Immobilization of the Oxidized Digitonin on Aminosilochrome. To the oxidation mixture (see the control solution of oxidized digitonin) was added 1 g of Aminosilochrome and the resulting mixture was stirred for another 6 h and was then kept at room temperature for 12 h and the supernatant liquid was poured off, after which the sorbent was washed with 20 ml of water and was dried in the air. It was stored in the refrigerator in a dark vessel.

Determination of Digitonin Immobilized on Aminosilochrome. In a test-tube, 10 mg of digitonin-Aminosilochrome was covered with 4 ml of the anthrone reagent and 1 ml of 50% aqueous dioxane, the mixture was heated in a boiling water bath for 10 min, and the amount of immobilized digitonin was determined in milligrams per 1 g of sorbent from the control curve for oxidized digitonin.

CONCLUSION

1. A colorimetric method has been developed for determining oxidized digitonin in the free and immobilized states.

2. A correspondence of the amount of immobilized digitonin on the sorbent and of the sorption of cholesterol from blood serum has been shown.

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NEW SYNTHESIS OF (±)-O-METHYLDAURICINE

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A new synthesis of O-methyldauricine has been effected through an intermediate bisthioamide obtained by means of the Wilgerodt–Kindler reaction from 2-acetyl-5-methoxyphenyl 4'-acetylphenyl ether and homoveratrylamine. Subsequent Bischler–Napieralski cyclization, methylation, and reduction yielded racemic O-methyldauricine.

O-Methyldauricine, originally known as an unnatural derivative of dauricine obtained by methylating the alkaloid with diazomethane, was first detected in plant sources (*Colubrina asiatica* and others) only in 1970 [1-3]. The synthetic racemic compound obtained exhibited antitumoral activity [4]. The first attempt to synthesize this alkaloid dates back to 1935 [5]. Several schemes of synthesis of (±)-O-methyldauricine (V) including the stage of obtaining a bisamide and differing only by the method of obtaining the initial diphenyl ether have been published [5-7]. We have previously described a method of obtaining the intermediate bisamide from a bis(aminovinyl sulfide) [8]. Another method for synthesizing the alkaloid is based on the use of a Reissert compound [9, [0] and the Ullmann condensation of benzylisoquinoline fragments [11, [2]. However, the low overall yield of the desired compound is stimulating the search for new synthetic routes. We have also previously described a simple method for obtaining thioamides by the Wilgerodt–Kindler method which has been used for the synthesis of thioamides derived from 2-phenylethylamine and, from these, derivatives of N-methyl-

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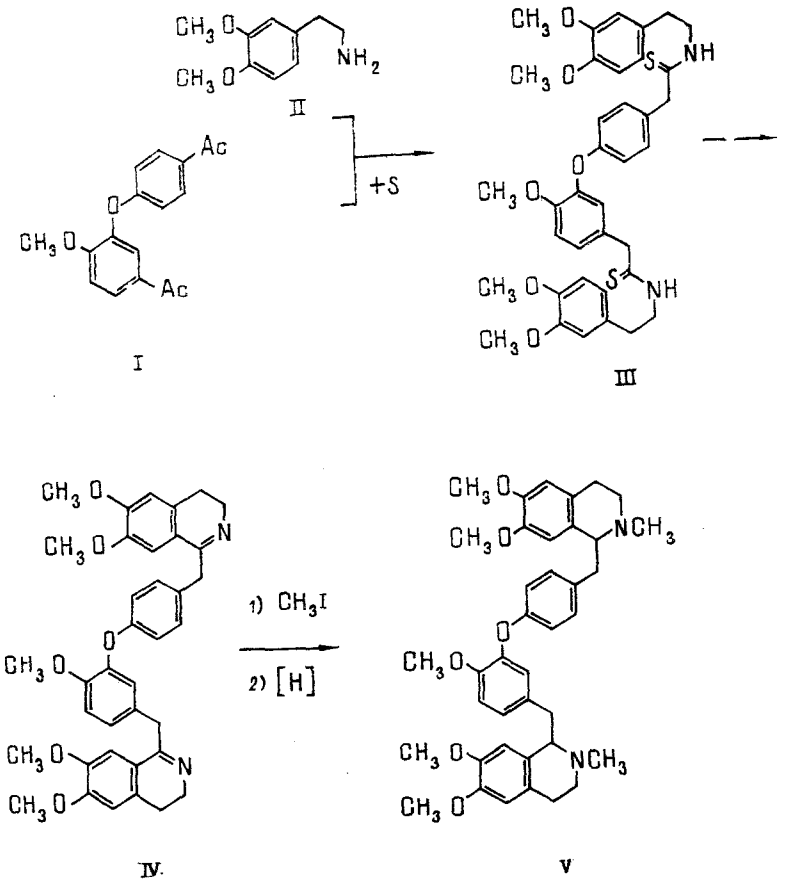
coclaurine and armepavine [13-15]. The use of this scheme considerably reduces the number of stages of synthesis.

In the present communication the synthesis of (±)-O-methyldauricine using this reaction is considered [16]. 2-Acetyl-5-methoxyphenyl 4'-acetylphenyl ether (I) [4] was condensed with homoveratrylamine (II) and sulfur. This gave a bishomoveratrylthioamide with the structure (III) in a yield of 69%. The use of rhombic sulfur in this reaction in place of polymeric sulfur requires an increase in the time and temperature and also lowers the yield of the desired compound (62%). The bisthioamide (III) was purified chromatographically on alumina. Its IR spectrum showed absorption bands at 1510 cm^{-1} (S=C-NH) and 3300 cm^{-1} (NH). The PMR spectrum ($CDCl_3$, 0 — TMS) contains singlets of five methoxy groups at 3.78 and 3.60 ppm, a triplet of two methylene CH_2N protons at 2.82 ppm, and the signals of aromatic protons in the 6.40-7.40 ppm region.



Scheme 1

The bisthioamide (III) was cyclized under the conditions of the Bischler–Napieralski reaction in the presence of phosphorus oxychloride in chloroform. The salt of the bisdihydroisoquinoline derivative of structure (IV) formed was separated off and converted into the base, and the reaction of the latter with methyl iodide in methanol gave a bismethiodide. This was reduced with zinc dust in acetic acid or with sodium tetrahydroborate to (±)-O-methyldauricine (V). The compound had the same chromatographic mobility as the methyl ether of natural magnoline (a diastereoisomer of O-methyldauricine) on alumina and Silufol.

EXPERIMENTAL

Elementary analyses were performed on a Hewlett-Packard model 185-B CHN analyzer. The IR spectra of the compounds were taken on a UR-10 spectrophotometer in paraffin oil, PMR spectra on a Varian HA-100 instrument ($CDCl_3$, 0 — TMS), and UV spectra on a Hitachi EPS-3T spectrophotometer. Melting points were determined on a Boetius heated microstage. The purity of the compounds were determined in a thin layer of alumina (activity grade II), and also on Silufol silica gel.

Preparation of the Bis{[β-(3",4"-dimethoxyphenyl)ethyl]thioamide} of 2-Methoxy(diphenyl oxide)-4',5'-diacetic acid (III). A. A mixture of 2.5 g of homoveratrylamine, 1.8 g of 5-acetyl-2-methoxyphenyl 4'-acetylphenyl ether and 0.97 g of polymeric sulfur was heated at 140-150°C for 3 h. The reaction mixture began to foam 5 min after the beginning of the reaction and this continued for 25-30 min. The color of the reaction mixture changed from dark red to brown. The evolution of hydrogen sulfide ceased when the temperature dropped below 145°C. After the first hour of heating, practically all the diphenyl ether had reacted. The reaction products were separated on a column of alumina (activity grade II). Benzene and benzene–chloroform (80:20) fractions yielded, after the solvents had been distilled off, an oily substance which crystallized on trituration with petroleum ether or with hexane. Yield 2.93 g (69%), mp 56-58°C, R_f 0.10 (alumina; carbon tetrachloride–chloroform (1:2) system, $C_{37}H_{42}O_6N_2S_2$.

B. A mixture of 1.66 g of homoveratrylamine, 1.6 g of 2-methoxy(diphenylether)-4 ,-5-diacetic acid, and 0.8 g of rhombic sulfur was heated at 150-165°C for 5 h (for the first 30 min the bath temperature was kept at 165-175°C). Then it was worked up as in the preceding experiment. Yield was 2.36 g (62.3%). When the reaction temperature was lowered or the time of heating was reduced, the yield of desired product fell. mp 56-58°C.

Petroleum ether fractions after chromatography yielded unchanged sulfur.

Preparation of 4',5-Bis(6,7-dimethoxy-3,4-dihydroisoquinolin-1-ylmethyl)-2-methoxy(diphenyl ether) (IV). A solution of 1.65 g of the bisthioamide (III) in 5 ml of anhydrous chloroform and 3 ml of phosphorus oxychloride was boiled under reflux for 2.5 h. The reaction mixture was evaporated in vacuum, the residue was treated with ether (20-30 ml) of water acidified with 1-2 ml of hydrochloric acid, the resulting solution was made alkaline with ammonium hydroxide to pH 10, and the precipitate that deposited was separated off and was washed with hot water. This gave 1.1 g of the bisdihydroisoquinoline derivative. An additional amount of the substances was obtained from the aqueous solution by extraction with chloroform. The total yield was 1.48 g (97.9%), mp 121-122°C (def. at 115°C).

IR spectrum (cm^{-1}): 1580 (N=C), 1215 and 1280 (ether bonds). UV spectrum (CH_3OH, nm): λ_{max} 278 and 311. $C_{37}H_{38}N_2O_6 \cdot 2H_2O$.

Preparation of 4',5-Bis(6,7-dimethoxy-3,4-dihydroisoquinolin-1-ylmethyl(-2-methoxy(diphenyl ether) Dimethiodide. A mixture of 1.40 g of the bisdihydroisoquinoline derivative (IV), 4 ml of methyl iodide, and 4 ml of methanol was boiled under reflux for 3 h. Then the reaction mixture was concentrated in vacuum and the residue was triturated with ether until it had assumed a pulverulent state. Yield 1.65 g (92.5%). Yellow powder with mp 176-181°C (decomp., from benzene), which was used for reduction without additional purification (according to the literature: 181°C, 165-170°C [4]).

Preparation of (±)-O-Methyldauricine (V). A. A mixture of 1.65 g of the dimethiodide (IV), 10 ml of dilute (11:1) acetic acid, and 3 g of zinc dust was boiled under reflux for 3 h. The excess of zinc dust was separated off, the filtrate was cooled and was treated with an excess of ammonium hydroxide, and the free base that separated out was extracted with benzene (150 ml) and chloroform (150 ml). After the solvents had been distilled off the residue was triturated with ether or with ethanol until it assumed a pulverulent state. Yield 0.98 g (91%), mp 141-142°C (def. at 137°C). Oxalate, mp 207-209°C (according to the literature: 210-212°C [4]).

UV spectrum (ethanol, nm): λ_{max} 283 (log ε 4.04).

B. With cooling to 0°C, 3 g of sodium tetrahydroborate was added over 45 min to a solution of 3 g of the dimethiodide of the bisdihydroisoquinoline derivative (IV) in 40 ml of methanol, and then the mixture was left at 20°C for 1.5 h. The resulting solution was evaporated, and the residue was dissolved in 30 ml of water and was extracted with benzene (200 ml) and chloroform (150 ml). The residue after the solvents had been distilled off was treated first with ether and then with acetone. Yield 2.04 g (95%), mp 140-141°C (def. at 137°C).

IR spectrum (cm^{-1}): 2850 (NCH_3), 1610 (C=C), 1220 and 1280 (ether bonds).

The camphorsulfonate was obtained by the addition to the base of a saturated ethanolic solution of (±)-camphor-β-sulfonic acid. mp 124-126°C. Picrate, mp 153-156°C. $C_{39}H_{46}N_2O_6 \cdot 2H_2O$.

R_f 0.48 (Silufol, benzene-chloroform-methanol (5:4:2)).

CONCLUSION

A new synthesis of O-methyldauricine has been effected through an intermediate bisthioamide obtained by the Wilgerodt–Kindler reaction from 5-acetyl-2-methoxyphenyl 4'-acetylphenyl ether and homoveratrylamine. Subsequent Bischler–Napieralski cyclization, methylation, and reduction yielded racemic O-methyldauricine.

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STRUCTURE OF ISOSOPHORIDINE

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A complete x-ray study of the structure of a stereoisomer of the alkaloid matrine — isosophoridine — has been made. Rings A and B have the cis type of linkage. Rings A, B, and C have the chair form and D the half-chair form.

For a definitive answer to the question of the configurational ambiguity of the structure of isosophoridine, we have made an x-ray structural study of it. Preliminary results have been reported previously [1]. In the present paper the geometry of the isosophoridine molecule is discussed in more detail.

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