2-BENZOPYRYLIUM SALTS.

29.* A NEW APPROACH TO THE SYNTHESIS OF THE NATURAL ALKALOID SALSOLIDINE USING 2-BENZOPYRYLIUM SALTS

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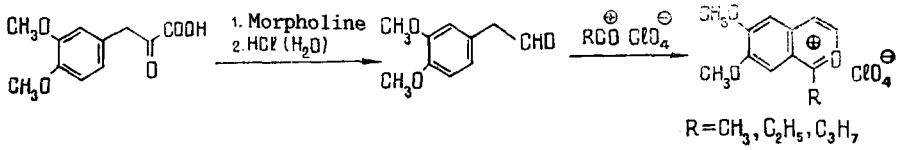
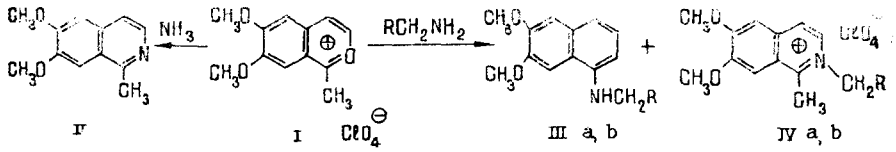
The reaction of 6,7-dimethoxy-1-methyl-2-benzopyrylium salt with ammonia forms the corresponding isoquinoline, and its reaction with methylamine and benzylamine forms mixtures of the corresponding isoquinolinium salts and naphthylamines. The reduction of 2-benzyl-1-methyl-6,7-dimethoxyisoquinolinium perchlorate with sodium tetrahydroborate has given the corresponding tetrahydroisoquinoline, the hydrogenolysis of which has led to salsolidine. The products have been characterized by elementary analyses and IR and PMR spectroscopy.

It is known that 2-benzopyrylium salts can easily be converted into isoquinoline bases [2], which are component parts of some natural alkaloids and posess a diverse biological activity [3]. The essence of the method consists in the simple replacement of the oxygen hetero atom by nitrogen, which, in a number of cases makes it competitive with classical methods of synthesizing isoquinolines [4].

It is obvious that in order to apply this approach to the synthesis of the natural alkaloid salsolidine (VI) 2-benzopyrylium salts unsubstituted in position 3 must be used. We obtained the latter by the following scheme [5]



It was found that when 6,7-dimethoxy-1-methyl-2-benzopyrylium perchorate (I) reacted not only with an aqueous, but also, at 0°C, with an ethanolic solution of ammonia, 6,7-dimethoxy-1-methylisoquinoline (II) was formed with yields of 60 and 75%, respectively.



The isoquinoline (II) is a dehydro analog of salsolidine and it was assumed that its reduction using general methods should lead to salsolidine. However, attempts at reduction both with sodium in ethanol [6] and with tin in hydrochloric acid [7] did not prove to be preparative: in both cases only traces of the desired product were isolated.

Another approach to salsolidine is possible through the N-alkylisoquinolinium salts (IV) and their reduction to tetrahydroisoquinolines followed by hydrogenolysis. The last

*For communication 28 see [1].

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TABLE 1. Some Characteristics of the Compounds Synthesized

Compound	Yield, %	IR spectrum, cm^{-1}	mp, °C	Found, %				Empirical formula	Calculated, %			
				C	H	N	Cl		C	H	N	Cl
I	70	1620, 1600, 1275, 1100	235–237*	47,31	4,29	—	11,70	$C_{12}H_{13}ClO_7$	47,29	4,27	—	11,66
IIIa	30	3400, 1620, 1585, 1500, 1255	134–135	71,92	6,92	6,46	—	$C_{13}H_{15}NO_2$	71,89	6,91	6,45	—
IIIb	21	3400, 1625, 1590, 1490, 1240	158	77,79	6,48	4,75	—	$C_{19}H_{19}NO_2$	77,81	6,48	4,78	—
IVa	58	1600, 1500, 1295, 1100	280*	49,24	5,08	4,42	11,18	$C_{13}H_{16}ClNO_6$	49,14	5,04	4,41	11,18
IVb	47	1610, 1505, 1280, 1090,	220*	57,96	5,11	3,90	9,11	$C_{19}H_{20}ClNO_6$	57,94	5,08	3,55	9,02
V·$HClO_4$	99	3500, 2700, 1620, 1525, 1240, 1080,	126	57,39	6,10	3,61	8,97	$C_{19}H_{24}ClNO_6$	57,35	6,03	3,52	8,93

*From acetic acid.

TABLE 2. PMR Spectra of the Compounds Synthesized

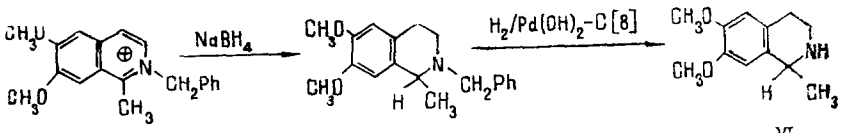
Compound	O–CH_3	I–CH_3	>N–CH_2R	Aromatic protons	Other protons
IIIa	s 3,90 (6H)	—	s 2,92 (3H)	m 6,50 (1H), m 7,08 (4H)	s 3,58 (NH)
IIIb	s 3,69 (6H)	—	s 4,38 (2H)	m 6,48 (1H), m 7,13 (9H)	s 3,98 (NH)
IVa	s 3,75 (6H)	s 2,75 (3H)	s 3,95 (3H)	s 7,03 (1H), s 7,30 (1H) two d 7,36 (2H)	—
IVb	s 3,79 (6H)	s 2,78 (3H)	s 5,54 (2H)	m 6,80 (2H), m 7,03 (3H), s 7,20 (1H), s 7,41 (7H), two d 7,88 (2H)	—
V·$HClO_4$	s 3,45 (6H)	d 1,35 (3H), J=6 Hz	s 3,58 (2H)	s 6,30 (1H), s 6,35 (1H), s 7,08 (5H)	br. s 2,75 (2H), q 3,15 (1H), br.s s 4,05 (2H), br.s. s 4,30 ($\overset{\diagup}{\underset{\diagdown}{\overset{\oplus}{NH}}}$)

stage in the case where R = CH_2Ph has been described and takes place with good yield [8]. It was assumed that the corresponding isoquinolinium salt can be obtained by the reaction of the 2-benzopyrylium salt (I) with benzylamine. However, it was found that the treatment of the salt (I) with aqueous ethanolic solutions of methylamine or benzylamine led to a mixture of the corresponding naphthylamines (IIIa, b) and isoquinolinium salts (IVa, b). Nevertheless, thanks to the different solubilities of the products in chloroform, the mixtures were easily separated, and the isoquinolinium salts (IVa, b) were isolated with yields of 58 and 47%, respectively.

The PMR spectra of the naphthlyamines (IIIa, b) showed, in addition to the signals of the two methoxy groups and of the appropriate number of aromatic protons (Table 2), the signals of the proton of the amino group at 3.58 and 3.98 ppm, respectively, which disappeared on deuteration. The PMR spectra of the salts (IVa, b) also confirmed their structure (Table 2).

It is curious that with less basic amines the reaction takes place with the formation solely of the isoquinolinium salts; for instance, aniline gives the N-phenylisoquinolinium salt [5].

When the salt (IVb) was reduced with sodium tetrahydroborate in methanol, an 87% yield was obtained of the racemate of the tetrahydroisoquinoline (V), which was identified in the form of its hydrochloride [9] and also on the basis of the PMR spectrum of its perchlorate (Table 2).



IV b V VI

(±)-Salsolidine

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-487 instrument with a working frequency of 60 MHz at 20°C using solutions in $CDCl_3$ (compounds (II) and (IIIa,b)) and in CF_3COOH (compounds (IVa,b) and ($V \cdot HClO_4$)), with HMDS as internal standard. IR spectra were obtained on a Specord 71-IR instrument in paraffin oil. The purity of compounds (II), (IIIa, b), and (V) was checked by TLC on alumina (with chloroform as the mobile phase).

6,7-Dimethoxy-1-methyl-2-benzopyrylium Perchlorate (I) [5]. With ice-water cooling, 0.4 ml (0.004 mole) of a 70% aqueous solution of perchloric acid was carefully added to a solution of 0.9 g (0.002 mole) of homoveratraldehyde [10] in 4 ml of acetic anhydride. The mixture was carefully diluted with ether until the salt that had precipitated began to become greasy. After being left to stand overnight, the precipitate was filtered off, washed with ether, and dried. This gave 1.06 g of the salt (I) (Table 1).

6,7-Dimethoxy-1-methylisoquinoline (II). A. A suspension of 0.3 g (0.001 mole) of 6,7-dimethoxy-1-methyl-2-benzopyrylium perchlorate (I) in 2 ml of a 28% aqueous solution of ammonia was kept at room temerature for three days. Then the precipitate was separated off and was purified via the hydrochloride as described in paragraph B by the procedure of Müller et al. [11]. This gave 0.12 g (60%) of the isoquinoline (II) with mp 112°C (according to the literature, mp 111-112°C [12]). PMR spectrum (ppm): 2.80 (s, CH_3); 3.93 (s, two OCH_3); 6.90, 7.10 (two s, H-5 and H-8); 7.27 (d, H-3); 8.19 (d, H-4). $J_{3,4}$ = 6 Hz.

B. A suspension of 0.3 g (0.01 mole) of salt (I) in 3 ml of methanol was saturated with gaseous ammonia at 0°C. The mixture was kept at 0°C for 2 days, the solvent was distilled off under reduced pressure, the residue was treated with 10 ml of water, and the mixture was made alkaline with 3 ml of a 28% aqueous solution of ammonia and was extracted with ether (4 × 20 ml). The ethereal extract was treated with a 5% solution of hydrochloric acid (3 × 10 ml) and the aqueous extract was brought to pH ∿ 10 by the addition of ammonia solution, after which the desired product was extracted with ether (5 × 15 ml) and the ethereal solution was dried and evaporated. This gave 0.5 g (75%) of a product completely identical with that described in paragraph A.

N-Methyl-6,7-dimethoxy-1-naphthylamine (IIIa) and 6,7-Dimethoxy-1-methylisoquinolinium Perchlorate (IVa). A suspension of 0.6 g (0.002 mole) of the salt (I) in 3 ml of ethanol was treated with 1 ml of an aqueous solution of methylamine obtained by saturating water with gaseous methylamine at −10°C. The salt dissolved and a colorless precipitate rapidly deposited. After a day, the product was filtered off, washed with water, dried, and washed with 30 ml of chloroform. This gave 0.36 g of the salt (IVa) as the chloroform-insoluble residue and 0.12 g of the amine (IIIa) after the evaporation of the chloroform extract (Tables 1 and 2).

N-Benzyl-6,7-dimethoxy-1-naphthylamine (IIIb) and N-benzyl-6,7-dimethoxy-1-methylisoquinolium Perchlorate (IVb) (Tables 1 and 2) were obtained similarly from the salt (I) and benzylamine.

N-Benzyl-6,7-dimethoxy-1-methyltetrahydroisoquinoline (V) was obtained by reducing the N-benzyl-6,7-dimethoxy-1-methylisoquinolinium perchlorate (IVb) with sodium tetrahydroborate in methanol, with a yield of 87%, by the typical procedure for the reduction of isoquinolium salts [11] and was identified in the form of the hydrochloride with mp 161°C (according to the literature, mp 161°C [9]. N-Benzyl-6,7-dimethoxy-1-methyltetrahydroisoquinolium perchlorate was obtained by treating a solution of the base (V) in methanol with an excess of 70% perchloric acid (Tables 1 and 2).

SUMMARY

1. The interaction of 6,7-dimethoxy-1-methyl-2-benzopyrylium perchlorate with ammonia and primary amines has been studied.

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

LITERATURE CITED

1. I. V. Korobka, Yu. V. Revinskii, and E. V. Kuznetsov, Khim. Geterotsikl. Soedin., 932 (1985).
2. G. N. Dorofeenko and E. V. Kuznetsov, Khim. Geterotsikl. Soedin., 2, 207 (1970).
3. M. Shamma and J. L. Moniot, Isoquinoline Alkaloids Research, 1972-1977, Plenum Press, New York (1978), p. 18.
4. Organic Reactions, Wiley, New York, Vol. 6 (1951), pp. 74-206.
5. I. V. Shcherbakova, V. G. Brovchenko, and E. V. Kuznetsova, Khim. Geterotsikl. Soedin., 702 (1984).
6. A. Ladenburg, Chem. Ber., 17, 156 (1884).
7. R. Forsyth, C. I. Kelly, and F. L. Pyman, J. Chem. Soc., 1659 (1925).
8. T. Kametani, J. Chem. Soc., I, 579 (1977).
9. G. Bernáth, K. Koczka, J. Kobor, L. Radics, and M. Kajár, Acta Chim. Acad. Scient. Hung., 55, 331 (1968).
10. I. K. Stamos, Tetrahedron Lett., 23, 459 (1982).
11. A. Müller, M. M. El-Sawy, M. Mésraros, and F. Ruff, Acta Chem. Hung., 52, 261 (1967).
12. E. Späth and N. Polgar, Monatsh, 51, 190 (1929).

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

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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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