

A Modified Synthesis of Codamine under Eschweiler-Clarke Conditions (1)

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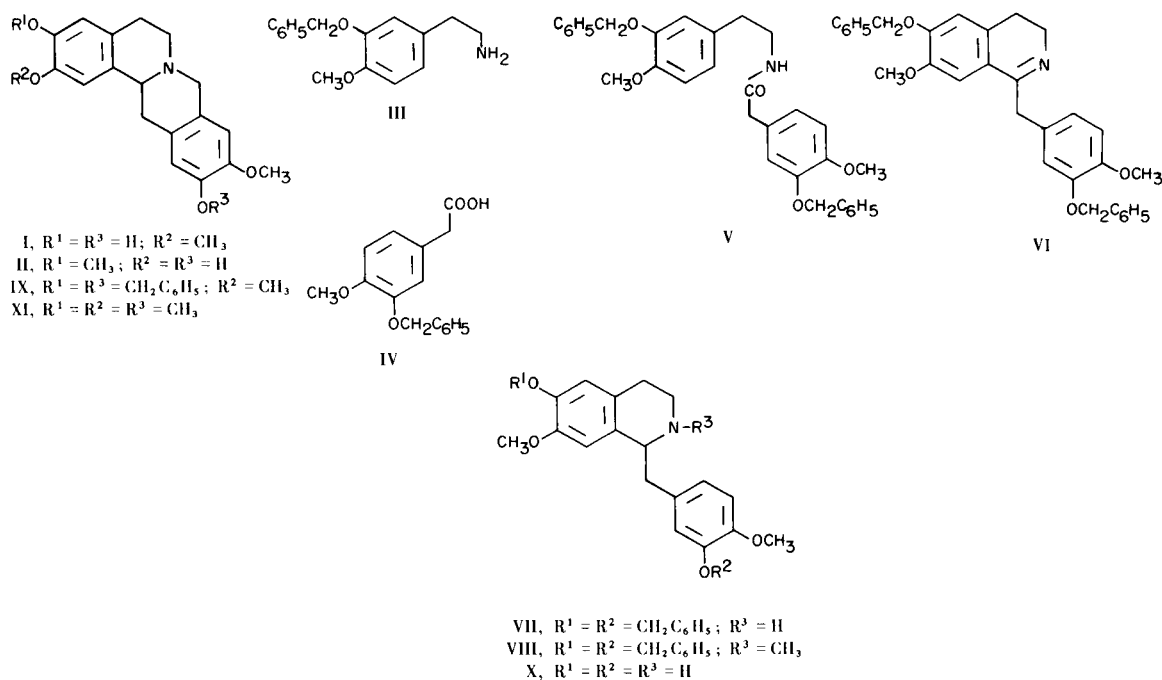
Codamine (1) was obtained in 88.4% yield by Eschweiler-Clarke reaction of X with formalin and formic acid, whereas it formed in 46.2% yield in case of Mannich reaction of X with formalin and hydrochloric acid.

Codamine, an alkaloid isolated from *Corydalis pseudo-adunca* by Yunusov and co-workers (3) in 1965, was assigned to the structure (1) through the classical chemical degradations by the same authors (4) in 1966, whose structure was shown as an isomer of coreximine (II). We here report a synthesis of 3,11-dihydroxy-2,10-dimethoxyprotoberberine (1), namely, codamine (5), by the formation of the so-called "berberine bridge" under Eschweiler-Clarke conditions.

The fusion of 3-benzyloxy-4-methoxyphenethylamine (III) with 3-benzyloxy-4-methoxyphenethylamine (III) with 3-benzyloxy-4-methoxyphenylacetic acid (IV)

at 180° for 2 hours in a current of nitrogen gave the corresponding amide (V), which was subjected to Bischler-Napieralski conditions with phosphoryl chloride in benzene. Reduction of the resultant 3,4-dihydroisoquinoline (VI), which was characterized as its perchlorate, with sodium borohydride in methanol gave 1,2,3,4-tetrahydroisoquinoline (VII).

At first, this tetrahydroisoquinoline (VII) was treated with 37% formalin in 98-100% formic acid at 100° for 5 hours, in order to get the corresponding *N*-methyl derivative (VIII). These conditions corresponded to the



Eschweiler-Clarke reaction. The usual work-up afforded a yellow glass (compound A), which was isolated in 80% yield, m.p. 218-221° dec. The microanalysis verified the molecular formula of $C_{33}H_{33}O_4N$ and the infrared spectrum of the free base showed a characteristic Bohlmann band at 2720-2850 cm^{-1} . An *N*-methyl resonance could not be detected in its nmr spectrum. These data showed the product (A) to be 3,11-dibenzyloxy-2,10-dimethoxyprotoberberine (IX), and this was proved by the synthesis of the same compound (IX) by the usual Mannich reaction. Thus, this protoberberine (IX) was obtained by treatment of tetrahydroisoquinoline (VII) hydrochloride with 37% formalin in ethanol for 45 minutes, in 75% yield.

Secondly, the tetrahydroisoquinoline (VII) was debenzylated with ethanolic hydrochloric acid and the resulting diphenolic base (X) was also treated with 37% formalin in 98-100% formic acid at 100° for 5 hours. The product (B), $C_{19}H_{21}O_4N$, m.p. 237-239° [lit., m.p. 233-234° (5)], obtained in 88.4% yield, showed a typical Bohlmann band in its infrared spectrum and *N*-methyl signal in the nmr spectrum could not be observed. The same compound as (B) was also obtained by heating the diphenolic base (X) hydrochloride with 37% formalin in ethanol for 6 hours or by debenylation of protoberberine (IX) with ethanolic hydrochloric acid, and the methylation of the product (B) with diazomethane gave xylopinine (XI), m.p. 147-148°. These facts showed the product (B) to be 3,11-dihydroxy-2,10-dimethoxyprotoberberine (codamine) (I), but the natural product was not available for direct comparison.

Attempts to obtain the protoberberines (I and IX) by reaction of tetrahydroisoquinolines (X and VII) with sodium hydroxymethanesulfonate, followed by treatment with acid (7), or phenolic cyclization of diphenolic base (X) with 37% formalin (8) were carried out. Unfortunately the expected compounds (I and IX) could not be separated on a preparative scale, but they were observed in its thin layer chromatogram. Regarding this point, further examination is in progress.

Thus, modified syntheses of codamine and xylopinine under Eschweiler-Clarke conditions have been accomplished in good yield.

EXPERIMENTAL

Infrared spectra were measured with a Type EPI-3 Hitachi recording spectrophotometer, and nmr spectra were run on a Hitachi H-60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal reference.

N-(3-Benzyloxy-4-methoxyphenethyl)-3-benzyloxy-4-methoxyphenylacetamide (V).

A mixture of 5.2 g. of 3-benzyloxy-4-methoxyphenethylamine

(III) and 5.4 g. of 3-benzyloxy-4-methoxyphenylacetic acid (IV) was heated at 180° for 2 hours in a current of nitrogen. After the reaction mixture was taken up in 50 ml. of chloroform, the extract was washed with 5% sodium bicarbonates (20 ml. x 2), 10% hydrochloric (20 ml. x 2) and 30 ml. of water and dried over sodium sulfate. The solvent was evaporated to give the amide (V) as a brown solid, which was recrystallized from benzene-hexane to give 8.8 g. of V as colorless needles, m.p. 112-113°; infrared cm^{-1} ν max (chloroform), 3380 (NH), 1655 (C=O).

Anal. Calcd. for $C_{32}H_{33}O_5N$: C, 75.12; H, 6.50; N, 2.74. Found: C, 74.88; H, 6.20; N, 2.70.

6-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-7-methoxyisoquinoline (VI).

A mixture of 8.8 g. of the amide (V), 5.5 ml. of phosphoryl chloride and 80 ml. of dry benzene was refluxed for 2 hours. After cooling, excess hexane was added to the above reaction mixture which was allowed to stand for 12 hours. The upper layer was removed by decantation and the residue was extracted with 100 ml. of chloroform. The extract was washed with water (30 ml. x 2), dried over sodium sulfate and evaporated to leave 9 g. of the hydrochloride of 3,4-dihydroisoquinoline (VI) as a reddish brown gum; infrared cm^{-1} , ν max (chloroform), 2750-2380 ($\cong NH$), 1648 ($>C=NH$). Recrystallization of the perchlorate from ethanol gave colorless needles, m.p. 150-151° (sintered at 146-147°).

Anal. Calcd. for $C_{32}H_{31}O_4N \cdot HClO_4 \cdot \frac{1}{2}H_2O$: C, 63.72; H, 5.51; N, 2.32. Found: C, 63.64; H, 5.73; N, 2.49.

6-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxyisoquinoline (VII).

To a mixture of 8 g. of VI hydrochloride and 150 ml. of methanol was added in small portions with stirring 3 g. of sodium borohydride at 0-5° during 30 minutes, and the mixture was stirred for 30 minutes at room temperature. After refluxing for 30 minutes, the solvent was evaporated and the residue was treated with 150 ml. of water and extracted with chloroform (50 ml. x 3). The extract was washed with 50 ml. of water, dried over sodium sulfate and evaporated to leave 5.9 g. of tetrahydroisoquinoline (VII) as a reddish orange syrup; nmr (τ) (in deuteriochloroform), 6.22, 6.16 (3H, each, singlets, 2 x OCH_3), 4.92 (4H, singlet, 2 x $OCH_2C_6H_5$), 3.40 (2H, singlet, C_5 -H and C_8 -H), 3.20 (3H, broad singlet, C_2' -H, C_5' -H and C_6 -H), 2.62 (10H, broad singlet, 2 x $OCH_2C_6H_5$).

Recrystallization of the hydrochloride from methanol gave colorless needles, m.p. 206-209°, whose m.p. was identical with that of the sample, m.p. 207-210°, reported by Tomita and Kunitomo (5).

3,11-Dibenzyloxy-5,6,13,13a-tetrahydro-2,10-dimethoxy-8H-dibenzo[*a,g*]quinolizine (IX).

(a) The reaction with formalin and formic acid.

A mixture of 550 mg. of tetrahydroisoquinoline (VII), 2 ml. of 37% formalin and 2 ml. of 98-100% formic acid was heated at 100° for 5 hours. The reaction mixture was basified with 5% aqueous sodium bicarbonate solution and extracted with chloroform (30 ml. x 2). The extract was washed with 20 ml. of water, dried over sodium sulfate and evaporated to leave 470 mg. (84.5%) of protoberberine (IX) as a brown glass; infrared cm^{-1} , ν max (chloroform), 2720-2850 (Bohlmann band), nmr (τ) (in deuteriochloroform) 6.21, 6.19 (3H each, singlet, 2 x OCH_3), 4.95 (4H, singlet, 2 x $OCH_2C_6H_5$), 3.25-3.40 (4H, multiplet, C_1 -H, C_4 -H, C_9 -H and C_{12} -H), 2.65 (10H, broad singlets, 2 x $OCH_2C_6H_5$).

Recrystallization of the hydrochloride from ethanol afforded colorless needles, m.p. 218-221° dec.

Anal. Calcd. for $C_{33}H_{33}O_4N \cdot HCl$: C, 72.85; H, 6.24; N, 2.55. Found: C, 72.66; H, 6.22; N, 2.45.

(b) The reaction with formalin and hydrochloric acid.

A mixture of the hydrochloride of (VII) [prepared from 500 mg. of free tetrahydroisoquinoline by the usual method] and 4 ml. of 37% formalin, and 10 ml. of ethanol was refluxed for 45 minutes. After removal of the solvent, the residue was suspended in 30 ml. of water and basified with 10% ammonium hydroxide. The oil separated and was extracted with chloroform (20 ml. x 3). The extract was washed with 30 ml. of water, dried over sodium sulfate and evaporated to leave 400 mg. (78.9%) of a brown glass, whose hydrochloride, after several recrystallizations from ethanol, showed m.p. 218-221° dec.

1,2,3,4-Tetrahydro-6-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7-methoxyisoquinoline (X).

A mixture of 2 g. of dibenzyl ether (VII), 20 ml. of concentrated hydrochloric acid and 20 ml. of ethanol was refluxed for 16 hours and the excess of hydrochloric acid and ethanol was removed by distillation. The residue was washed with ether (30 ml. x 2) and dissolved in 20 ml. of ethanol and 20 ml. of benzene. The solvents were removed by distillation to leave 1.2 g. of diphenolic base (X) as a brown caramel, whose hydrochloride was recrystallized from water to give colorless needles, m.p. 151-153° (sintered at 143-146°) [lit., m.p. 152-153° (5)].

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

(a) The reaction with formalin and formic acid.

A mixture of diphenolic base [prepared from 500 mg. of the hydrochloride of (X)], 5 ml. of 37% formalin and 5 ml. of 98-100% formic acid was heated at 100° for 5 hours. The reaction mixture was basified with 5% aqueous sodium bicarbonate solution and extracted with chloroform (50 ml. x 2). The extract was washed with 30 ml. of water, dried over sodium sulfate and evaporated to give a grey powder, which was recrystallized from ethanol to afford 410 mg. (88.4%) of protoberberine (I) as pale yellow prisms, m.p. 237-239°; infrared cm^{-1} , ν max (chloroform), 2740-2830 (Bohlmann band), 3480 (OH), nmr (τ) (in deuteriochloroform), 6.50-7.51 (8H, methylene protons), 6.30 (1H, triplet, $J = 6.0$ cps, C_{13a} -H), 6.15, 6.10 (3H each, singlets, 2 x OCN_3), 4.60-5.40 (4H, 2 x OH and H_2O ; exchanged with D_2O), 3.40 (1H, singlet, aromatic proton), 3.30 (1H, singlet, aromatic proton), 3.23 (2H, singlet, two aromatic protons).

Anal. Calcd. for $C_{19}H_{21}O_4N \cdot H_2O$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.46; H, 6.89; N, 4.07.

(b) The reaction with formalin and hydrochloric acid.

A mixture of 350 mg. of the hydrochloride of diphenolic base (X), 2 ml. of 37% formalin and 5 ml. of ethanol was refluxed for 6 hours, and, after the reaction, the solvent was evaporated. The residue was basified with 10% ammonia and extracted with chloroform (15 ml. x 3). The extract was washed with water

(15 ml. x 3), dried over sodium sulfate and evaporated to leave a brown gum, which was triturated with ether to give 150 mg. (46.2%) of a yellowish brown solid. Recrystallization from ethanol gave protoberberine (I) as yellow prisms, m.p. 237-239°, whose infrared spectrum was superimposable on that of the sample prepared by method (a).

(c) Debenzylation of (IX).

A mixture of 500 mg. of protoberberine (IX), 10 ml. of concentrated hydrochloric acid and 15 ml. of ethanol was refluxed for 5.5 hours, and the excess of hydrochloric acid and ethanol was distilled off. The residue was washed with ether (20 ml. x 2) and dissolved in 50 ml. of chloroform. The extract was washed with 10% ammonium hydroxide (30 ml. x 3) and water (30 ml. x 2) and dried over sodium sulfate. The solvent was distilled off to leave a yellowish brown solid, which was recrystallized from ethanol to give I as pale yellow prisms, m.p. 237-239°. This specimen was also identical with the above sample.

Xylopinine (XI).

To a solution of 80 mg. of the preceding protoberberine (I) in 30 ml. of methanol was added a solution of diazomethane in 150 ml. of ether (prepared from 5 g. of *p*-toluenesulfonylmethylnitrosamide) and the mixture was allowed to stand for 2 days at room temperature. The usual work up gave xylopinine (XI) as colorless needles, m.p. 147-148°, after recrystallization from ether-hexane, whose infrared spectrum was superimposable with that of an authentic sample (6).

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