-Methoxy-1,4-cyclohexadien-1-yl)methyl]-1,2,3,4-tetrahydro-7-methoxy-6-isoquinolinol (**9**).

Method A.

To a solution of 10.2 g. of 1,2,3,4-tetrahydro-7-methoxy-1-(*p*-methoxybenzyl)-6-isoquinolinol in 400 ml. of tetrahydrofuran was added 800 ml. of ammonia. Over a 2 hour interval, 8.2 g. of sodium and 20 ml. of *t*-butyl alcohol were added alternately in six equal portions. The ammonia was allowed to evaporate, the residue was poured into 1.2 l. of water, and the *p*H of the solution was adjusted to 8. On standing there was deposited a solid, which after recrystallization from benzene afforded 7.3 g. (71%) of a solid, m.p. 169-170.5°.

Method B.

To a solution of 14.3 g. of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(*p*-methoxybenzyl)isoquinoline in 200 ml. of tetrahydrofuran was added 400 ml. of ammonia. Over a 1.5 hour interval, 5.5 g. of sodium and 23 ml. of *t*-butyl alcohol were added in ten equal portions. The ammonia was allowed to evaporate and the residue was poured into 1.2 l. of water. The *p*H was adjusted to 8, and the solution 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 isopropyl ether gave 2.9 g. (20%) of a solid, m.p. 148-163°. Recrystallization from benzene gave an analytical sample, m.p. 170-172°. This sample was shown to be identical to the sample from method A by the methods of mixture melting point and infrared analysis.

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.46; H, 7.67; N, 4.52.

4-[(6-Acetoxy-2-acetyl-1,2,3,4-tetrahydro-7-methoxy-1-isoquinolyl)methyl]-2-cyclohexen-1-one (**11**).

A solution of 0.50 g. of 1-[(4-methoxy-1,4-cyclohexadien-1-yl)methyl]-1,2,3,4-tetrahydro-7-methoxy-6-isoquinolinol and 15 ml. of hydrochloric acid was refluxed for 1 hour. The methanol was removed *in vacuo* and 100 ml. of water was added to the residue. The *p*H was adjusted to 9 with 10% sodium hydroxide solution and the solution was extracted with methylene chloride. The methylene chloride layer was dried over sodium sulfate and the solvent was removed. A solution of the residue (0.46 g.) and 10 ml. of acetic anhydride in 10 ml. of pyridine was allowed to stand at room temperature for 20 hours. Removal of the volatiles *in vacuo* afforded 0.30 g. (49%) of a crystalline solid m.p. 230-233°. Recrystallization from benzene gave an analytical sample, m.p. 243-244.5°.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77; O, 21.54. Found: C, 68.18; H, 6.91; N, 3.83; O, 21.39.

5,6,7a,8,11,11a,12,12a-Octahydro-3-hydroxy-2-methoxyindole-[2,1-*a*]isoquinolin-9(10*H*)one (**12**).

A solution of 1.0 g. of 1-[(4-methoxy-1,4-cyclohexadien-1-yl)-methyl]-1,2,3,4-tetrahydro-7-methoxy-6-isoquinolinol, and 50 ml. of hydrochloric acid in 50 ml. of 2-propanol was refluxed for 48 hours. The reaction mixture was poured into 200 ml. of water. The *p*H of the resulting solution was adjusted to 8 with 40% sodium

hydroxide solution and the solution was extracted with chloroform. The chloroform layer was dried over sodium sulfate and the solvent was removed. Crystallization of the residue from ethyl acetate-Skellysolve B gave 0.32 g. (34%) of a solid, m.p. 156-157.5°. Recrystallization from isopropyl ether gave an analytical sample m.p. 159-160.5°.

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.28; H, 7.63; N, 5.04.

REFERENCES

(1) For the previous paper related to this work see 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) The melting points were determined using a Thomas-Hoover apparatus which had been calibrated against known standards.