SYNTHESIS OF STEBISIMINE, (±)-OBABERINE, AND (±)-ISOTETRANDRINE BY WILLGERODT–KINDLER CYCLOBISCONDENSATION. II.

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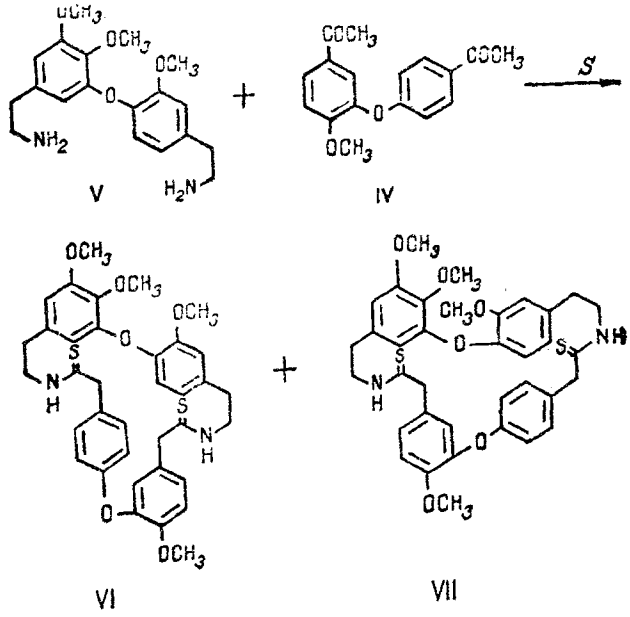
A synthesis of stebisimine, (±)-obaberine, and (±)-isotetrandrine has been performed by the cyclocondensation of 5-acetyl-2-methoxyphenyl 4'-acetylphenyl ether and 5-(β-aminoethyl)-2,3-dimethoxyphenyl 4'-(β-aminoethyl)-2'-methoxyphenyl ether and sulfur through the stage of formation of the corresponding biscyclophenylthioacetamides which, by Bischler–Napieralski cyclization and reduction of the corresponding bismethiodides, have been converted into the desired compounds.

We have previously described the synthesis of stebisimine (I), (±)-obaberine [(±)-O-methyloxyacanthine] (II), and (±)-isotetrandrine (III) by the double cyclocondensation of an enamino sulfide with a diamine to form a mixture of cyclobisamides the Bischler–Napieralski cyclization of one of which led to compound (I). The subsequent N-methylation of the bisdihydroisoquinoline bases and reduction yielded (II) and (III) [1]. In the present paper we consider the synthesis of these alkaloids by a scheme the key reaction of which is the double Willigerodt–Kindler cyclocondensation of 5-methyl-2-methoxyphenyl 4'-acetylphenyl ether (IV) with 5-(β-aminoethyl)-2,3-dimethoxyphenyl 4'-(β-aminoethyl)-2'-methoxyphenyl ether (V). We have already used this reaction to obtain simple 1-benzylisoquinoline derivatives [2-5] and (±)-O-methyldauricine [6, 7]. However, it has not been used previously to obtain cyclobisthioamides. The initial bisamide (V) was obtained by a known method [8] in which the first stage of the Ullmann condensation of the unprotected aldehyde components – 5-bromoveratraldehyde and O-acetylvanillin – was modified [9]. Compound (V) was synthesized by a method described in [10].



Scheme 1

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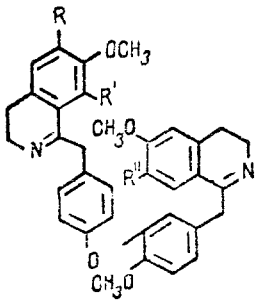
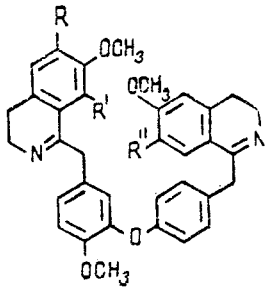


I. R=OCH$_3$, R'+R"=–O–
VIII. R'=OCH$_3$, R+R"=–O–



IX. R=OCH$_3$, R'+R"=–O–
X. R'=OCH$_3$, R+R"=–O–

Scheme 1 (continued)

The reaction of (IV), (V), and sulfur taken in a ratio of 1:1.1:2.2 was performed at 150-170°C. The resulting mixture of cyclobisthioamides was separated chromatographically. This led to the isolation of the isomeric compounds (VI) in two crystalline forms, (VIa) and (VIb), and also of (VII). Compounds (VIa) and (VIb) apparently differed by the configuration at the thioamide bond. Subsequent cyclization was performed under the conditions of the Bischler–Napieralski reaction as in the case of the corresponding bisamides [1]. As a result, stebisimine (I) was obtained from the thioamides (VIa) and (VIb), together with a base (VIII) isomeric with it, and the corresponding bisdihydroisoquinoline bases (IX) and (X) from the bisthioamide (VIII). Compounds (VIII) and (X) have unnatural structures and were not used in the subsequent synthesis. Stebisimine (I) and its structural isomer (X), after N-methylation and reduction with sodium tetrahydroborate were converted into (±)-obaberine (II) and (±)-isotetrandrine (III), respectively. The latter proved to be identical with the natural alkaloids (±)-obaberine and (±)-isotetrandrine.

EXPERIMENTAL

The IR spectra of the compounds were taken on a Pye–Unicam SP-200G instrument; and NMR spectra, on a Varian JHA-100D instrument (0 — TMS). Melting points were determined in a Kofler apparatus without correction. Elementary analyses were determined on a Hewlett–Packard model 185B CHN analyzer. The purity of the compounds obtained was checked by chromatography in a thin layer of alumina (activity grade II), and also on Merck silica gel.

4-Methoxy-N,N'-[3',4"',5"'-trimethoxy-3"',4'-oxybis(phenylethyl)]-3,4"- oxybis(phenylthioacetamide) (VI) and 4-Methoxy-N,N'-(3"',4',5'-trimethoxy-3',4"'-oxybis(phenylethyl)]-3,4" oxybis(phenylthioacetamide) (VII). A mixture of 0.7 g of the bisamine (V), 0.6 g of 5-acetyl-2-methoxyphenyl 4'-acetylphenyl ether (IV), and 0.3 g of sulfur was heated at 150-170°C for 3.5-4 h. During the first 15-20 min a vigorous evolution of hydrogen sulfide took place. After the reaction mixture had been cooled, a solid product was obtained which was separated on a column of alumina (about 60 g). The fractions eluted with petroleum ether–benzene (2:1 and 1:1 total, about 500 ml), after the solvent had been distilled off and the residue had been recrystallized from hexane, yielded the cyclobisthioamide (VIa), $C_{36}H_{38}N_2O_6S_2$, in the form of yellow plates with mp 40-41°C, R_f 0.91 ($CHCl_3$–methanol (10:0.1) system). ν_{max} ($CHCl_3$): 1522, 1475, 1340 cm^{-1}. Yield of 0.27 g (20%).

NMR spectrum ($CDCl_3$), δ, ppm: 2.90 (m, NCH_2); 3.78 and 3.81 (OCH_3); 3.55-4.10; 6.70-7.15; 788-8.01.

Fractions eluted by benzene and by benzene–chloroform (9:1, 7:3, and 1:1, total about 700 ml), after the solvent had been distilled off *in vacuo* and the residue had been crystallized from petroleum ether, yielded another form of the cyclobisthioamide (VIb) as a microcrystalline substance with a beige tinge, $C_{36}H_{38}N_2O_6S_2$, mp 72-74°C. R_f 0.71 ($CHCl_3$–methanol (10:0.1) system). Yield 0.32 g (23.6%). ν_{max} ($CHCl_3$): 1520, 1470, 1360, 1335 cm^{-1}. NMR spectrum ($CHCl_3$), δ, ppm: 2.78 (m, NCH_2); 3.82 and 3.77 (OCH_3); 6.55-7.20; 7.80-8.00 ppm.

The fractions eluted by C_6H_6–$CHCl_3$ (3:7), by chloroform and by chloroform–ethanol (1:1; total about 700 ml), after the solvent had been distilled off and the residue had been recrystallized from hexane, yielded pale yellow crystals, $C_{36}H_{38}N_2O_6S_2$, mp 97-99°C. R_f 0.64 ($CHCl_3$–methanol (10:0.1) system). The yield of the cyclobisthioamide (VII) was 0.60 g (44.0%).

ν_{max} ($CHCl_3$): 1523, 1450, 1360 cm^{-1}. NMR spectrum ($CDCl_3$), δ, ppm: 2.73 (NCH_2); 3.72 (OCH_3); 3.30-4.04; 6.35-7.60.

The total yield of the cyclobisthioamides (VIa, b) and (VII) was 87.7%.

Stebisimine (I). A solution of 0.28 g of the cyclobisthioamide (VIa) in 50 ml of dry chloroform was heated at 70-75°C with 3 ml of phosphorus oxychloride under reflux for 7 h. The reaction mixture was evaporated *in vacuo* and the residue was trituated with ether and was dissolved in a small amount of water, the solution was neutralized with 10% ammonium hydroxide (pH 11), and the case that separated out was extracted repeatedly with ether (about 700 ml). The extract was dried with sodium sulfate, the solvent was distilled off, and the residue was recrystallized from ether—hexane. Colorless crystalline substance with mp 104.5-106°C, R_f 0.87 ($CHCl_3$—methanol (10:1) system), R_f 0.60 ($CHCl_3$—acetone—methanol (5:4:1) system. The compound showed no differences in its IR and NMR spectra or in its chromatographic mobility from a sample of the authentic alkaloid stebisimine.

From the alkaline aqueous solution after ether extraction, re-extraction with chloroform as in [1] led to the isolation of the isomeric bisdihydroisoquinoline with the structure (VIII). mp 207-211°C (from isopropanol). R_f 0.73 ($CHCl_3$—methanol (10:1) system). Yield 0.10 g (40.7%). ν_{max} ($CHCl_3$): 1615 cm^{-1}.

Similar results were obtained on the cyclization of the bisthioamide (VIb).

Stebisimine Dimethiodide. This was obtained as described in [1]. mp 128-130°C (decomp.). Yield 84.5%.

(±)-Obaberine (II). A solution of 0.10 g of stebisimine dimethiodide in 30 ml of methanol and 3 ml of chloroform was reduced at 0°C with the aid of 0.3 g of sodium tetrahydroborate for 50 min, and then at 20°C (2 h). The solvents were distilled off *in vacuo*, the residue was dissolved in water, the solution was extracted with chloroform, and the organic layer was dried with sodium sulfate and distilled *in vacuo*. The residue — a vitreous mass — crystallized on trituration with ether (mp 166.5-169°C). It was dissolved in acetone, and an acetone solution of picric acid was added, to give a picrate with mp 177.5-180°C (decomp.). This was converted into the base, which was recrystallized from a mixture of acetone and ether. Colorless crystalline substance with mp 189-190.5°C. Yield 0.03 g (41.6%). R_f 0.66 ($CHCl_3$—methanol (10:1) system). In relation to its IR and NMR spectra and chromatographic mobility, the compound was identical with an authentic sample of natural (±)-obaberine. A mixture of synthetic and natural samples gave no depression of the melting point.

3,3",4,4"-Tetrahydro-6,6",7"-trimethoxy-1,1"-[4"'-methoxy-3"',4'-oxy(bisbenzyl)]-7,8"-oxybisisoquinoline (IX) and 3,3",4,4"-Tetrahydro-6,7",8"-trimethoxy-1,1"'-[4"'-methoxy-3"', 4'-oxy(bisbenzyl)]-6",7-oxybisisoquinoline (X). The cyclobisthioamide (VII) (0.1 g) was dissolved in 30 ml of dry chloroform and 2.5 ml of phosphorus oxychloride and was then cyclized as described for stebisimine. A mixture of two bisdihydroisoquinolines was obtained, which was separated on a column of silica gel (about 10 g). The fractions eluted by chloroform—methanol (98:2-95:5; about 300 ml), after the solvent had been distilled off and the residue had been triturated with ether, yielded (IX), $C_{36}H_{34}N_2O_6 \cdot 1.5H_2O$. mp 154-155°C (acetone—hexane). R_f 0.85 ($CHCl_3$—methanol (5:2) system). Yield 0.036 g (38.8%). ν_{max} ($CHCl_3$): 1615 cm^{-1}. NMR spectrum ($CDCl_3$), δ, ppm: 3.60, 3.68, 3.72, 3.76 (4 × OCH_3); 6.50-7.40.

The bisdihydroisoquinoline (X) was obtained similarly from the fractions eluted by chloroform—methanol (95:5-1:1; about 300 ml). Crystalline substance with a brownish tinge, mp 167-169°C (from $CHCl_3$—hexane). R_f 0.71 ($CHCl_3$—methanol (5:2) system). Yield 0.039 g (42.2%). ν_{max} ($CHCl_3$); 1615 cm^{-1}. Dimethiodide was obtained in a similar manner to stebisimine dimethiodide. Yellow crystals with mp 138-140.5°C. Yield 95.5%. ν_{max} (KBr): 1615 cm^{-1}.

(±)-Isotetrandrine (III). This was obtained by reducing the dimethiodide of the bisdihydroisoquinoline derivative (IX) with sodium tetrahydroborate in a similar way to compound (II). mp 165-168°C. Picrate with mp 256-258°C. Yield 52.5%. The compound had IR and NMR spectra identical with those of natural (±)-isotetrandrine, and also the same chromatographic mobility as the alkaloid. A mixture with a sample of the natural alkaloid gave no depression of the melting point.

SUMMARY

A new synthesis of stebisimine, (±)-obaberine, and (±)-isotetrandrine has been effected by a scheme the key stage of which is the double Willgerodt—Kindler cyclobiscondensation of 5-

acetyl-2-methoxyphenyl 4'-acetylphenyl ether with 5-(β-aminoethyl)-2,3-dimethoxyphenyl 4'-(β-aminoethyl)-2'-methoxyphenyl ether.

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CORUMDEPHINE — A NEW ALKALOID FROM *Delphinium corumbosum*

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The epigeal part of *Delphinium corumbosum* Rgl., collected in the flowering phase in the environs of Pokatilovka (Dzhungarian Ala-Tau) has yielded — in addition to the known alkaloids methyllycaconitine, lycoctonine, delcorine, deoxydelcorine, delcoridine, dehydrodelcorine, dephatine, browniine, dictysine, and dictysine acetonide — a new diterpene alkaloid with the composition $C_{25}H_{39}NO_6$ (I), which has been called corumdephine. The structure of corumdephine has been established on the basis of a passage from (I) to deoxydelcorine and spectral characteristics.

We have studied the epigeal part of *Delphinium corumbosum* Rgl. collected in the flowering phase in the environs of the village of Pokaitilovka (Dzhungarian Ala-Tau). The alkaloids methyllycaconitine, delcorine, and deoxydelcorine have been isolated previously from the epigeal part of this plant collected in the budding period in the upper reaches of the R. Baskan (Dzhungarian Ala-Tau) [1]. Chloroform extraction yielded 0.56% of combined alkaloids, from which methyllycaconitine, delcorine, deoxydelcorine, lycoctonine [2], delphatine [3], browniine [4], dictysine and dictysine acetonide [5], delcorine [6], dehydrodelcorine [7], and a new base $C_{25}H_{39}NO_6$ (I), which has been called corumdephine, were isolated.

The IR spectrum of (I) showed absorption bands at 3500 cm^{-1} (hydroxy group) and 1100 cm^{-1} (ether C–O bonds). In the PMR spectrum there were the signals of a N–CH_2CH_3 group (1.00 ppm, triplet with J = 7 Hz, 3 H), of three methoxy groups (3.14, 3.18, and 3.39 ppm, singlets, 3 H each), and of a methylenedioxy group (4.80 and 4.90 ppm, singlets, 1 H each). The mass spectrum of (I) contained the peaks of ions with m/z 449 (M^+), 434, 419, 418 (100%).

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