A NEW SYNTHESIS OF STEBISIMINE, (±)-OBABERINE, AND (±)-ISOTETRANDRINE FROM ENAMINO SULFIDES. I.

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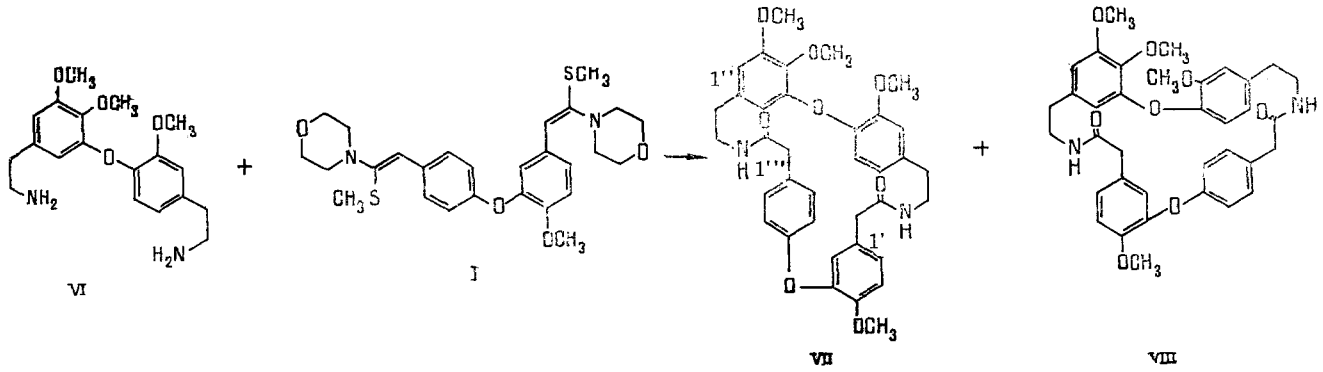
The synthesis of stebisimine, (±)-obaberine, and (±)-isotetrandrine has been effected by the cyclocondensation of 5-acetyl-2-methoxyphenyl 4'-acetylphenyl ether with 5-(β-aminoethyl)-2,3-dimethoxyphenyl 4'-(β-aminoethyl)-2'-methoxyphenyl ether and sulfur through the stage of obtaining the corresponding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

Reactions based on highly reactive sulfur-containing compounds are not only of theoretical but also of practical interest. The chemistry of sulfur compounds has been the subject of numerous publications in recent years. In particular, they have been used repeatedly in the synthesis of natural compounds, including alkaloids, as protective groupings, etc. In a number of cases, the use of sulfur compounds permits the scheme of synthesis to be simplified and the yields to be raised.

The Willgerodt—Kindler reaction is widely used to obtain phenylacetic acid derivatives, the starting components in the synthesis of benzylisoquinolines, antibiotics of the penicillin group, and other natural compounds. It has been shown previously that thioamides — the products of the Willgerodt-Kindler reaction — react with alkyl halides to form salts of imino sulfides (tautometers of enamino sulfides) [1, 2]. When the latter are heated with amines in the presence of bases, aryl ethyl-N-arylacetamides are formed, which we have used in the synthesis of 1-benzyl-3,4-dihydroisoquinolines [3, 4]. The reaction has been applied to the product of monofunctional and of bifunctional derivatives [1]. For example, from 2-methoxy-5-(β-methylthio-β-morpholinovinyl)phenyl 4'-(β-methylthio-β-morpholinovinyl)phenyl ether (I) the corresponding bishomoveratrylamide has been obtained, which has been used previous in the synthesis of (±)-O-methyldauricine (II) [1]. In this way, a new formal synthesis of (II) has been effected.



Scheme 1

The present paper is devoted to an expansion of the field of application of enamino sulfides for the synthesis of bisbenzylisoquinoline alkaloids with two ether bridges: stebisime (III), (±)-obaberine (IV), and (±)-isotetrandrine (V). Alkaloids of this type possess a broad spectrum of biological activity: curare activity [5] and antipyretic [6], antiarrhythmic [7], antitumoral [8], antitubercular [9], and other activities. Stebisime was first isolated from *Stephania japonica* [10], *Anisocyclea grandidieri* [11], etc., and

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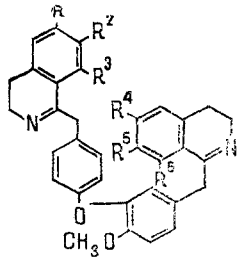
obaberine from various species of barberry [12-14], mahonia [15-18], and other plants. These alkaloids have been synthesized by Kametani et al. [20-22] who used the condensation of 5-chlorocarbonyl-methyl-2-methoxyphenyl 4'-chlorocarbonylmethylphenyl ether with the diamine (VI). This gave the isomeric bisamides (VII) and (VIII),. the separate condensation, reduction, and methylation of which led to the desired compounds.

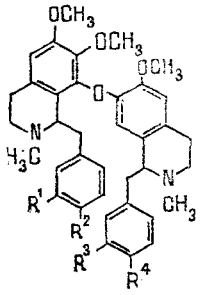


III. $R^1 = R^2 = R^3 = OCH_3$, $R^4 + R^5 = -O-$, $R^6 =$

IX. $R^2 = R^3 = R^4 = OCH_3$, $R^1 + R^5 = -O-$, $R^6 = H$

X. $R^1 = R^4 = R^5 = OCH_3$, $R^2 + R^3 = -O-$, $R^6 = H$

XI. $R^3 = R^4 = R^5 = OCH_3$, $R^1 + R^2 = -O-$, $R^6 = H$



VII. $R^1 = H$, $R^2 + R^3 = -O-$, $R^4 = OCH_3$

V. $R^1 + R^4 = -O-$, $R^3 = H$, $R^2 = OCH_3$

Scheme 2

The bis(enamino sulfide) (I) that we have obtained from the corresponding bisthiomorpholide [3] by reaction with a small excess of 5-(β-aminoethyl)-2,3-dimethoxyphenyl 4'-(β-aminoethyl)-2'-methoxyphenyl ether (VI) [23, 24] forms a mixture of the bisamides (VII and VIII) identical with the corresponding compounds described by Kametani et al. [20-22]). When each of them separately was cyclized, a mixture of two isomeric bisdihydroisoquinoline derivatives ((III) and (IX), and (X) and (XI), respectively) was formed. The first of them coincided in its properties with the natural alkaloid stebisimine. Compounds (IX) and (XI) are bases of an unnatural type and were therefore not used subsequently in synthesis. The dimethiodides of (III) and (X), obtained by the usual method were converted on reduction with $NaBH_4$ into (±)-obaberine (IV) and (±)-isotetrandrine (V), identical with the natural racemic alkaloids, respectively. A comparison with the results reported by Kametani et al. [20-22] is given below [a) $CHCl_3$—ether—methanol (25:25:2) system, neutral alumina, activity grade II; b) $CHCl_3$—methanol (5:4), silica gel; c) $CHCl_3$—acetone—methanol (5:4:1), silica gel; d) $CHCl_3$—methanol (10:1), silica gel; e) $CHCl_3$—methanol (9:2), silica gel; f) $CHCl_3$—methanol (5:1), silica gel]:

Compound	Our results			Kametani *et al.* [20—22]		
	Yield %	mp, deg C	R_f	Yield, %	mp, deg C	R_f
VII	37	118—120	0,74[a]	16	120—121	0,45[b]
VIII	35	139—141	0,50[a]	19	138—140	0,32[b]
III	47,8	105—107	0,60[c] 0,87[d]	—	105—106	0,58[c]
IX	42,5	206—210	0,73[d]	—	203—210	—[e]
X	35,7	155—157	0,84[e]	—	154 - 156	0,82[e]
XI	38,7	163—166	0,72[e]	—	168—170	0,73[e]
Dimethiodide of III	69,9	126—129 (decomp.)	—	—	—	—
Dimethiodide of X	63,5	138—140	—	—	—	—
IV	52,5	190—191	0,66[d]	—	189—190	0,64[d]
V	50	166—168	0,69[f]	—	—	0,66[f]

EXPERIMENTAL

The compounds synthesized were identified on the basis of a comparison of their physicochemical property and details of their spectra with published characteristics and also by direct comparison with authentic samples of the substances. IR spectra were taken on a Pye—Unicam SP-200G spectrophotometer; and NMR spectrum, on a Varian HA-100D instrument (0 — TMS). Melting points were determined on a Kofler apparatus without correction. Elementary analyses were determined on a Hewlett—Packard model 185B CHN analyzer.

4'-Methoxy-N,N'-[3,4",5"-trimethoxy-3",4-oxybis(phenyl)]-3',4"-oxybis(phenylacetamide) (VII) and 4'-Methoxy-N,N'-[3",4,5-trimethoxy-3,4"-oxybis(phenylethyl)]-3',4"'-oxybis(phenylacetamide) (VII). A mixture of 0.3 g of 5-(β-aminoethyl)-2,3-dimethoxyphenyl 4'-(β-aminoethyl)-2'-methoxyphenyl ether (VI), 0.6 g of the dihydroiodide of 2-methoxy-5-(β-methylthio-β-morpholinovinyl)phenyl 4'-(β-methylthio-β-morpholinovinyl)phenyl ether (I) (1.1:1) and 3-4 ml of triethylamine was heated at 115-120°C under reflux for 3 h, after which 3-4 ml of water was added and heating was continued for another 45 min. Then the excess of triethylamine was distilled off in vacuum and the oily residue was triturated with ether until a viscous mass had been obtained. This was dissolved in chloroform and the solution was washed with water (3 × 15 ml), with dilute acid, and again with water and was dried with sodium sulfate, the solvent was distilled off in vacuum, and the residue (0.45 g) was chromatographed on a column of silica gel. Elution was performed successively with chloroform and chloroform—methanol (99:1), (98:2), (97:3), (95:5), and (90:10). The fractions obtained when the $CHCl_3$—CH_3OH (99:1) and (98:2) solvents were distilled off were combined, and the oily residue was triturated with n-hexane until pale yellow crystals had formed, and there were recrystallized from a mixture of ether and hexane. A crystalline substance with a faint yellowish tinge was obtained; $C_{36}H_{38}N_2O_8$, mp 118-120°C, R_f 0.74 ($CHCl_3$—ether—methanol (25:25:2) system). The yield was 0.19 g (35%). λ_{max} (KBr): 1645, 3375 cm^{-1}. NMR ($CDCl_3$), δ, ppm: 3.80, 3.68, 3.56, 3.38, 5.72-6.05, 6.40-7.40, 2.50-2.72.

The second amide (VIII) was obtained from the $CHCl_3$—CH_3OH (97:3) and (95:5) fractions after the solvents had been distilled off in vacuum. The residue was triturated with hexane until it crystallized, and it was then recrystallized from isopropanol. A crystalline substance was obtained with the composition $C_{36}H_{38}N_2O_8$ in the form of beige plates with mp 139-141°C, R_f 0.50 (same system as for (VII)). Yield 0.39 g (72%). ν_{max}: 1640, 3320 cm^{-1}. NMR spectra ($CDCl_3$), δ, ppm: 2.50-2.80, 3.30-3.90, 3.78, 3.70, 3.60, 3.40, 5.30-5.80, 6.40-7.50.

Stebisimine (III). A mixture of 0.2 g of the bisamide (VII), 25 ml of dry chloroform, and 2 ml of phosphorus oxychloride was heated under reflux at 60-70°C for 14-15 h with prevention of the access of moisture to the apparatus. The solvent and the excess of phosphorus oxychloride were distilled off *in vacuo*, and the residue was triturated with ether (a total of about 100 ml), until it solidified. Then it was dissolved in water (25 ml) and the solution was brought to pH 11 with ammonium hydroxide (5-6%) and was extracted with ether (about 300 ml). The ethereal extract was washed with water (2 × 30 ml), dried with sodium sulfate, and evaporated, and the residue, on being redissolved in ether, crystallized. Its recrystallization from a mixture of ether and hexane yielded a colorless crystalline substance with the composition $C_{36}H_{34}N_2O_6 \cdot C_6H_{14} \cdot H_2O$ with mp 105-107°C. Yield 0.09 g (47.8%). ν_{max} (KBr): 1610 cm^{-1}. NMR spectrum ($CDCl_3$), δ, ppm: 3.24, 3.89, 3.91, 3.98 (4 × OCH_3); 5.92, 6.20-7.50 (aromatic protons).

After drying *in vacuo* for 20 h, colorless crystals were obtained which had mp 232.5-234°C. The substance had the same IR spectrum and chromatographic mobilities as natural stebisimine. R_f 0.60 ($CHCl_3$—acetone—methanol (5:4:1) and 0.87 ($CHCl_3$—methanol (10:1) system).

The alkaline aqueous solution after extraction with ether was additionally treated with chloroform (about 150 ml), and the organic phase was washed with water (2 × 30 ml), dried with sodium sulfate, and evaporated *in vacuo*. The residue, after recrystallization from isopropanol, consisted of a light brownish crystalline powder with mp 206-210°C. Yield 0.08 g (42.5%). ν_{max} (KBr): 1610 cm^{-1}. The substance consisted of an unnatural isomer of a bis-dihydroisoquinoline derivative of structure (IX), which was not used further.

Stebisimine Dimethiodide. A mixture of 0.06 g of stebisimine, 3 ml of methanol, and 1.5 ml of methyl iodide were distilled off *in vacuo*, and the residue was triturated with ether to give orange-yellow crystals with mp 126-129°C (decomp.). Yield 0.04 g (69.9%). ν_{max} (KBr): 1610, 3420, 2960 cm^{-1}. The substance was used without additional purification for reduction to (±)-obaberine.

(±)-Obaberine (IV). A solution of 0.04 g of stebisimine dimethiodide in 25 ml of methanol and 2 ml of chloroform was cooled to 0°C and, with continuous stirring, 0.1 g of sodium tetrahydroborate was added in portions over 60-70 min with the temperature of the reaction mixture being kept constant, and after this it was allowed to rise to 20°C over two hours. The solvent was distilled off *in vacuo*, the residue was dissolved in water (about 30 ml), and the reaction product was extracted with chloroform (about 100 ml). After being dried with sodium sulfate, the extract was evaporated to dryness *in vacuo*. The residue crystallized on being treated with ether; mp 165-168°C. After recrystallization from a mixture of acetone and ether and drying *in vacuo*, a colorless crystalline substance was obtained; $C_{38}H_{42}N_2O_6 \cdot 0.5H_2O$ with mp 190-191°C. Yield 0.015 g (52.5%). R_f 0.66 ($CHCl_3$—methanol (10:1) system). NMR spectrum (DMSO), δ, ppm: 2.58 and 2.67 (2 × NCH_3); 3.22, 3.60, 3.79, 3.90 (4 × OCH_3); 6.30-7.50 (aromatic protons). The substance gave no depression of the melting point with a sample of O-methyloxyacanthine — (±)-obaberine — obtained by a different method. Their IR spectra and chromatographic mobilities were identical.

3,3",4,4"-Tetrahydro-6,6",7"-trimethoxy-1,1"-(4"'-methoxy-3"',4'-oxybisbenzyl)-7,8"-oxybisisoquinoline (X) and 3,3",4,4"-Tetrahydro-6",7,8-trimethoxy-1,1"-(4-methoxy-3',4"'-oxybisbenzyl)-6,7"-oxybisisoquinoline (XI). These compounds were obtained from 0.2 of the second bisamide (VIII) by cyclization under the conditions described for compound (VII) with a total yield of 0.165 g (75%). The mixture of bisdihydroisoquinolines was separated chromatographically on a column of silica gel. Compound (X) was obtained from the fractions eluted with chloroform—methanol (98:2) and (95:5) and after recrystallization from a mixture of acetone and hexane it had mp 153-155°C. Colorless crystalline substance, $C_{36}H_{34}N_2O_6 \cdot 1.5H_2O$. Yield 0.088 g (38.7%). R_f 0.84 ($CHCl_3$—methanol (9:2) system). ν_{max} (KBr): 1610 cm^{-1}. NMR spectrum ($CDCl_3$), δ, ppm: 3.60, 3.68, 3.72, 3.76 (4 × OCH_3); 6.50-7.40 (aromatic protons).

The fractions eluted by $CHCl_3$—methanol (90:10) and (1:1) yielded the second bisdihydroisoquinoline structure (XI), which consisted of a substance with a brownish tinge, mp 166-169°C. Yield 0.072 g (35.7%). ν_{max} (KBr): 1610 cm^{-1}; R_f 0.72 ($CHCl_3$—methanol (9:2) system).

Dimethiodide of 3,3',4,4'-Tetrahydro-6,6",7"-trimethoxy-1,1"-(4"'-methoxy-3"',4'-oxybisbenzyl)-7,8"-oxybisisoquinoline. This compound was obtained in a similar manner to stebisimine dimethiodide. Dark yellow crystals with mp 138-140°C (decomp.). Yield 63.5%. ν_{max} (KBr): 1610, 3320 cm^{-1}.

(±)-Isotetrandrine (V). This was obtained by the reduction of the dimethiodide of compound (X) in a similar manner to stebismine dimethiodide. The reaction product was dissolved in acetone, and an acetone solution of picric acid was added. The picrate of (±)-isotetrandrine that deposited was separated off, mp 253-255°C, and was then converted into the free base and this was recrystallized from acetone—hexane. $C_{38}H_{42}N_2O_6 \cdot H_2O$, mp 165.5-168°C. R_f 0.69 ($CHCl_3$—methanol (5:2) system). Yield 0.03 g (50%). NMR spectrum (CD_3COCD_3), δ, ppm: 2.20 and 2.60 (2 × NCH_3); 3.20, 3.63, 3.80, 3.96 (4 × OCH_3); 6.20-7.60 (aromatic protons).

The compound was identical with natural (±)-isotetrandrine according to its IR spectrum and chromatographic mobility and gave no depression of the melting point with the latter.

SUMMARY

A new synthesis has been effected of the bisbenzylisoquinoline alkaloids stebisimine, (±)-obaberine, (±)-O-methyloxyacanthine and (±)- isotetrandrine from 2-methoxy-4-(β-methylthio-β-morpholinovinyl)phenyl 4'-(β-methylthio-β-morpholinovinyl)phenyl ether.

LITERATURE CITED

1. M. A. T. Rogers, J. Chem. Soc., 3350 (1950).
2. P. Chabrier and S. H. Renard, C. R. Acad. Sci. Paris, 228, 850 (1949).
3. E. P. Nakova, O. N. Tolkachev, and R. P. Evstigneeva, in: 2nd Symposium with International Participation on Structure and Reactivity of Organic Compounds, Manuscripts of Contributed Papers, Burgas, Bulgaria (1975), p. 124.
4. E. P. Nakova, O. N. Tolkachev, A. I. Vukulova, G. I. Aranovich, and R. P. Evstigneeva, Zh. Obshch. Khim., 44, No. 2, 410 (1974).
5. M. Okada and A. Asoda, Ann. Rep. ITSUU Lab., 4, 65 (1953); I. R. Bick and L. J. McLeod, J. Pharm. Pharmacol., 26, No. 2, 988 (1974).
6. Y. Yamahara, T. Sawada, M. Kozuka, and H. Fujimura, Shoyakugaky Zasshi, 26, No. 2, 83 (1974); Chem. Abstr., 83, 53481 (1975).

7. H. Kuroda, S. Nakazawa, K. Katagiri, O. Shiratori, M. Kozuka, K. Fujitani, and M. Tomita, Chem. Pharm. Bull., 24, No. 10, 2413 (1976); A. C. Santos, Acta Manilana, Ser. A, 12, 48 (1974); Chem. Abstr., 82, 95236m (1975).
8. Y. Yamahara, T. Sawada, and H. Fujimura, Shoyukugaku Zasshi, 28, No. 2, 96 (1974); Chem. Abstr., 83, 53482d (1975).
9. D. H. R. Barton, G. W. Kirby, and A. Wiechers, J. Chem. Soc. (C), 2313 (1966).
10. E. Schlittler and N. Weber, Helv. Chim. Acta, 55, 2061 (1972).
11. A. N. Tackie, D. Dwuma-Badu, T. Okarer, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Lloydia, 37, 1 (1974).
12. M. R. Falko, J. X. Devries, A. C. Debrovetto, Z. Maccio, S. Rubuffo, and I. R. C. Bick, Tetrahedron Lett., 1953 (1968).
13. M. Tomita and T. Kugo, Yakugaky Zasshi, 79, 317 (1959); Chem. Abstr., 53, 17161e (1959).
14. W.-N. Wu, J. L. Beal, and R. W. Doskotch, Lloydia, 39, No. 5, 378 (1976).
15. T. H. Yang and S. Lu, Yakugaku Zasshi, 80, 847 (1960); Chem. Abstr., 54, 23187i (1960).
16. T. H. Yang and S. Lu, Yakugaku Zasshi, 80, 849 (1960); Chem. Abstr., 54, 23188a (1960).
17. T. Tomita and T. H. Yang, Yakugaki Zasshi, 80, 846 (1960); Chem. Abstr., 54, 23187h (1960).
18. M. Tomita and M Sugamoto, Yakugaku Zasshi, 81, 1090 (1961); Chem. Abstr., 56, 3564e (1962).
19. T. H. Yang, Yakugaku Zasshi, 80, 1304 (1960); Chem. Abstr., 55, 3005h (1961).
20. G. Agular-Santos and S. Villareal, Proc. Symp. Phytochem. Univ., Hong Kong, 48 (1961); Chem. Abstr., 61, 16442d (1964).
21. A. A. Sioumis and V. N. Vashist, Austral. J. Chem., 25, 2251 (1972).
22. F. V. Bruchhausen, G. A. Santos, and C. Schäfer, Arch. Pharm., 293, 2193 (1960).
23. T. Kametani, H. Iida, S. Kano, S. Tanaka, K. Fukumoto, S. Shibuya, and H. Yagi, J. Heterocyclic Chem., 4, 85 (1967).
24. T. Kametani, O. Kusuma, and K. Fukumoto, J. Chem. Soc. (C), 1798 (1968).
25. T. Kametani, K. Wakisaka, and K. Kigasawa, J. Heterocyclic Chem., 7, 509 (1970).
26. S. M. Kupchan and H. W. Altland, J. Med. Chem., 16, 913 (1973).
27. E. P. Nakova, Bulgarian Patient No. 26,438 (1979).