2. It has been shown that 2-benzopyrylium salts can be used in the synthesis of the natural isoquinoline alkaloids and, in particular, salsolidine.

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SEARCH FOR METHODS OF SYNTHESIZING 1,9,10-TRIMETHOXY-2,3-METHYLENEDIOXYAPORPHINE. I.

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UDC 547.944/955

Several possible methods of obtaining 4-methoxy-2,3-methylenedioxybenzaldehyde have been considered. A method ensuring the synthesis of this aldehyde with a yield of 35-40% has been developed which consists in the bromination of isovanillin followed by the replacement of the halogen by a hydroxy group and methylation. A number of substituted benzylidene- and benzyltetrahydroisoquinolines have been synthesized. It has been shown that the irradiation of these substances leads to N-dealkylation accompanied by oxidative processes.

Several pentasubstituted derivatives of the aporphine alkaloids with a methylenedioxy group in the 2,3 position the NMR spectra of which do not exhibit a number of the features characteristic for aporphine bases have been described in the literature [1]. The structures of the substances isolated were shown by spectral methods, and we therefore considered it desirable to confirm the structure of baicaline by synthesis. In the present paper we consider the preparation of 4-methoxy-2,3-methylenedioxyphenylethylamine and of 1-benzylidenetetrahydroisoquinolines from it, and the results of the photocylization of the latter.

Two methods of obtaining 4-methoxy-2,3-methylenedioxybenzaldehyde (I) have been discussed in the literature [2]. We have tested the simplest method with mainly good yields using scheme 1, given below, but it led to a mixture of products difficult to separate. The oxidation of o-vanillin (II) gave 40% yield of the 1-monomethyl ether of pyrogallol (III) [3]. The results of a study of methylenation reactions showed that (IV) was formed with good yield by the method of Bick and Russell [4]. Subsequent formylation by the Vilsmeier–Haack reaction [5] gave a mixture of products which was not separated on deactivated alumina and decomposed on ordinary alumina (Brockman activity grade II, neutral) [4].

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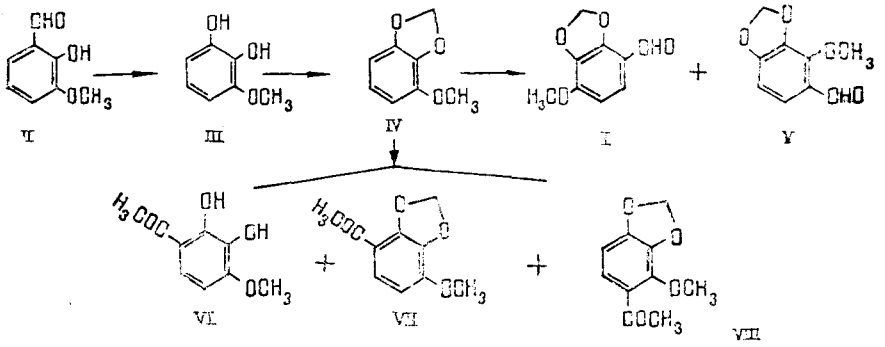
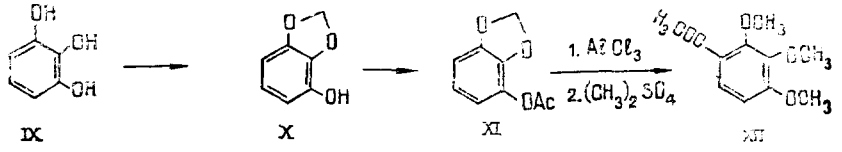
In the course of the work, an interesting route was discovered: from the acetophenone (VII) by the Willgerodt reaction to the required amide. With this aim, we performed the Friedel–Crafts acetylation of (IV) in various solvents: nitrobenzene, petroleum ether, acetyl chloride. In nitrobenzene, three substances were obtained: (VI) and a difficultly separable mixture of (VII) and (VIII) (scheme 1).

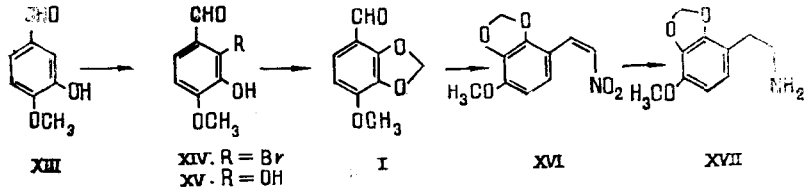
Another possibility for obtaining the acetophenone (VII) is the Fries rearrangement of 1-acetoxy-2,3-methylenedioxybenzene (XI), synthesized from pyrogallol (IX). In this reaction, the methylenedioxy grouping opened and the methylation of the resulting product gave (XII) (scheme 2).



Scheme 1



Scheme 2



Scheme 3

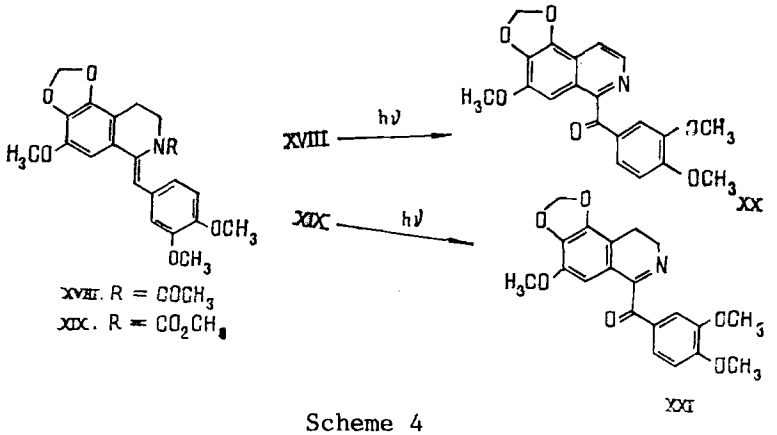
Consequently, not one of the reactions gave the expected results.

We have found a simple method for obtaining (I) starting from isovanillin (XIII) with its subsequent conversion into the amide (XVII) by scheme 3. This method, consisting in the bromination of (XIII) [6] followed by the replacement of the halogen by a hydroxy group [7] and in the methylenation of the diphenol (XV) gave the expected aldehyde (I) with a mean yield of 35-40% calculated on the initial (XIII). The subsequent reaction of the aldehyde (I) with nitromethane followed by reduction of the nitrostyrene derivative (XVI) obtained led to 4-methoxy-2,3-methylenedioxyphenylethylamine (XVII).

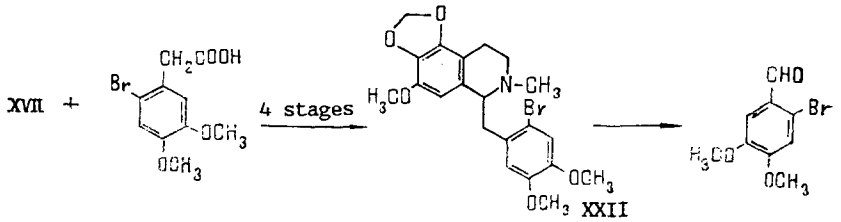
The condensation of the amine (XVII) with 3,4-dimethoxyphenylacetic acid [8] and the Bischler–Napieralski cyclization of the amide so synthesized followed by acetylation or carboxylation gave the corresponding N-substituted benzylidenetetrahydroisoquinolines (XVIII) and (XIX). The structures of all the products were confirmed by their IR, NMR, and mass spectra.

A large number of examples of the photocyclization of substances of types (XVIII) and (XIX) but with different substitutions of ring A to aporphines is given in the literature [9]. We performed the photocyclization of these substances by the method of Carva et al.

[10] using a medical high-pressure mercury lamp. From the reaction mixtures it was possible to isolate, in addition to the initial compound, the product (XX) or (XXI) (scheme 4) for which the corresponding structure was proposed on the basis of an analysis of literature information and their IR, NMR, and mass spectra.



Scheme 4



Scheme 5

The results of the experiments showed that in our case no substances with an aporphine structure were formed but N-alkylation and oxidation took place.

Papers [11, 12] on the photocyclization of substituted benzyl-N-methylisoquinolines induced us to synthesize 1-(6-bromo-3,4-dimethoxybenzyl)-7-methoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XXII) and to perform the analogous reactions with it in an alkaline medium using potassium tert-butanolate and also in an acid medium. It was found that in this case, as well, no compounds with an aporphine skeleton were present among the reaction products and neither the initial (XXII) nor its decomposition product — 6-bromo-3,4-dimethoxybenzaldehyde was isolated (scheme 5).

EXPERIMENTAL

IR spectra (in KBr tablets) were taken on a UR-20 spectrophotometer, NMR spectra on a JNM-4H-100/100 MHz spectrometer relative to HMDS as internal standard in $CDCl_3$ solution, and mass spectra on a MKh-1303 instrument.

The monomethyl ether of pyrogallol (III) was synthesized by a standard method [3] or from methyl gallate [13], which was selectively methylated [14] and then decarboxylated [15].

1-Methoxy-2,3-methylenedioxybenzene (IV) was obtained from (III) by the method of Bick and Russell [4].

Acylation of (IV). AT 0°C, 1 g of aluminum chloride was added over 3 h to a solution of 1 g of (IV) in 5 ml of solvent (nitrobenzene, petroleum ether, or acetyl chloride) and 1 ml of acetyl chloride. The reaction mixture was left in the refrigerator for 12 h and was then poured on to ice. The mixture was acidified and extracted with ether. A mixture of substance was isolated in all the experiments.

The best results, relatively, were obtained in nitrobenzene. When the reaction mixture was separated, the phenolic fraction yielded 2,3-dihydroxy-4-methoxyacetophenone (VI) [NMR spectrum, δ, ppm): 2.5 s ($COCH_3$); 3.85 s (OCH_3); 5.60 br.s (OH); 6.37 d (J = 8 Hz, ortho-H); 7.21 d (J = 8 Hz, ortho-H); 12.4 s (OH)], and a mixture of 4-methoxy-2,3-methylenedioxy- and 2-methoxy-3,4-methylenedioxyacetophenones in a ratio of 2:3; M^+ 194.

Fries Rearrangement of (XI). A solution of 2,3-methylenedioxyphenol (X, [5]) (2 g) in acetic anhydride (5 ml) was treated with three drops of pyridine and the mixture was left at room temperature for two days. After the solvent had been distilled off, the residue was dissolved in 500 ml of ether and the solution was washed with 0.5% KOH (with ice) and with water and was dried with sodium sulfate. The O-acetyl derivative (XI) was obtained in quantative yield in the form of an oil; IR spectrum (film): 1780 cm^{-1} (—OAc).

Compound (XI) was dissolved in nitrobenzene at 0°C, and aluminum chloride (in a ratio of 1:2 or 1:3) was added in 6-8 portions. The mixture was stirred for 2 h at the given temperature and was left in the refrigerator for 12 h and was then poured onto ice. After the appropriate working up, in all the reactions a substance of phenolic nature was obtained as the product which, on methylation with dimethyl sulfate in acetone in the presence of potassium carbonate, gave 2,3,4-trimethoxyacetophenone (XII); M^+ 210.

2-Bromoisovanillin (XIV) was obtained by the method of Kametani et al. [6] from the isovanillin obtained previously [8].

2,3-Dihydroxy-4-methoxybenzaldehyde (XV). In an atmosphere of nitrogen, a mixture of 65 g of (XIV), 37 g of $CuSO_4 \cdot 5H_2O$, and 1500 ml of 4 N caustic soda (240 g) was boiled with vigorous stirring for 5 h. Then it was cooled, the precipitate was filtered off with suction, and the mother liquor was acidified with hydrochloric acid to pH 3-4 and was extracted with ether. The ethereal extracts were dried with magnesium sulfate. After the solvent had been distilled off, the residue was crystallized from water. The yield of (XV) was 40 g (85%), mp 116°C.

4-Methoxy-2,3-methylenedioxybenzaldehyde (I). To a solution of 37 g of (XV) in 220 ml of dry dimethylformamide were added 75 g of anhydrous potassium carbonate, 21 ml of methylene bromide, and 3.5 g of copper oxide. The mixture was boiled in an atmosphere of nitrogen with stirring for 7 h. After cooling, it was filtered, and the residue was washed with chloroform. The solvent was distilled off in vacuum and the residue was extracted with ether and was washed with 4% KOH and then with water. This gave 24.2 g of (I) (60%). Mp 81°C from ethanol.

4-Methoxy-2,3-methylenedioxyphenylethylamine (XVII). A mixture of 35 g of (I), 15 g of ammonium actetae, 150 ml of glacial acetic acid, and 25 ml of nitromethane was boiled under reflux for 1 h 45 min. After cooling, the yellow crystals were filtered off with suction, giving 35 g of the nitrostryene (XVI) with mp 155°C (decomp.); yield 81%.

Compound (XVI) (9.8 g) was placed in a Soxhlet apparatus and was reduced with lithium tetrahydroaluminate (20 g) in 1 liter of absolute ether for 38 h. Then the reaction mixture was diluted with water and the amine was extracted exhaustively with ether. The ethereal solution was washed with water and was dried with sodium sulfate. The residue after the solvent had been distilled off gave 6.1 g (70%) of the amine (XVII) in the form of an oil; M^+ 195.

N-[2-(4-Methoxy-2,3-methylenedioxyphenyl)ethyl]-3,4-dimethoxyphenylacetamide. A mixture of 2.2 g of the amine (XVII) and 2.4 g of 3,4-dimethoxyphenylacetic acid was heated in a current of nitrogen at 180°C for 4 h. Then it is dissolved in chloroform and the solution was washed with 5% solutions of acid and ammonia and then with water. The residue after the solvent had been distilled off was recrystallized from methanol, giving 2.8 g (67%) of the amide; M^+ 373.

2-Acetyl-1-(3,4-dimethoxybenzylidene)-7-methoxy-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XVIII) and (XIX). To 2.8 g of the amide in 200 ml of benzene was added 15 ml of $POCl_3$ and the mixture was boiled under reflux for 3 h. Then the solvent was distilled off and the residue was treated with n-hexane three times, The residue after the decantation of the hexane was treated with 25 ml of water and 25 ml of a hot 20% solution of sodium carbonate. After cooling, 10 ml of chloroform and 8 ml of acetyl chloride in 15 ml of chloroform at 0°C were added to the suspension. The resulting mixture was stirred at 0°C for 1 h and was then extracted with chloroform, and the extract was washed with 5% sulfuric acid and with water. The residue, on trituration with acetone, gave 1.6 g of the N-acetyl derivative (XVIII) with mp 160-165°C; M^+ 399.

Compound (XIX) [mp 190-191°C (decomp.); M^+ 413] was obtained similarly except that methyl chloroformate was used in place of acetyl chloride.

Photocyclization of (XVIII) and (XIX). A mixture of 0.5 g of substance (XVIII) or (XIX), 0.77 g of iodine, and 0.24 g of copper acetate in 300 ml of ethanol was irradiated with a medical high-pressure mercury lamp (400-DRT) with stirring and water cooling for 35 h. The reaction was performed in a quartz flask in a current of nitrogen. The ethanol was distilled off and the residue was dissolved in chloroform, the undissolved material being filtered off. The mother solution was concentrated and deposited on a column of deactivated alumina (15 g). Elution was performed with ether, ether–chloroform, and chloroform.

Compound (XVIII) gave 40 mg of (XX) with mp 216-218°C; R_f 0.7 (chloroform–MeOH (4:1)); and 70 mg of a mixture of (XX) and (XXI) (R_f 0.7 and 0.6). For compound (XX) – IR spectrum: 1648 cm^{-1} (O=C–C=N); mass spectrum: m/z 367 (M^+, $C_{20}H_{17}O_6$); 165 ($C_6H_9O_3^+$, 100%); NMR spectrum, δ, ppm): 3.86 s (3-OCH_3); 6.15 s (O–CH_2–O–); 6.74 d (J = 8 Hz, C^5–H); 7.16 d (J = 1.8 Hz, $C^{2'}$–H); 7.26 dd (J = 8 and 1.8 Hz, $C^{6'}$–H); 7.50 d (J = 5.5 Hz, C^4–H).

Compound (XIX) gave 50 ml of the initial (XIX), 30 mg of a mixture of (XIX) and (XXI), and 40 mg of (XXI).

For compound (XXI) – mp 207-210°C; IR spectrum: 1655 cm^{-1} (O=C–C=N); mass spectrum: m/z 369 (M^+); 165 (100%); NMR spectrum (δ, ppm): 3.70, s (1-OCH_3); 3.85 s (2-OCH_3); 5.93 s (–O–CH_2–O–); 6.50 s (C^8–H); 6.74 d (j = 8 Hz, $C^{5'}$–H); 7.43 dd (J = 8 and 1.7 Hz, $C^{6'}$–J); 7.51 s ($C^{2'}$–H).

1-(2'-Bromo-4',5'-dimethoxybenzyl)-7-methoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline. The preparation of the amide followed by Bischler-Napieralski cyclization was carried out in a similar manner to the reactions described above except that in place of 3,4-dimethoxyphenylacetic acid its 6-bromo derivative [8] was used. The dihydroisoquinoline synthesized (3 g) was dissolved in 200 ml of methanol and to the resulting solution, at 5°C, 4 g of sodium tetrahydroborate was added in portions. The solvent was driven off in vacuum. The residue was extracted with chloroform and the extract was washed with water. The material remaining after the solvent had been distilled off (2.1 g) was boiled with a mixture of 5 ml of formamide and 100 ml of methanol for 1 h. After cooling, 2.5 g of sodium tetrahydroborate was added to the mixture. Appropriate working up yielded the amorphous N-methyl derivative (XXII) with a yield of 2.0 g; M^+ 450.

Photocyclization of (XXII). The reaction was performed by analogy with a procedure described in the literature [12]. After the appropriate working up and separation on a column of alumina, in addition to the initial (XXII), 2-bromo-4,5-dimethoxybenzaldehyde was isolated with mp 149°C (decomp.); M^+ 244, 245, 246.

SUMMARY

1. A simple method for the synthesis of 4-methoxy-2,3-methylenedioxybenxaldehyde had been developed which ensures the production of the corresponding phenylethylamine in good yield.

2. It has been shown that when 2-acetyl- or 2-methoxycarbonyl-1-(3',4'-dimethoxybenzylidene)-7methoxy-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline and 1-(2'-bromo-4',5'-dimethoxybenzyl)-7-methoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline are irradiated, N-dealkylation, accompanied by oxidative processes, take place.

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ALKALOIDS OF *Haplophyllum foliosum*.

III. STRUCTURE OF FOLIDINE

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and S. Yu. Yunusov

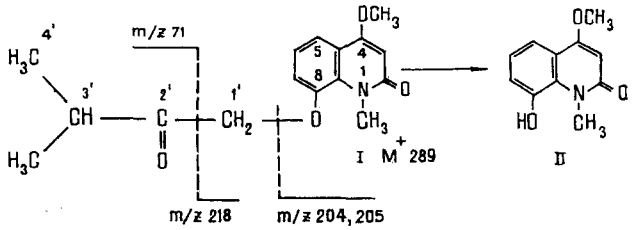
UDC: 547.944/945

The new alkaloid folidine with mp 148-149°C (acetone–petroleum ether) has been isolated from the epigeal part of the plant *Haplophyllum foliosum* Vved., and on the basis of spectral characteristics and passage to the known alkaloid folifidine (8-hydroxy-4-methoxy-1-methyl-2-quinoline) its structure has been established as 4-methoxy-1-methyl-8-(2'-oxo-3'-methylbutoxy)-2-quinolone.

Continuing an investigation of the alkaloid composition of the epigeal part of the plant *Haplophyllum foliosum* Vved. [1], from the graveoline mother liquor we have isolated a new base with mp 148-149°C (acetone–petroleum ether) which we have called folidine (I). The substance is readily soluble in ether, chloroform, acetone, and ethanol, sparingly soluble in petroleum ether and benzene, and insoluble in water and alkalis.

The IR spectrum of (I) has absorption bands at 1730 cm^{-1} (CO) and 1640 cm^{-1} (amide carbonyl group of a 2-quinolone [2, 3]). The UV spectrum of folidine – λ_{max} 233, 249, 273, 286, 325 nm (log ε 3.42, 3.32, 2.89, 2.84, 2.60) – is typical for 4,8-dialkoxy-substituted derivatives of 2-quinolone alkaloids [3, 4].

The fact that (I) belonged to this group of substances was confirmed by its NMR spectrum which exhibited the signals of the protons of a 2-quinolone nucleus at (δ, ppm) 7.72 (q, 1 H, J_{ortho} = 7.5 Hz, J_{meta} = 3 Hz; H_5); 7.45-6.85 (m, 2 H; $H_{6,7}$); 6.08 (s, 1 H; H_3); of a methoxy and an N-methyl group at 3.94 and 3.9 (s, 3 H each) and of an isoprenoid substituent at 4.78 (s, 2 H; CH_2O); 2.80 (q, 1 H, J = 7.5 Hz, $C\underline{H}-(CH_3)_2$; 1.14 (d, 6 H, J = 7.5 Hz; $CH-(C\underline{H}_3)_2$). The absence of coupling between the protons of the methine and O-methylene groups indicated that the carbonyl group belonging to (I) shown above was located between them, i.e., the isoprenoid substituent had the structure $O-CH_2-CO-CH(CH_3)_2$. This was confirmed by the mass spectrum of (I), which contained the peak of the molecular ion with m/z 289 (89%) and the peaks of ions with m/z (62%), 205 (59%), 204 (100%), and 71 (26%) (scheme)



When compound (I) was fused with alkali, the known alkaloid folifidine (II) was obtained [5]. The passage to folifidine confirmed the structure of the heterocyclic skeleton of (I) and showed that the isoprenoid substituent in the folidine molecule was located at C_8.

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