Mannich and Eschweiler-Clarke Reaction of 1-Benzyl-1,2,3,4-tetrahydroisoquinolines. Studies on the Syntheses of Heterocyclic Compounds. Part CCCXVIII. (1)

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Modified Mannich reactions of a number of 1-benzyl-1,2,3,4-tetrahydroisoquinolines (Ia-Ie) were attempted to afford the corresponding protoberberine derivatives (IIa-IIe) in good yield. Treatment of both If and Ig with formalin under a variety of Mannich or Eschweiler-Clarke conditions did not give the expected protoberberine derivatives IIf and IIg, but afforded the *N*-methyl derivatives (VIIa) and (VIIb), respectively.

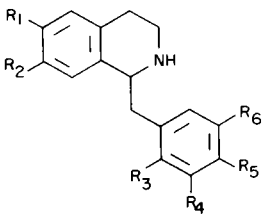
Pictet and Gams (3) have attempted to cyclise 1,2,3,4-tetrahydro-1-(3,4-dimethoxybenzyl)-6,7-methylenedioxyisoquinoline (Ia) into canadine (IIh) by the Mannich reaction; however, unexpectedly the tetrahydro-ψ-berberine (IIa) was obtained.

In previous papers (4,5,6), we have reported the syntheses of a number of protoberberine alkaloids by the modified Mannich reaction using formalin in acetic acid.

Since the modified Mannich reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinolines (Ia-Ig) had not yet been examined, Mannich cyclisation of these compounds was carried out and we wish to report these interesting results.

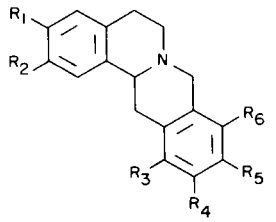
The starting materials (Ia-Ig) were prepared by usual methods. Namely, fusion of 3,4-methylenedioxyphenethylamine (IIIa) (7) with 3-benzyloxyphenylacetic acid (IVa) (8) afforded the amide (Va), whose cyclisation with phosphoryl chloride gave the 3,4-dihydroisoquinoline derivative (VIa). Reduction of VIa with sodium borohydride gave 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (Id).

SCHEME 1



I

a: $R_1 + R_2 = OCH_2O$, $R_3 = R_6 = H$, $R_4 = R_5 = OMe$
b: $R_1 = R_2 = OMe$, $R_3 = R_5 = R_6 = H$, $R_4 = OCH_2Ph$
c: $R_1 = OMe$, $R_2 = R_4 = OCH_2Ph$, $R_3 = R_5 = R_6 = H$
d: $R_1 + R_2 = OCH_2O$, $R_3 = R_5 = R_6 = H$, $R_4 = OCH_2Ph$
e: $R_1 = R_2 = OMe$, $R_3 = R_6 = H$, $R_4 = R_5 = OCH_2Ph$
f: $R_1 + R_2 = OCH_2O$, $R_3 = Br$, $R_4 = H$, $R_5 = R_6 = OMe$
g: $R_1 = OMe$, $R_2 = R_3 = OCH_2Ph$, $R_4 = H$, $R_5 + R_6 = OCH_2O$

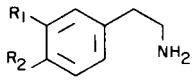


II

a: $R_1 + R_2 = OCH_2O$, $R_3 = R_6 = H$, $R_4 = R_5 = OMe$
b: $R_1 = R_2 = OMe$, $R_3 = R_5 = R_6 = H$, $R_4 = OCH_2Ph$
c: $R_1 = OMe$, $R_2 = R_4 = OCH_2Ph$, $R_3 = R_5 = R_6 = H$
d: $R_1 + R_2 = OCH_2O$, $R_3 = R_5 = R_6 = H$, $R_4 = OCH_2Ph$
e: $R_1 = R_2 = OMe$, $R_3 = R_6 = H$, $R_4 = R_5 = OCH_2Ph$
f: $R_1 + R_2 = OCH_2O$, $R_3 = Br$, $R_4 = H$, $R_5 = R_6 = OMe$
g: $R_1 = OMe$, $R_2 = R_3 = OCH_2Ph$, $R_4 = H$, $R_5 + R_6 = OCH_2O$
h: $R_1 + R_2 = OCH_2O$, $R_3 = R_4 = H$, $R_5 = R_6 = OMe$
i: $R_1 = R_2 = OMe$, $R_3 = R_5 = R_6 = H$, $R_4 = OH$
j: $R_1 = R_2 = OMe$, $R_3 = R_6 = H$, $R_4 = R_5 = OH$
k: $R_1 = OMe$, $R_2 = R_4 = OH$, $R_3 = R_5 = R_6 = H$

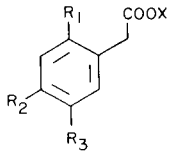
In a similar way 1-(3,4-bisbenzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (Ie) was prepared from 3,4-dimethoxyphenethylamine (IIIb) (9) and 3,4-bisbenzyloxyphenylacetic acid (IVb) (10) through the amide (Vb) and the 3,4-dihydroisoquinoline derivative (VIb). 1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (If) was also prepared from 3,4-methylenedioxyphenethylamine (IIIa) and methyl 2-bromo-4,5-dimethoxyphenylacetate (IVc) (11) by way of Vc and VIc. Borohydride reduction of 7-benzyloxy-1-(2-benzyloxy-4,5-methylenedioxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (VId) (12) gave the 1,2,3,4-tetrahydroisoquinoline (Ig) quantitatively.

SCHEME 2



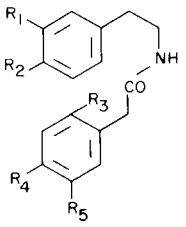
III

a: $R_1 + R_2 = OCH_2O$
b: $R_1 = R_2 = OMe$



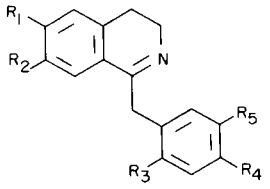
IV

a: R_1 = R_2 = H, R_3 = OCH_2Ph, X = H
b: R_1 = H, R_2 = R_3 = OCH_2Ph, X = H
c: R_1 = Br, R_2 = R_3 = OMe, X = Me



V

a: R_1 + R_2 = OCH_2O, R_3 = R_4 = H, R_5 = OCH_2Ph
b: R_1 = R_2 = OMe, R_3 = H, R_4 = R_5 = OCH_2Ph
c: R_1 + R_2 = OCH_2O, R_3 = Br, R_4 = R_5 = OMe



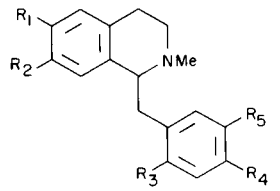
VI

a: R_1 + R_2 = OCH_2O, R_3 = R_4 = H, R_5 = OCH_2Ph
b: R_1 = R_2 = OMe, R_3 = H, R_4 = R_5 = OCH_2Ph
c: R_1 + R_2 = OCH_2O, R_3 = Br, R_4 = R_5 = OMe
d: R_1 = OMe, R_2 = R_3 = OCH_2Ph, R_4 + R_5 = OCH_2O
e: R_1 = OMe, R_2 = R_5 = OCH_2Ph, R_3 = R_4 = H

The Mannich reaction of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives (Ia-Ie) with formalin in acetic acid gave the corresponding protoberberine derivatives (IIa-IIe) in good yield. In these instances no cyclisations at the *ortho* position to the alkoxyl were detected under these conditions.

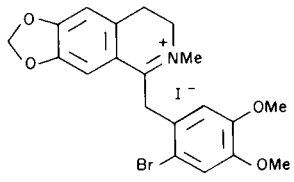
This fact prompted us to examine the Mannich reaction of the compounds If and Ig blocked with some substituents at the *para* position to the alkoxyl group. First, treatment of If with formalin in acetic acid did not afford the expected protoberberine (IIf) but gave the *N*-methyl derivative, 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (VIIa), which was shown to be identical with an authentic sample derived from the methiodide (VIII) by microanalysis and spectral comparisons. Secondly, a modified Mannich reaction of Ig afforded 7-benzyloxy-1-(2-benzyloxy-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (VIIb) with no trace of the protoberberine (IIg) being formed. Attempts to cyclise the 1-benzyl-1,2,3,4-tetrahydroisoquinolines at the *ortho* position to the alkoxyl group resulted in failure and the protoberberines were obtained only in case of the hydroxy derivatives (I3,I4,I5,I6,I7). Thus, conversion of 1-benzyl-1,2,3,4-tetrahydroisoquinoline into protoberberine by cyclisation *ortho* to the alkoxyl group would seem to be prevented by steric hindrance. Furthermore, due to the relatively low electron density, an *N*-methyl derivative was obtained. On the other hand, the bromo-compound (If) was treated with formalin under a variety of conditions in order to investigate the mechanism of Eschweiler-Clarke reaction. Treatment of If with 37% formalin in both acetic acid-ethanol and methanol-concentrated hydrochloric acid gave the *N*-methyl derivative (VIIa). Likewise treatment of If with 37% formalin also afforded the *N*-methyl derivative in good yield. In addition, compound If was methylated with 37% formalin to give the *N*-methyl derivative (VIIa) even in basic media, such as piperidine and triethylamine. However, attempted methylation of If with paraformaldehyde under a variety of conditions yielded only unchanged starting material or a mixture of unexpected products.

SCHEME 3



VII

a: R_1 + R_2 = OCH_2O, R_3 = Br, R_4 = R_5 = OMe
b: R_1 = OMe, R_2 = R_3 = OCH_2Ph, R_4 + R_5 = OCH_2O



VIII

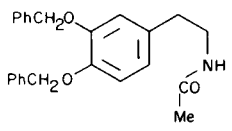
Concerning the mechanism of the Eschweiler-Clarke reaction, it has been hitherto proposed that formic acid would reduce the *N*-methylol derived from the secondary

amine and formaldehyde to give the *N*-methyl derivative.

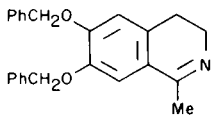
Eschweiler (18) has already treated a number of amines with formalin to obtain the corresponding *N*-methyl derivatives. Werner (19) has also investigated the methylated products of ammonia with formalin and proposed an enamine theory for the mechanism of the Eschweiler reaction. Considering the fact that the treatment of If with formalin under a variety of conditions, even in basic media, afforded the *N*-methyl derivative (VIIa), it is assumed that the *N*-methylol would be reduced to VIIa by attack of a hydride anion due to formaldehyde in the absence of any trace of formic acid.

Finally, the same reaction of 6,7-bisbenzyloxy-1,2,3,4-tetrahydro-1-methylisoquinoline (XI) which was derived from the amide (IX) through the 3,4-dihydroisoquinoline (X) gave 6,7-bisbenzyloxy-1,2,3,4-tetrahydro-1,2-dimethylisoquinoline (XII) quantitatively.

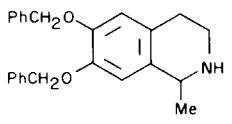
SCHEME 4



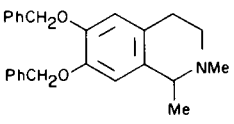
IX



X



XI



XII

EXPERIMENTAL

Nmr spectra were determined on a Hitachi H-60 spectrometer in deuteriochloroform with tetramethylsilane as internal reference.

5,6,13,13a-Tetrahydro-10,11-dimethoxy-2,3-methylenedioxy-8*H*-dibenzo[*a*,*g*]quinolizine (IIa).

To a solution of 2.0 g. of 1,2,3,4-tetrahydro-1-(3,4-dimethoxybenzyl)-6,7-methylenedioxyisoquinoline (3) (Ia) in 20 ml. of acetic acid was added 25 ml. of 37% formalin and the mixture was heated under reflux for 2 hours. After cooling, the reaction mixture was basified with ammonia and extracted with benzene. The usual work-up gave 0.9 g. of the protoberberine (IIa) as pale yellow needles, m.p. 170-172° (from chloroform-ether-hexane) [lit. (3) m.p. 168°], ν max (chloroform) cm^{-1}: 2800-2700 (*trans*-quinolizidine).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.80; H, 6.28; N, 3.98.

5,6,13,13a-Tetrahydro-11-hydroxy-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizine (IIi).

A mixture of 1.9 g. of 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (Ib) (8), 20 ml. of 37% formalin, and 20 ml. of acetic acid was heated under reflux for 2 hours. The reaction mixture was basified with ammonia and extracted with benzene. The usual work-up gave 1.2 g. of the protoberberine (IIb) as a colorless syrup, ν max (chloroform) cm^{-1}: 2800-2700 (*trans*-quinolizidine). To a solution of 1.0 g. of the preceding protoberberine (IIb) in 20 ml. of ethanol was added 20 ml. of concentrated hydrochloric acid and the mixture was boiled under reflux for 2 hours. Evaporation of the solvent gave a colorless powder, which was suspended in ethyl acetate and basified with ammonia. The crystalline substance precipitated was extracted with ether. Work-up as usual gave 0.3 g. of the phenolic protoberberine (IIi) as colorless needles, m.p. 256-259° [lit. (8), m.p. 261-263°].

5,6,13,13a-Tetrahydro-2,11-dihydroxy-3-methoxy-8*H*-dibenzo-[*a*,*g*]quinolizine (IIk).

To a stirred solution of 1.6 g. of 7-benzyloxy-1-(3-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (VIe) (20) hydrochloride in 100 ml. of methanol was added 0.6 g. of sodium borohydride and the mixture was heated under reflux for 1 hour. Removal of the solvent gave a syrup which was extracted with benzene. The extract was washed with water, dried over potassium carbonate and evaporated to afford 1.4 g. of 7-benzyloxy-1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (Ic) as a colorless syrup, ν max (chloroform) cm^{-1}: 3300 (NH).

A mixture of 1.2 g. of Ic, 20 ml. of 37% formalin, and 20 ml. of acetic acid was heated under reflux for 3 hours. Work-up as described for IIa gave 0.8 g. of the protoberberine (IIc) as a pale yellowish gum, ν max (chloroform) cm^{-1}: 2810-2700 (*trans*-quinolizidine).

A mixture of 0.6 g. of IIc, 15 ml. of ethanol, and 25 ml. of concentrated hydrochloric acid was refluxed for 2 hours. The solvent was evaporated to afford a colorless residue, which was recrystallized from methanol-ether to give 0.3 g. of the phenolic protoberberine (IIk) hydrochloride as a colorless powder, m.p. 240° dec.

Anal. Calcd. for $C_{18}H_{19}NO_3 \cdot HCl$: N, 4.19. Found: N, 4.03.

11-Benzyloxy-5,6,13,13a-tetrahydro-2,3-methylenedioxy-8*H*-dibenzo[*a*,*g*]quinolizine (IId).

A mixture of 2.2 g. of 3,4-methylenedioxyphenethylamine (IIIa) (7) and 2.0 g. of 3-benzyloxyphenylacetic acid (IVa) (8) was heated at 170-180° for 4 hours. The reaction mixture was extracted with chloroform. The extract was washed with 10% hydrochloric acid and water, dried over potassium carbonate and evaporated to give 3.2 g. of the amide (Va) as a brownish gum, ν max (chloroform) cm^{-1}: 1660 (C=O).

A mixture of 2.8 g. of Va, 8 ml. of phosphoryl chloride, and 100 ml. of dry benzene was heated under reflux for 2 hours, and an excess of hexane was added to the reaction mixture. The precipitated syrup was separated by decantation and washed with hexane several times. To a stirred solution of the above 3,4-dihydroisoquinoline (VIa) hydrochloride [ν max (chloroform) cm^{-1}: 1655 ($C=N^+$)] in 100 ml. of methanol was added 1.0 g. of sodium borohydride and the reaction mixture was heated under reflux for 1 hour. Work-up as described for Ic afforded 1.2 g. of 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (Id) as a colorless syrup, ν max (chloroform) cm^{-1}: 3300 (NH).

A mixture of 0.9 g. of Id, 15 ml. of 37% formalin, and 10 ml. of acetic acid was heated under reflux for 3 hours. Work-up as described for IIa gave a brownish gum, which was recrystallized from chloroform-ether-hexane to afford 0.5 g. of the protoberberine

(IId) as pale yellow needles, m.p. 141-142°, ν max (chloroform) cm^{-1}: 2820-2700 (*trans*-quinolizidine).

Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.18; H, 6.18; N, 3.53.

5,6,13,13a-Tetrahydro-10,11-dihydroxy-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizine (IIj).

A mixture of 2.0 g. of 3,4-dimethoxyphenethylamine (9) (IIIb) and 2.5 g. of 3,4-bisbenzyloxyphenylacetic acid (10) (IVb) was heated at 170-175° for 3 hours. Work-up in the usual way gave 3.0 g. of the amide (Vb) as colorless plates, m.p. 130-131° (from ethyl acetate-ether).

Anal. Calcd. for $C_{32}H_{33}NO_5$: C, 75.12; H, 6.50; N, 2.74. Found: C, 74.68; H, 6.49; N, 2.81.

A mixture of 2.6 g. of the amide (Vb), 4 ml. of phosphoryl chloride, and 50 ml. of dry benzene was heated under reflux for 3 hours, and then poured into an excess of hexane. The crystalline substance precipitated, was separated by decantation, washed with hexane several times, and recrystallized from ethanol-ether to give 1.8 g. of the 3,4-dihydroisoquinoline (VIb) hydrochloride as pale yellow needles, m.p. 188-189°.

Anal. Calcd. for $C_{32}H_{31}NO_4 \cdot HCl$: N, 2.64. Found: N, 2.80.

To a stirred solution of 1.5 g. of the preceding 3,4-dihydroisoquinoline (VIb) hydrochloride in 80 ml. of methanol was added 0.9 g. of sodium borohydride and the reaction mixture was heated under reflux for 30 minutes. Removal of the solvent gave a residue which was extracted with benzene. Usual work-up afforded 1.1 g. of 1-(3,4-bisbenzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (Ie) as a colorless syrup, ν max (chloroform) cm^{-1}: 3300 (NH).

A mixture of 1.0 g. of the 1,2,3,4-tetrahydroisoquinoline (Ie), 20 ml. of 37% formalin, and 20 ml. of acetic acid was heated under reflux for 2 hours. Work-up as described for IIa gave 0.6 g. of the protoberberine (IIe) as a pale yellowish gum, ν max (chloroform) cm^{-1}: 2810-2700 (*trans*-quinolizidine). Debenzylation of 0.5 g. of the protoberberine (IIe) with concentrated hydrochloric acid in ethanol afforded 0.2 g. of the phenolic protoberberine (IIj) hydrochloride as a colorless powder, m.p. 250° dec.

Anal. Calcd. for $C_{19}H_{21}NO_4 \cdot HCl \cdot H_2O$: C, 59.74; H, 6.33; N, 3.67. Found: C, 59.40; H, 6.66; N, 3.85.

N-(3,4-Methylenedioxyphenethyl)-2-bromo-4,5-dimethoxyphenylacetamide (Vc).

A mixture of 6.5 g. of 3,4-methylenedioxyphenethylamine (IIIa) (7) and 10.4 g. of methyl 2-bromo-4,5-dimethoxyphenylacetate (11) (IVc) was heated at 160-170° for 4 hours, cooled, and extracted with chloroform. The usual work-up gave a brownish gum, which was recrystallized from methanol-ether to afford 6.0 g. of the amide (Vc) as pale yellow prisms, m.p. 155-156°, ν max (chloroform) cm^{-1}: 1670 (C=O).

Anal. Calcd. for $C_{19}H_{20}BrNO_5$: C, 53.95; H, 4.77; N, 3.31. Found: C, 53.74; H, 5.06; N, 3.66.

1-(2-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (VIc).

A mixture of 5.5 g. of the amide (Vc), 100 ml. of dry benzene, 50 ml. of chloroform, and 20 ml. of phosphoryl chloride was heated under reflux for 2 hours. Work-up as described for VIb gave 3.5 g. of the 3,4-dihydroisoquinoline (VIc) hydrochloride as pale yellow needles, m.p. 217-219° (methanol-ether), ν max (chloroform) cm^{-1}: 1650 ($C=\overset{+}{N}$).

Anal. Calcd. for $C_{19}H_{18}BrNO_4 \cdot HCl$: C, 51.74; H, 4.35; N, 3.16. Found: C, 52.09; H, 4.74; N, 3.24.

1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (If).

To a stirred solution of 2.8 g. of the 3,4-dihydroisoquinoline (VIc) hydrochloride in 100 ml. of methanol was gradually added 1.0 g. of sodium borohydride and the reaction mixture was then heated under reflux for 30 minutes. Work-up as described for Ic gave a yellow residue, which was recrystallized from ether-hexane to afford 1.8 g. of the 1,2,3,4-tetrahydroisoquinoline (If) as colorless prisms, m.p. 159-160°, ν max (chloroform) cm^{-1}: 3300 (NH), 930 (OCH_2O); nmr δ (deuteriochloroform); 7.08 (1H, singlet, C_3'-*H*), 6.81 (2H, broad singlet, C_8 and C_6'-*H*), 6.60 (1H, singlet, C_5-*H*), 5.93 (2H, singlet, -OCH_2O-), 3.88, 3.86 ppm (6H, singlet respectively, 2 x OCH_3).

Anal. Calcd. for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.98; N, 3.44. Found: C, 56.48; H, 4.79; N, 3.55.

1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (VIIa).

1-(2-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (VIc) prepared from 1.0 g. of its hydrochloride as usual was dissolved in 10 ml. of methyl iodide. After being kept at room temperature for 2 hours, the excess of methyl iodide was distilled to give the methiodide (VIII) as a brownish gum, ν max (chloroform) cm^{-1}: 1620 (C=N). To a stirred solution of the methiodide in 50 ml. of methanol was gradually added 0.5 g. of sodium borohydride and the reaction mixture was heated under reflux for 1 hour. The solvent was evaporated to give a colorless gum which was extracted with benzene. Work-up as usual gave 0.6 g. of the 1,2,3,4-tetrahydroisoquinoline (VIIa) as a colorless syrup, ν max (chloroform) cm^{-1}: 2805 (NCH_3), 940 (OCH_2O); nmr δ (deuteriochloroform): 7.00 (1H, singlet, C_3'-*H*), 6.58, 6.54 (2H, singlet respectively, C_5 and C_6'-*H*), 6.24 (1H, singlet, C_8-*H*), 5.83 (2H, singlet, OCH_2O), 3.85, 3.74 (6H, singlet respectively, 2 x OCH_3), 2.48 ppm (3H, singlet, NCH_3).

This formed an oxalate as colorless prisms, m.p. 183-185°.

Anal. Calcd. for $C_{20}H_{22}BrNO_4 \cdot C_2H_2O_4$: C, 51.76; H, 4.73; N, 2.75. Found: C, 51.57; H, 5.07; N, 2.99.

N-Methylation of If.

a) Modified Mannich Reaction.

A mixture of 1.0 g. of 1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (If), 15 ml. of 37% formalin, and 20 ml. of acetic acid was heated under reflux for 3 hours. The reaction mixture was basified with ammonia and extracted with benzene. Work-up as usual gave a brownish gum, which was chromatographed on 15 g. of silica gel with chloroform as eluant to give 68 mg. of the *N*-methyl derivative (VIIa) as a colorless syrup. Its ir and nmr spectra were superimposable on those of an authentic sample.

The treatment of If with 37% formalin in both acetic acid-ethanol (1:1) and methanol-concentrated hydrochloric acid (20:1) gave the same product (VIIa) as above.

b) A mixture of 50 mg. of If and 5 ml. of 37% formalin was heated at 100-110° for 4 hours. The reaction mixture was poured into 20 ml. of water and extracted with benzene. Work-up as usual gave a brownish gum, which was chromatographed on 1.0 g. of silica gel with chloroform as eluant to afford 17 mg. of the *N*-methyl derivative (VIIa) as a colorless syrup. Its ir and nmr spectra were superimposable on those of an authentic sample.

The treatment of If with 37% formalin in methanol also yielded the same product (VIIa) as above.

c) A mixture of 100 mg. of If, 10 ml. of triethylamine, and 10 ml. of 37% formalin was heated under reflux for 3 hours. The

solvent was distilled off to give a brownish residue, which was extracted with ether. The extract was washed with water, dried over potassium carbonate and evaporated to afford 48 mg. of the *N*-methyl derivative (VIIa) as a pale yellowish gum, which was identical with an authentic sample by its spectral comparisons.

The treatment of If with 37% formalin in ethanol-piperidine also afforded the same product (VIIa).

7-Benzyloxy-1-(2-benzyloxy-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (VIIb).

To a stirred solution of 1.0 g. of 7-benzyloxy-1-(2-benzyloxy-4,5-methylenedioxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (VId) hydrochloride in 50 ml. of methanol was gradually added 0.3 g. of sodium borohydride and the reaction mixture was heated under reflux for 30 minutes. The solvent was evaporated to give a brownish gum, which was extracted with benzene. Removal of the solvent gave 0.7 g. of 7-benzyloxy-1-(2-benzyloxy-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (Ig) as a colorless syrup, ν max (chloroform) cm^{-1}: 3300 (NH). A mixture of 0.6 g. of Ig, 8 ml. of 37% formalin, and 10 ml. of acetic acid was heated under reflux for 2 hours. Work-up as described for IIa gave a brownish gum, which was recrystallized from ether-hexane to afford 0.2 g. of the *N*-methyl derivative (VIIb) as colorless prisms, m.p. 103-104°, ν max (potassium bromide) cm^{-1}: 2805 ($N\text{-}CH_3$), 940 (OCH_2O); nmr δ (deuteriochloroform): 7.29, 7.27 (10H, broad singlet respectively, 2 x C_6H_5), 6.54, 6.50 (3H, singlet respectively, C_5, C_8 and C_6'-*H*), 6.02 (1H, singlet, C_3'-*H*), 5.81 (2H, broad singlet, OCH_2O), 4.86, 4.67 (4H, singlet respectively, 2 x OCH_2Ph), 3.79 (3H, singlet, OCH_3), 2.38 ppm (3H, singlet, $N\text{-}CH_3$).

Anal. Calcd. for $C_{33}H_{33}NO_5 \cdot \frac{1}{2}H_2O$: C, 74.36; H, 6.43; N, 2.63. Found: C, 73.90; H, 6.33; N, 2.81.

6,7-Bisbenzyloxy-3,4-dihydro-1-methylisoquinoline (X).

A mixture of 1.5 g. of *N*-3,4-bisbenzyloxyphenethylacetamide (IX), ν max (chloroform) cm^{-1}: 1660 (C=O), which was prepared from 3,4-bisbenzyloxyphenethylamine (21) and acetyl chloride, 30 ml. of dry benzene and 4 ml. of phosphoryl chloride was heated under reflux for 2 hours. The reaction mixture was poured into an excess of hexane and the crystalline substance which precipitated was separated by decantation and recrystallized from ethanol to give 0.6 g. of the 3,4-dihydroisoquinoline (X) hydrochloride as pale yellow needles, m.p. 202-204° dec., ν max (chloroform) cm^{-1}: 1650 ($C=N^+$).

Anal. Calcd. for $C_{24}H_{23}NO_2 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 71.52; H, 6.25. Found: C, 71.10; H, 6.22.

6,7-Bisbenzyloxy-1,2,3,4-tetrahydro-1,2-dimethylisoquinoline (XII).

To a stirred solution of 300 mg. of X hydrochloride in 50 ml. of methanol was gradually added 100 mg. of sodium borohydride and the reaction mixture was refluxed for 30 minutes. The solvent was evaporated to give a brownish gum, which was extracted with benzene. Usual work-up afforded 200 mg. of 6,7-bisbenzyloxy-1,2,3,4-tetrahydro-1-methylisoquinoline (XI) as a colorless syrup, ν max (chloroform) cm^{-1}: 3300 (NH). A mixture of 150 mg. of XI and 15 ml. of 37% formalin was heated at 100-110° for 2 hours. The reaction mixture was then poured into 20 ml. of water and the amorphous substance precipitated was extracted with benzene. Work-up in the usual way gave 60 mg. of the *N*-methyl derivative (XII) as a colorless syrup, ν max (chloroform) cm^{-1}: 2805 ($N\text{-}CH_3$); nmr δ (deuteriochloroform): 7.36, 7.34 (10H, singlet respectively, 2 x C_6H_5), 6.64 (2H, broad singlet, C_5-*H*), 5.09 (4H, singlet, 2 x OCH_2Ph), 3.46 (1H, quartet, J = 6.4 cps, CH), 2.44 (3H, singlet, $N\text{-}CH_3$), 1.30 ppm (3H, doublet, J = 6.4 cps, $C_1\text{-}CH_3$). The picrate prepared as usual was recrystallized from ethanol to give yellow needles, m.p. 146-148°.

Anal. Calcd. for $C_{25}H_{27}NO_2 \cdot C_6H_3N_3O_7$: C, 61.79; H, 5.02; N, 9.30. Found: C, 61.44; H, 5.06; N, 8.96.

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