SEARCH FOR A METHOD OF SYNTHESIZING 1,9,10-TRIMETHOXY-2,3-METHYLENEDIOXY-APORPHINE.

II. SYNTHESIS OF BAICALIDINE

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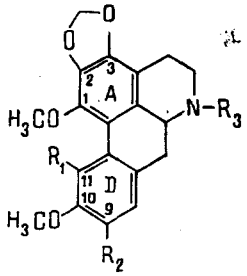
UDC 547.944/945

The synthesis of baicalidine has been effected by the intramolecular oxidative cyclization of 1-(3,4-dimethoxybenzyl)-7-methoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline with thallium trifluoroacetate, confirming the structure proposed for it previously as 1,9,10-trimethoxy-2,3-methylenedioxy-aporphine.

At the present time, five aporphine alkaloids are known that have a methylenedioxy group in the 2,3 position of ring A. Ocokryptine (I), the first alkaloid of this series, was found in 1968 by M. Cava et al. in the plant Ocotea sp. [1]. Beginning in 1982, S. Kh. Maekh et al. [2] have published communications on the isolation of another three bases (II, III, and IV) with a similar arrangement of substituents in ring A.



I. R_1 = OH, R_2 = H, R_3 = CH_3
II. R_1 = OCH_3, R_2 = H, R_3 = CH_3
III. R_1 = H, R_2 = OCH_3, R_3 = H
IV. R_1 = H, R_2 = OCH_3, R_3 = CH_3
V. R_1 = H, R_2 = OCH_3, R_3 = $COCH_3$

Structures were proposed for the substances isolated mainly on the basis of the results of a study of UV and PMR spectra. This permitted Cava et al. [1] to establish the positions of the substituents in ring D, while for the methylenedioxy group the 1,2 position was excluded and the 2,3 position was decided upon.

Analysis of the PMR spectra of the aporphine alkaloids (I-V) shows that these spectra have some special features and differences from the common features revealed previously in this series [3]. Thus, for example, the methoxy group at C_1 in each of the aporphine alkaloids studied previously gives a signal in a stronger field (3.41-3.83 ppm) than that from the same group at C_9 or C_{10} (3.80-4.08 ppm). Practically no such shift of the signal of the methoxy group at C_1 is observed for the bases (I-V) [2a]. Also unusual is the nature of the signal of the methylenedioxy group. When the latter is present at C_1–C_2 or C_{10}–C_{11}, its protons are revealed in the form of two one-proton doublets (J = 1.5 and 1.8 Hz) with chemical shift differences of from 10 to 20 Hz [4], and when it is at C_8–C_9 or C_9–C_{10} it is in the form of a two-proton singlet [5]. For each of the alkaloids (I-V), the signal from this group appears in the form of two close (2-6 Hz) one-proton doublets ($J \approx 1.5$ Hz), fusing into a broadened singlet in the case of baicaline (III) [2a].

It is known that the chemical shift of the proton in position 11 depends on the nature of the oxygen-containing substituent at C_1 [3, 4]. A comparison of the PMR spectra of substances having the same substituents at C_9 and C_{10} has shown that the chemical shift of the proton at C_{11} also depends on the nature of the substituents at C_2 and C_3. Thus, the chemical shift of the proton at C_{11} for (III-V) (7.94-7.75 ppm) proved to be between those for 1,2,3,9,10-pentamethoxyaporphine (7.89, 7.98 ppm) and 3,9,10-trimethoxy-1,2-methylenedioxyaporphine (7.61 ppm, Table 1).

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 460-464, July-August, 1986. Original article submitted January 31, 1986.

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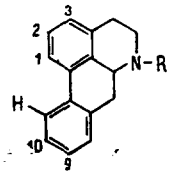
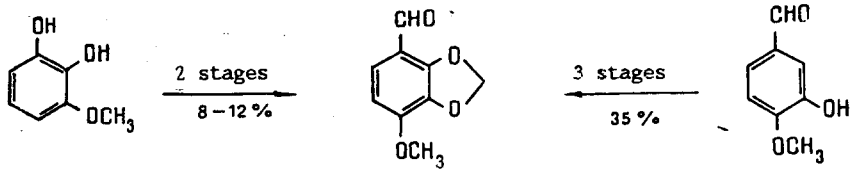
TABLE 1. Dependence of the H_{11} Chemical Shift in the PMR Spectra of the Aporphine Alkaloids on the Nature of the Substituent at C_1

	Substituents in the following positions					R	Chemical shift of H_{11} δ, ppm
	1	2	3	9	10		
Northalicmine	O—CH_2—O		OCH_3	OCH_3	OCH_3	H	7,61
Thalicmine	O—CH_2—O		OCH_3	OCH_3	OCH_3	CH_3	7,61
O-Methylisoboldine	OH	OCH_3	H	OCH_3	OCH_3	CH_3	8,08
Preocoteine	OH	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	7,99
Predicentrine	OCH_3	OH	H	OCH_3	OCH_3	CH_3	7,96
Norglaucine	OCH_3	OCH_3	H	OCH_3	OCH_3	H	8,11
Glaucine	OCH_3	OCH_3	H	OCH_3	OCH_3	CH_3	8,21
O-Demethylpurpureine	OCH_3	OH	OCH_3	OCH_3	OCH_3	CH_3	7,89
Northalicsimidine	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H	7,98
Thalicsimidine	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	7,89
Baicaline (III)	OCH_3	O—CH_2—O		OCH_3	OCH_3	H	7,94
Baicalidine (IV)	OCH_3	O—CH_2—O		OCH_3	OCH_3	CH_3	7,80
N-Acetylbaicaline (V)	OCH_3	O—CH_2—O		OCH_3	OCH_3	$COCH_3$	7,75

The above-described features of the PMR spectra of the alkaloids isolated, the absence of other methods of proving their structure apart from spectral methods, and also the theoretical possibility of a different position of the substituents impelled us to synthesize baicalidine (IV) [2b]. No aporphines with ring A substituted in this way have been synthesized previously.

The synthesis of (IV) included the preparation of the key compound 4-methoxy-2,3-methylenedioxyphenethylamine (VI) from 4-methoxy-2,3-methylenedioxybenzaldehyde (VII).

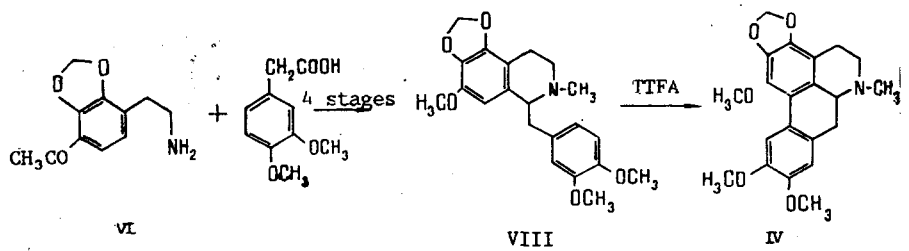


Scheme 1

We [6] have previously proposed a new method of obtaining (VII) permitting this substance to be synthesized with an overall yield of 35%, which is three times greater than that described in the literature (scheme 1). We observed [6] that on the photoreaction of 2-acetyl- (or 2-methoxycarbonyl-) -1-(3,4-dimethoxybenzylidene)-7-methoxy-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline and 1-(6-bromo-3,4-dimethoxybenzyl)-7-methyoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline no cyclization products with the aporphine structure were detected.

In the present paper we describe the intramolecular oxidative cyclization of 1-(3,4-dimethoxybenzyl)-7-methoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VIII) with thallium(III) trifluoroacetate [8, 9] giving a 15% yield of N-methylbaicaline (IV).

The benzylisoquinoline (VIII) was obtained in four stages as shown in scheme 2.



VI VIII IV

Scheme 2

Thus, the synthesis performed has confirmed a structure of baicalidine (IV) proposed previously as 1,9,10-trimethoxy-2,3-methylenedioxyaporphine.

EXPERIMENTAL

For general observations, see [6].

Thallium(III) trifluoroacetate (TTFA) was obtained by the method of McKillop et al. [10] with a reaction time of 130 h.

N-(4-Methoxy-2,3-methylenedioxyphenethyl)-3,4-dimethoxyphenylacetamide was obtained as described previously [6].

1-(3,4-Dimethoxybenzyl)-7-methoxy-2-methyl-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VIII). To 3.2 g of the amide [6] in 150 ml of absolute benzene was added 15 ml of phosphorus oxychloride. The mixture was boiled under reflux for 3 h. The solvent was distilled off, and the residue was treated with n-hexane three times. The residue after the decantation of n-hexane was dissolved in 100 ml of methanol, and to the resulting solution at 5°C was added 4 g of sodium tetrahydroborate in portions over 1 h. The solvent was evaporated off in vacuum, and the residue was diluted with water and was exhaustively extracted with ether.

The residue after the distillation of the solvent (2.3 g) was boiled in a mixture of 5 ml of formamide and 50 ml of methanol for 1 h. After cooling to 5°C, 3.0 g of sodium tetrahydroborate was added in portions. Suitable working-up of the reaction mixture yielded 1 g of the hydrochloride of (VIII) from methanol with mp 180-182°C, R_f 0.8 (chloroform–methanol (4:1) system). Mass spectrum: m/z 371 (M^+), 220, 205.

PMR spectrum ($CDCl_3$, δ, ppm): 2.45 (s, N–CH_3); 3.51, 3.71, 3.76 (3 × OCH_3); 5.65 (s, 1H); 5.87 (s, O–CH_2–O); 6.56 and 6.62 (2 d, J = 8.5 Hz, 2H each); 6.68 (s, 1H).

Cyclization of (VIII) with Thallium(III) Trifluoroacetate (TTFA). A. At 0°C, 0.2 g of N-methylisoquinoline (VIII) in 5 ml of dry methylene chloride and, simultaneously, 1 ml of boron trifluoride etherate were added to 0.280 g of TTFA in 100 ml of freshly distilled trifluoroacetic acid. On the addition of the substance the solution acquired a green coloration. It was stirred at 0°C for four hours. The solvent was distilled off in vacuum and the residue was diluted with water, made alkaline with 5% ammonia, and extracted with chloroform. The extract was dried with Na_2CO_3, and the residue after the solvent had been distilled off was transferred to a column of deactivated alumina (8 g). The first ethereal eluate contained baicalidine (VI). Yield about 10%.

B. At 0°C, a mixture of (VIII) (0.38 g), carbon tetrachloride (20 ml) and boron trifluoride etherate (5 ml) was added in a current of nitrogen to 0.78 g of TTFA in a mixture of 80 ml of acetonitrile and 15 ml of carbon tetrachloride. The reaction mixture was stirred at room temperature for 2 h and after a working-up procedure similar to that described above for reaction A and purification on deactivated alumina (23 g), baicaline (IV) was obtained with a yield of 15%.

Compound (IV) had the form of a light yellow oil with R_f 0.75 (chloroform–methanol (4:1) system). Mass spectrum: m/z 369 (M^+), 368, 354, 338, 326, 311.

The PMR spectrum was taken on a Tesla BS-567 A instrument (0 – HMDS, 100 MHz, in $CDCl_3$, δ, ppm): 2.48 (s, N–CH_3); three-proton and six-proton singlets at 3.82 and 3.87 (3 × OCH_3); 6.72 (s, H-8); 7.79 (s, H-11); 5.90 and 5.95 (2H, J ≈ 1.5 Hz, O –CH_2–O).

The mass and PMR spectra and also the IR spectrum taken in chloroform, of the synthetic (IV) were identical with those of the natural alkaloid baicalidine (IV).

SUMMARY

The synthesis of baicalidine has been effected, confirming the structure proposed for it previously as 1,9,10-trimethoxy-2,3-methylenedioxyaporphine.

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SYNTHESIS OF REGECOLINE

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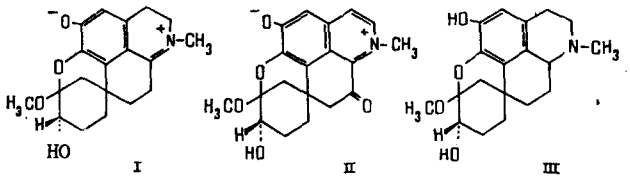
UDC 547.944.6

An improved synthesis of the quaternary homoproaporphine alkaloid regecoline from the main alkaloid of Colchicum kesselringii Rgl. – kesselringine – has been carried out by two methods: by photochemical conversion (yield 77%) and by iodine oxidation (yield 86%). It has been shown that the iodine oxidation of homoproaporphines of the kesselringine type leads to C_{6a}-dehydro derivatives.

Regecoline (I), isolated from the epigeal parts of the plant Colchicum kesselringii Rgl. is the first representative of the quaternary dehydrohomoproaporphine alkaloids with a spirocyclohexane ring [1]. The dehydrohomoproaporphine bases [1, 2] belong to the minor alkaloids of this plant, and their chemical and pharmacological properties have been little investigated. We have studied possible routes for their synthesis from structurally close compounds. In [1], we described the passage to regecoline from regelinone (I) – a 7-oxotetrahydrohomoproaporphine, and also a minor, alkaloid. Its synthesis from the main alkaloid of the plant – kesselringine (III) [3, 4] – by oxidation with iodine or with hydrogen peroxide led to a mixture of regecoline and unknown substances.



I II III

In the present communication we consider an improved synthesis of regecoline from kesselringine effected by two methods. A good yield was obtained both by the irradiation of kesselringine in solution with sunlight, and also by oxidation with iodine in dioxane solution. As is known, the oxidation of aporphines by iodine leads to 6a,7-didehydroaporphines [5]. On oxidation under similar conditions, however, kesselringine forms a 6a-dehydro derivative that is a quaternary base with a betaine nature, i.e., regecoline.

The regecoline obtained by the oxidation of kesselringine with iodine contained the initial base and regelinone as impurities. It was successfully isolated in the individual

V. I. Lenin Tashkent State University. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 464-465, July-August, 1986. Original article submitted February 6, 1986; revision submitted March 10, 1986.

