Studies on the Syntheses of Heterocyclic Compounds. Part DLIV (1). A Total Synthesis of (±)-Coreximine by Thermolysis

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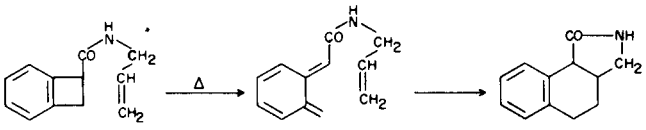
Received October 1, 1973

Thermolysis of the dibenzyloxy-substituted benzocyclobutene IXc effected cyclization and mono-*O*-debenzylation to provide a facile route to the total synthesis of the protoberberine isoquinoline (±)-coreximine (XIII).

The Oppolzer reaction (3), an application of the Woodward-Hoffmann rule (4), is an effective method for the thermolytic synthesis of the tetralin III from the benzocyclobutene I and probably involves the *o*-quinodimethane II as the intermediate.

In utilizing this reaction in the synthesis of isoquinoline alkaloids, we considered the *o*-quinonoid V, an intermediate postulated by Shamma (5) in the novel biogenesis of the spirobenzylisoquinoline VI from the protoberberine IV, to be electronically equivalent to the *o*-quinodimethane VII which could then be derived from the benzocyclobutene VIII. Indeed, based on this approach, we succeeded in preparing the protoberberine xylopinine (XI) and the spirobenzylisoquinoline ochotensine-analog XV from the benzocyclobutene derivatives IXa and IXb *via* the *o*-quinodimethanes Xa and Xb (6,7). As a further extension of this method, we now wish to report a facile synthesis of the phenolic protoberberine (±)-coreximine (XIII) based on the thermolytic cyclization and mono-*O*-debenzylation of the benzocyclobutene IXc.

SCHEME 1



I II III

4-Benzyloxy-3-bromo-5-methoxybenzaldehyde (XVI) (9) was condensed with cyanoacetic acid in the presence of pyridine to give the corresponding α-cyanocinnamic acid XVII as its pyridinium salt followed by reduction with sodium borohydride in ethanol to afford the dihydrocinnamic acid XVIII. Decarboxylation of XVIII provided the phenylpropionitrile XIX which was treated with sodium amide in liquid ammonia to give the benzocyclobutene XXI by *cine*-substitution which indicated that this reaction proceeded *via* the benzyne intermediate XX. Hydrolysis of the nitrile XXI furnished the corresponding carboxylic acid XXII which was treated with 4-benzyloxy-3-methoxyphenethylamine in the presence of dicyclohexylcarbodiimide to give the amide XXIII followed by Bischler-Napieralski

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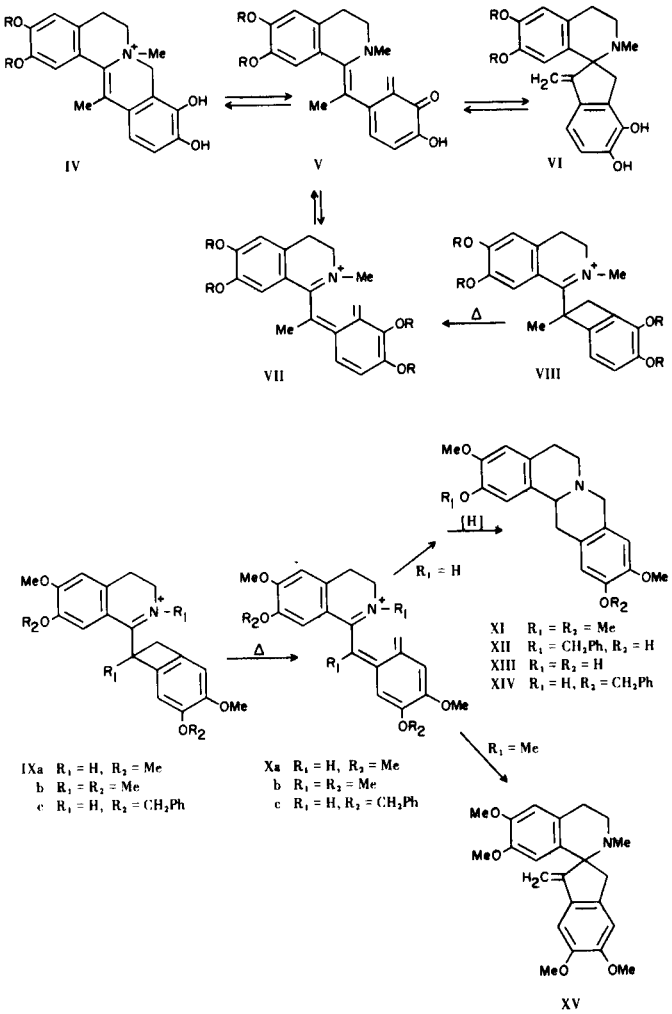

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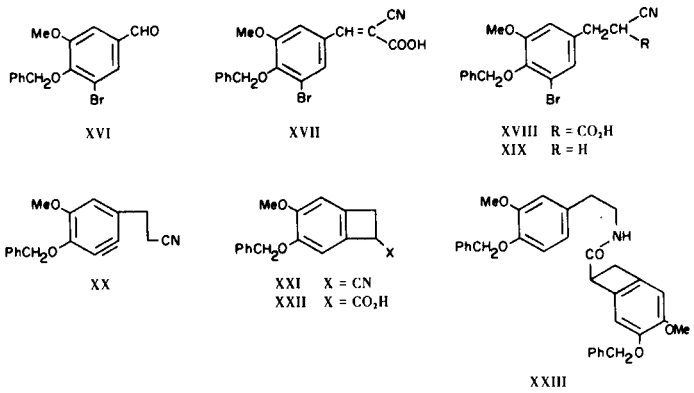

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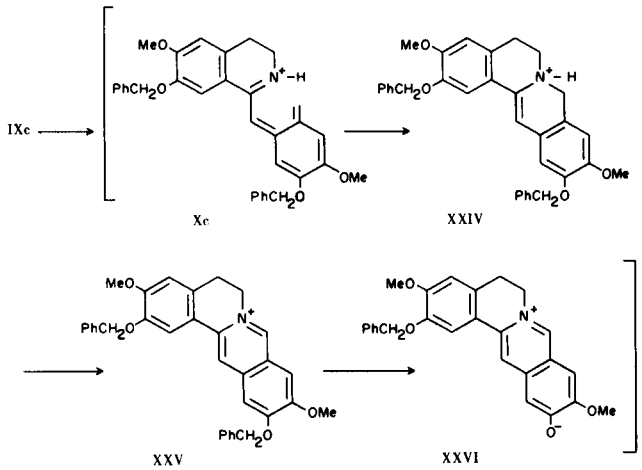
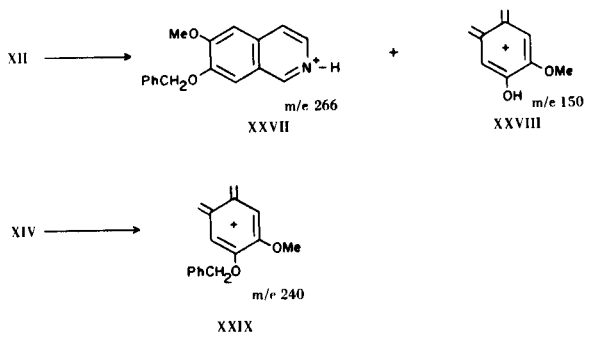


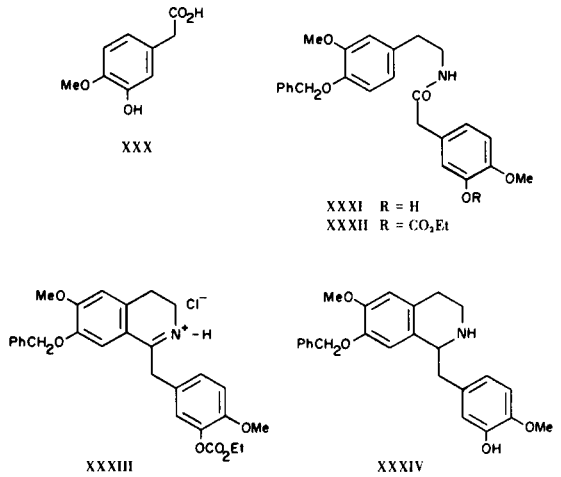
SCHEME 5



reaction to afford the starting 1-benzocyclobutenyl-3,4-dihydroisoquinoline hydrochloride (IXc).

Thermolysis of the dibenzyloxy-substituted benzocyclobutene IXc followed by sodium borohydride reduction afforded the monophenolic tetrahydroprotoberberine XII. The location of the phenolic function in ring D of XII, indicated by its mass spectrum-fragment ions m/e 266 (XXVII) and m/e 150 (XXVIII) but not m/e 240 (XXIX) that would be expected from the isomer XIV (Scheme 5),

SCHEME 6



was confirmed by an unequivocal synthesis of XII as well as by the acid-catalyzed debenzylation of XII to afford (±)-coreximine (XIII), identical in ir with authentic coreximine (10).

This novel mono-*O*-debenzylation that occurs on thermolytic cyclization of IXc could arise (Scheme 4) from the protoberberine XXVI (6) by dehydrogenation of the unstable dihydroprotoberberine XXIV (9) which would be formed from the *o*-quinodimethane intermediate Xc.

An alternative synthesis of the mono-phenolic tetrahydroprotoberberine XII was carried out by standard methods. Fusion of homoisovanillic acid (XXX) with 4-benzyloxy-3-methoxyphenethylamine gave the amide XXXI which was cyclized with phosphoryl chloride after protection of the phenolic hydroxyl group by ethoxycarbonylation to afford the 3,4-dihydroisoquinoline XXXIII. Sodium borohydride reduction of XXXIII gave the 1,2,3,4-tetrahydroisoquinoline XXXIV which was subjected to the Mannich reaction with formalin and acetic acid to yield the phenolic tetrahydroprotoberberine XII, identical in all aspects with XII obtained from IXc.

It would appear that this novel extension of the Oppolzer reaction involving *O*-debenzylation could be applied to the synthesis of 9- and 11-hydroxyprotoberberines.

EXPERIMENTAL

Nmr spectra were measured with a Hitachi H-60 spectrometer with TMS as an internal standard. Ir spectra were taken with a type Hitachi 215 grating spectrometer, uv spectra with a Hitachi recording spectrophotometer (EPS-3), and mass spectra on a Hitachi RMU-7 spectrometer.

4-Benzyloxy-3-bromo-5-methoxy-α-cyanocinnamic Acid (XVII).

A mixture of 32.1 g. of 4-benzyloxy-3-bromo-5-methoxybenzaldehyde (XVI), 8.7 g. of cyanoacetic acid, 1.0 g. of ammonium

acetate, 100 ml. of dry benzene, and 22 ml. of pyridine was heated under reflux using a Stark-Dean apparatus. After a calculated amount of water (1.8 ml.) had separated, the mixture was cooled and the crystals which separated were collected to give a pale yellow solid as the pyridinium salt of XVII; ir ν max (potassium bromide): 2200 (CN), 1700 (C=O) and 1630 cm^{-1} (C=C). After acidification of the above pyridinium salt with 10% hydrochloric acid followed by a usual work-up, recrystallization from benzene afforded 29 g. of the acid XVII as pale yellow needles, m.p. 196-198°; ir ν max (potassium bromide): 2200 (CN) and 1680 cm^{-1} (C=O); nmr δ (deuteriodimethylsulfoxide): 3.89 (3H, s, OCH_3), 5.10 (2H, s, $PhCH_2O$), 7.39 (5H, s, $C_6H_5CH_2O$), 7.76 (1H, d, J = 2.5 Hz, 6-*H*), 7.87 (1H, d, J = 2.5 Hz, 2-*H*), 8.21 (1H, s, Ar*CH*=C).

Anal. Calcd. for $C_{18}H_{14}BrNO_4$: C, 55.72; H, 3.64; N, 3.61. Found: C, 55.71; H, 3.74; N, 3.36.

β-(4-Benzyloxy-3-bromo-5-methoxyphenyl)-α-cyanopropionic Acid (XVIII).

To a solution of 21 g. of the above acid XVII in 300 ml. of ethanol, 10.5 g. of sodium borohydride was added in small portions with stirring at room temperature. After addition, the stirring was continued for 0.5 hour. The mixture was then acidified with 10% hydrochloric acid and the precipitate was extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to give 20 g. of the cyanopropionic acid XVIII as a colorless powder, m.p. 100-101° (from benzene-hexane); ir ν max (chloroform): 2250 (CN) and 1735 cm^{-1} (C=O); nmr δ (deuteriochloroform): 2.89-3.20 (2H, m, $ArCH_2$), 3.82 (3H, s, OCH_3), 5.00 (2H, s, $PhCH_2O$), 6.80 (1H, d, J = 2 Hz, 6-*H*), 7.05 (1H, d, J = 2 Hz, 2-*H*), 7.39 (5H, s, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{18}H_{16}BrNO_4$: C, 55.43; H, 4.14; N, 3.59. Found: C, 55.35; H, 4.20; N, 3.56.

4-Benzyloxy-3-bromo-5-methoxyhydrocinnamonitrile (XIX).

A solution of 7 g. of the acid XVIII in 14 ml. of dimethylacetamide was heated at 170° and an evolution of the calculated amount of carbon dioxide ceased after 0.5 hour. The mixture was poured into water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, evaporated and recrystallized from ether-hexane to give 5.5 g. of the nitrile XIX as colorless needles, m.p. 51-52°, ir ν max (chloroform); 2250 cm^{-1} (C=N); nmr δ (deuteriochloroform): 2.50-2.78 (4H, m, CH_2CH_2), 3.78 (3H, s, OCH_3), 4.96 (2H, s, $PhCH_2O$), 6.67 (1H, d, J = 2.0 Hz, 6-H), 6.92 (1H, d, J = 2.0 Hz, 2-*H*), 7.25-7.65 (5H, m, $C_6H_5CH_2O$).

Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.04. Found: C, 58.80; H, 4.75; N, 3.99.

5-Benzyloxy-1-cyano-4-methoxybenzocyclobutene (XXI).

To a suspension of sodium amide, prepared from 300 ml. of liquid ammonia and 1.9 g. of sodium, 6.6 g. of the nitrile XIX was added in portions and the mixture was stirred at room temperature for 3 hours. After evaporation of ammonia an excess of ammonium chloride and 300 ml. of water were added in portions, and the mixture was extracted with chloroform. The usual work-up of the extract gave 6.0 g. of a gum, which was chromatographed on 150 g. of silica gel with chloroform. Fractions 2-7 (each 300 ml.) gave the benzocyclobutene compound XXI. Recrystallization from ethanol gave 2.4 g. of XXI as colorless prisms, m.p. 90-92°; ir ν max (chloroform): 2230 cm^{-1} (CN); nmr δ (deuteriochloroform): 3.48 (2H, d, J = 4 Hz, CH_2), 3.83 (3H, s, OCH_3), 4.09 (1H, t, J = 4 Hz, C*H*), 5.09 (2H, s, $PhCH_2O$), 6.70 (1H, s, 3-*H*), 6.77 (1H, s, 6-*H*), 7.36 (5H, s, $C_6H_5CH_2O$).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.57; H, 5.91; N, 4.86.

5-Benzyloxy-4-methoxybenzocyclobutene-1-carboxylic Acid (XXII).

A solution of 1 g. of the nitrile XXI in 5 ml. of saturated ethanolic potassium hydroxide was kept at room temperature overnight and the mixture was then refluxed with 2 ml. of water for 3 hours. After the mixture had been poured into 50 ml. of water, the resulting alkaline layer was washed with ether, acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried over sodium sulfate, evaporated and recrystallized from benzene to give 1 g. of the carboxylic acid XXII as a colorless powder, m.p. 133-134°; ir ν max (chloroform): 1700 cm^{-1} (C=O); δ (deuteriochloroform): 3.34 (2H, d, J = 4 Hz, CH_2), 3.80 (3H, s, OCH_3), 4.15 (1H, t, J = 4 Hz, C*H*), 5.03 (2H, s, $PhCH_2O$) 6.68 (1H, s, 3-*H*), 6.75 (1H, s, 6-*H*), 7.31 (5H, s, $C_6H_5CH_2O$), 9.84 (1H, broad s, COO*H*).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67; Found: C, 71.66; H, 5.70.

N-(4-Benzyloxy-3-methoxyphenethyl)-5-benzyloxy-4-methoxybenzocyclobutene-1-carboxamide (XXIII).

To a solution of 1.1 g. of the acid XXII and 0.9 g. of the dicyclohexylcarbodiimide in 15 ml. of methylene chloride was added 1 g. of 4-benzyloxy-3-methoxyphenethylamine at room temperature with stirring and the mixture was stirred for 2 hours. After removal of an insoluble material, the filtrate was diluted with 20 ml. of methylene chloride. The organic layer was separated, washed with 5% hydrochloric acid, 5% sodium hydrogen carbonate and water, and dried over sodium sulfate. After evaporation of the solvent, recrystallization from ethanol gave 1.6 g. of the amide XXIII as colorless needles, m.p. 117-119°; ir ν max (chloroform): 3430 (NH) and 1660 cm^{-1} (C=O); nmr δ (deuteriochloroform): 2.67 (2H, t, J = 7 Hz, $ArCH_2CH_2N$), 2.92, 3.14 (1H, a pair of d, J = 13 and 3 Hz, CH_2), 3.39 (2H, t, J = 7 Hz, $ArCHCH_2N$), 3.83 (6H, s, 2 x OCH_3), 3.94, 4.03 (1H, a pair of d, J = 5 and 3 Hz, C*H*), 5.04 (4H, s, 2 x $PhCH_2O$), 6.45-6.95 (5H, m, Ar*H*), 7.34 (10H, s, 2 x C_6H_5-).

Anal. Calcd. for $C_{33}H_{33}NO_5$: C, 75.69; H, 6.35; N, 2.68. Found: C, 75.92; H, 6.26; N, 2.64.

7-Benzyloxy-1-(5-benzyloxy-4-methoxybenzocyclobutenyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride (IXc).

A mixture of 520 mg. of the amide XXIII, 400 mg. of phosphoryl chloride and 20 ml. of dry benzene was refluxed for 2 hours. After addition of an excess of hexane to the above mixture, yellow crystals separated on cooling. Recrystallization from ethanol gave 400 mg. of the 3,4-dihydroisoquinoline hydrochloride IXc as yellow hygroscopic needles, m.p. 108-110°; ir ν max (potassium bromide): 1635 cm^{-1} (C=N).

Anal. Calcd. for $C_{33}H_{32}ClNO_4.1.5H_2O$: C, 69.64; H, 6.20; N, 2.46. Found: C, 69.42; H, 6.61; N, 2.19.

2-Benzyloxy-7,8,13,13a-tetrahydro-11-hydroxy-3,10-dimethoxy-8H-dibenzo[*a*,*g*]quinolizine (XII).

a. Thermolysis:

Heating of 300 mg. of the above 3,4-dihydroisoquinoline hydrochloride IXc at 150-160° in a current of nitrogen for 18 minutes gave a brown caramel, λ max (methanol) 235 sh, 282 sh, 292, 318 and 379 nm, which was dissolved in 30 ml. of methanol. To the preceding solution was added 300 mg. of sodium borohydride in small portions with stirring at room temperature, and then the stirring was continued for 0.5 hour. The mixture was refluxed and evaporated under reduced pressure to leave a residue, which was

digested with 20 ml. of water, and an excess of ammonium chloride was added to this solution. After extraction with chloroform, the extract was washed with water, dried over sodium sulfate and evaporated to give 200 mg. of a pale yellow syrup, which was purified by column chromatography on 5 g. of silica gel. Elution with chloroform-methanol (99:1 v/v) gave the 7,8,13,13a-tetrahydro-11-hydroxyprotoberberine XII, which was recrystallized from ethanol to give 100 mg. of XII as colorless prisms, m.p. 174-175°; ir ν max (chloroform): 3550 cm^{-1} (OH); nmr δ (deuteriochloroform): 2.38-3.55 (8H, m, 4 x CH_2), 3.84 (6H, s, 2 x OCH_3), 5.12 (2H, s, $PhCH_2O$), 6.52, 6.63, 6.65, 6.74 (4H, s, Ar*H*), 7.39 (5H, s, $C_6H_5CH_2O$); m/e 417 (M^+), 266, 176, and 150.

Anal. Calcd. for $C_{26}H_{27}NO_4.0.5H_2O$: C, 73.22; H, 6.62; N, 3.28. Found: C, 73.65; H, 6.41; N, 3.06.

b. Mannich Reaction

A mixture of 150 mg. of the tetrahydroisoquinoline XXXIV, 2 ml. of acetic acid and 2 ml. of 37% formalin was refluxed for 3 hours. The reaction mixture was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give a pale yellow syrup, which was purified by column chromatography on 5 g. of silica gel. Elution with chloroform-methanol (99:1 v/v) gave a pale yellow solid, which was recrystallized from ethanol to give 100 mg. of XII as colorless prisms, m.p. 174-175°, identical with the product by a thermolysis of the benzocyclobutene (IXc).

(±)-Coreximine (XIII).

A mixture of 50 mg. of the above tetrahydroprotoberberine XII, 3 ml. of concentrated hydrochloric acid and 3 ml. of ethanol was refluxed for 3 hours, and the excess of hydrochloric acid and ethanol was distilled off. The residue was recrystallized from methanol to give 20 mg. of (±)-coreximine (XIII) hydrochloride as colorless prisms, m.p. 265-266° [lit. (11), m.p. 245-246°], which was identical with the authentic sample in ir spectral comparison.

N-(4-Benzyloxy-3-methoxyphenethyl)-3-hydroxy-4-methoxyphenylacetamide (XXXI).

A mixture of 2.57 g. of 4-benzyloxy-3-methoxyphenethylamine and 1.82 g. of 3-hydroxy-4-methoxyphenylacetic acid was heated in an oil bath at 170-180° for 1 hour, and the cooled mixture was then dissolved in chloroform. The chloroform layer was washed with 10% hydrochloric acid solution, water, 5% ammonia, and water, dried over sodium sulfate and evaporated to give 3.4 g. of the phenolic amide as colorless plates, m.p. 104-106° (from isopropyl ether); ir ν max (chloroform); 3500 (OH), 3420 (NH) and 1650 cm^{-1} (C=O); nmr δ (deuteriochloroform): 2.60 (2H, t, J = 6.8 Hz, $ArCH_2CH_2NH$), 3.15-3.55 (4H, $ArCH_2CH_2NH$ and $ArCH_2CO$), 3.77 (6H, s, 2 x OCH_3), 5.03 (2H, s, $PhCH_2O$), 5.59 (1H, broad, N*H*), 6.30-6.80 (6H, m, Ar*H*), 7.31 (5H, s, $C_6H_5CH_2O$).

Anal. Calcd. for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.58; H, 6.51; N, 3.56.

N-(4-Benzyloxy-3-methoxyphenethyl)-3-ethoxycarbonyloxy-4-methoxyphenylacetamide (XXXII).

To a solution of 1.2 g. of the phenolic amide XXXI and 0.36 g. g. of triethylamine in 30 ml. of benzene, 0.3 g. of ethyl chloroformate was added drop by drop with stirring at room temperature. After stirring for 2 hours, the benzene layer was washed with water, dried over sodium sulfate and evaporated to afford 1.3 g. of the non-phenolic amide which was chromatographed on silica gel to give a syrup; ir ν max (chloroform): 3450 (NH), 1760 (C=O) and 1660 (C=O); nmr δ (deuteriochloroform): 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 2.64 (2H, t, J = 6.8 Hz, $ArCH_2CH_2NH$), 3.20-3.60 (4H, $ArCH_2CH_2NH$ and $ArCH_2CO$), 3.78 (6H, s, 2 x OCH_3), 4.25 (2H, q, J = 7 Hz, OCH_2CH_3), 5.05 (2H, s, $PhCH_2O$), 5.65 (1H, broad, N*H*), 6.35-7.0 (6H, m, Ar*H*), 7.37 (5H, s, $C_6H_5CH_2O$).

Anal. Calcd. for $C_{28}H_{31}NO_7$: C, 68.14; H, 6.33; N, 2.84. Found: C, 68.58; H, 6.36; N, 2.63.

7-Benzyloxy-1-(3-ethoxycarbonyloxy-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride (XXXIII).

A mixture of 500 mg. of the above amide XXXII, 500 mg. of phosphoryl chloride, and 5 ml. of dry benzene was refluxed for 3 hours. The cooled mixture was poured into an excess of *n*-hexane and set aside overnight. The precipitate was recrystallized from methanol-benzene to give 400 mg. of XXXIII as colorless needles, m.p. 125-127°; ir ν max (potassium bromide); 1760 (C=O) and 1640 (C=N) cm^{-1}.

Anal. Calcd. for $C_{28}H_{30}ClNO_6.0.5H_2O$: C, 64.54; H, 6.00; N, 2.69. Found: C, 64.93; H, 6.08; N, 2.26.

7-Benzyloxy-1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6-methoxyisoquinoline (XXXIV).

To a solution of 400 mg. of the dihydroisoquinoline XXXIII in 15 ml. of methanol, 300 mg. of sodium borohydride was added in portions at room temperature with stirring. After stirring for further 30 minutes at room temperature, followed by addition of 0.5 ml. of 10% sodium hydroxide solution, the mixture was refluxed for 2 hours, then cooled, evaporated, and diluted with water. To the resulting mixture an excess of ammonium chloride was added and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give 300 mg. of the tetrahydroisoquinoline derivative XXXIV as colorless needles, m.p. 69-70° (from benzene); ir ν max (chloroform): 3550 cm^{-1} (OH); nmr δ (deuteriochloroform): 3.75, 3.80 (6H, s, 2 x OCH_3), 5.0 (2H, s, $PhCH_2O$), 6.44-6.80 (4H, m, Ar*H*).

Anal. Calcd. for $C_{25}H_{27}NO_4.1.5H_2O$: C, 69.42; H, 6.99; N, 3.24. Found: C, 69.62; H, 6.57; N, 3.09.

Acknowledgement.

We thank Mrs. A. Satoh, Mrs. C. Koyanagi, Miss A. Ujiie, Miss R. Kato, Miss C. Yoshida, and Mr. T. Ohuchi, Pharmaceutical Institute, Tohoku University, for microanalysis and spectral measurements.

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