2-BENZOPYRYLIUM SALTS

XI.* SYNTHESIS OF 2-BENZOPYRYLIUM SALTS AND STRUCTURAL ANALOGS OF ISOQUINOLINE ALKALOIDS BY ACYLATION OF HOMOVERATRIC ACID AND ITS DERIVATIVES

G. N. Dorofeenko and V. G. Korobkova

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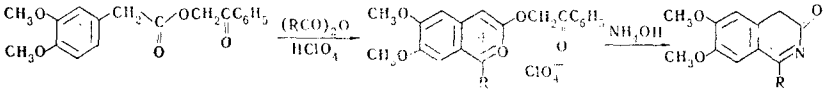
The acylation of homoveratric acid and its derivatives with carboxylic acids in the presence of polyphosphoric acid, which leads to the synthesis of 2-acylhomoveratric acids, was studied. The properties and transformations of the latter to 2-benzopyrylium salts and isoquinoline bases were investigated. The structural analogs of the alkaloid papaverine were synthesized.

The development of simple methods for the synthesis of 2-benzopyrylium salts seems of interest as a convenient method for obtaining isoquinoline alkaloids and their closest structural and synthetic analogs [1-4]. We have previously shown that the acylation of esters of 3,4-dialkoxyphenylacetic acids gives 2-benzopyrylium salts and the corresponding 1-alkyl-3-oxo-6,7-dimethoxy-4H-isoquinolines [1]. In a continuation of these investigations, we have studied the acylation of the phenacyl ester of homoveratric acid (I) with aliphatic acid anhydrides in the presence of 70% $HClO_4$. It was shown that, in this case, 1-alkyl-3-phenacyloxy-6,7-dimethoxy-2-benzopyrylium perchlorates are formed in high yields (78%) via the scheme



I IIa.b IIIa,b

II, III a R = CH_3, b R = C_6H_5

The IR spectra of the perchlorates obtained have intense absorption bands at 1710 (ν C=O), 1630, 1540 (ν of the pyrylium cation), 1220 (ν OCH_3), and 1090 cm^{-1} (ν ClO_4^-).

When II is treated with ammonium hydroxide, the phenacyloxy group is hydrolytically cleaved, and, instead of the expected 1-alkyl-3-phenacyloxy-6,7-dimethoxyisoquinolines, 1-alkyl-3-oxo-6,7-dimethoxy-4H-isoquinolines (IIIa, b), which were previously obtained by the action of ammonia on 1-alkyl-3,6,7-trimethoxy-2-benzopyrylium perchlorates [1], were isolated.

Attempts to synthesize 2-benzopyrylium salts and isoquinolines containing aryl and aralkyl substituents by the acylation of esters of homoveratric acid and its phenacyl derivatives with acid chlorides in the presence of $AlCl_3$ did not give good results.

In order to obtain isoquinoline bases with aryl and aralkyl groups in the 1 position of the isoquinoline ring, we therefore studied the acylation of homoveratric acid with aromatic acids in the presence of polyphosphoric acid (PPA). We found that, under these conditions, the acyl group is directed to the ortho po-

*See [9] for communication X.

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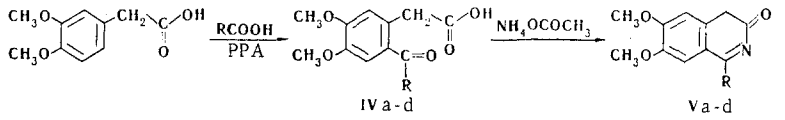
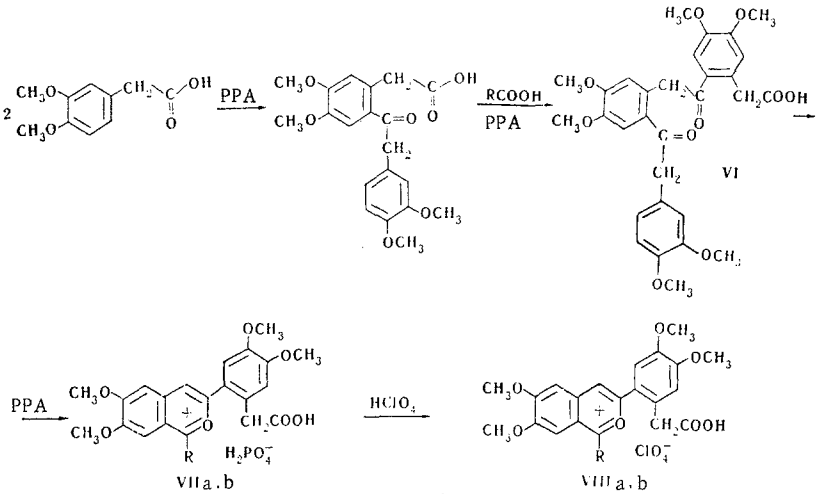
sition relative to the carboxymethylene group, which leads to the formation of the corresponding keto acids (IV) in high (90-95%) yields. In the presence of PPA, homoveratric acid is also readily acylated by acetic acid.



IV, V a R=CH_3, b R=$C_6H_5CH_2$, c R=$(p\text{-}CH_3O)C_6H_5CH_2$, d R=$3,4(CH_3O)_2C_6H_3CH_2$

The structures of the keto acids synthesized were confirmed by IR spectroscopy. The spectra contain absorption bands of carboxyl and carbonyl groups (1700-1720 and 1660-1670 cm^{-1}).

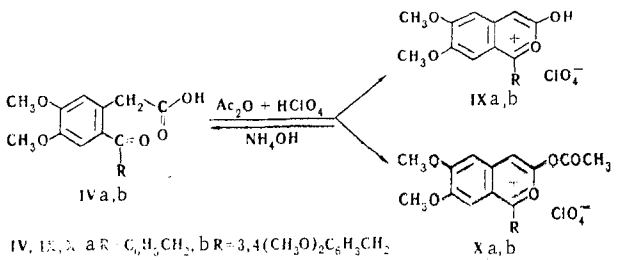
The recrystallization of IVb, d from benzene yielded insoluble products, which, from the results of an investigation of them, proved to be 1-aralkyl-3-(2-carboxymethylene-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium phosphates (VII). In these cases, the reaction proceeds as follows: the 2-homoveratroylhomoveratric acid formed as a result of autoacylation is again subjected to acylation by phenylacetic (a) or homoveratric (b) acids to give VIa, b, which, under the influence of PPA, cyclize to 2-benzopyrylium phosphates (VII). Phosphates VII are readily converted to perchlorates VIII by treatment with perchloric acid in glacial acetic acid.



VII, VIII a R=$C_6H_4CH_2$; b R=$3,4(CH_3O)_2C_6H_3CH_2$

The presence of absorption bands at 1700-1720 (ν C=O) and at 1600-1630 and 1510-1560 cm^{-1} (ν of the pyrylium cation) in the IR spectra of perchlorates VIII confirms the structures of the compounds obtained.

Keto acids IV in acetic anhydride solutions in the presence of perchloric acid form good yields of 1-aryl-3-acetoxy-6,7-dimethoxy-2-benzopyrylium perchlorates.



IV, IX, X a R=$C_6H_5CH_2$, b R=$3,4(CH_3O)_2C_6H_3CH_2$

It was assumed that the reaction products may be either 1-aryl-3-hydroxy-6,7-dimethoxy-2-benzopyrylium perchlorates (IX) or 1-aryl-3-acetoxy-6,7-dimethoxy-2-benzopyrylium perchlorates (X). The second structure (X) was favored on the basis of a study of the IR spectra (the absence of ν OH at 3500-3600 cm^{-1} and the presence of ν OCOR at 1720-1730 cm^{-1}).

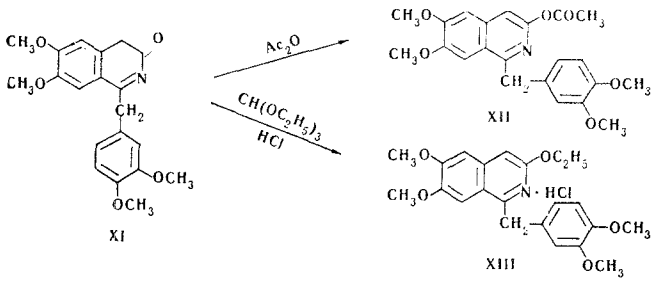
In order to obtain biologically active compounds, we studied the possibility of the cyclization of the keto acids (IV) to compounds of the isoquinoline series (V). It was shown that when keto acids IV are re-

fluxed with anhydrous ammonium acetate in glacial acetic acid, they cyclize readily to 1-aryl(aralkyl)-3-oxo-6,7-dimethoxy-4H-isoquinolines (V).

It is known that the existing methods for the preparation of isoquinoline bases are based on the condensation of homoveratrylamine or ω-aminoacetoveratroin with homoveratroyl chloride [5] and also on the reaction of the extremely accessible 2-benzopyrylium salts [1-4] with ammonia. Our proposed method for the preparation of substituted isoquinoline bases differs substantially from the above methods and makes it possible to prepare the hard-to-obtain 3-oxo-4H-isoquinolines in high yields (85-96%). In particular, this method was used to obtain 1-(3,4-dimethoxybenzyl)-3-oxo-6,7-dimethoxy-4H-isoquinoline (3-ketopapaverine) [6].

The IR spectra of the isoquinolines obtained contain an intense absorption band at 1640-1670 (ν C=O group), 1600 and 1560 cm^{-1} (ν of aromatic rings), 1220-1240, and 1010-1040 cm^{-1} (ν OCH_3).

In a study of the properties of the isoquinoline bases, it was observed that the keto group readily undergoes electrophilic addition. Thus 3-acetoxypapaverine (XII) was isolated when 3-ketopapaverine (XI) was heated in acetic anhydride.



The IR spectrum of 3-acetoxypapaverine displays a strong absorption band at 1750 cm^{-1} (ν $OCOCH_3$). This compound cannot be obtained from 1-(3,4-dimethoxybenzyl)-3-acetoxy-6,7-dimethoxy-2-benzopyrylium perchlorate, since it decomposes to the starting keto acid on treatment with ammonium hydroxide.

Alkylation also proved to be acceptable for isoquinolones V. Thus 3-ketopapaverine in ethyl orthoformate in the presence of concentrated mineral acids (HCl and $HClO_4$) formed 3-ethoxypapaverine salts (XIII). The papaverine derivatives obtained were previously unknown. Attempts to obtain papaverine (by reduction with zinc dust in vacuo) [7] and other derivatives – 3-chloropapaverine (with PCl_5, $POCl_3$, and $SOCl_2$) and 3-methylpapaverine (via the Grignard reaction) – did not give positive results.

EXPERIMENTAL

Phenacyl Ester of Homoveratric Acid (I). This compound was obtained in 53% yield as colorless crystals with mp 64° (from n-butanol) via the method in [8] from homoveratric acid and phenacyl bromide. Found: C 68.6; H 5.6%. $C_{18}H_{18}O_5$. Calculated: C 68.8; H 5.7%.

1-Methyl-3-phenacyloxy-6,7-dimethoxy-2-benzopyrylium Perchlorate (IIa). A total of 0.3 ml of 70% $HClO_4$ (0.0025 mole) was added dropwise to a solution of 0.79 g (2.5 mmole) of I in 3 ml of acetic anhydride. Cooling of the resulting mixture precipitated 0.86 g (78%) of yellow crystals with mp 193° (from glacial acetic acid). IR spectrum, ν, cm^{-1}: 1712 strong (s), 1630 s, 1542 medium (m), 1218 s, 1095 s, 995 m. Found: C 54.4; H 4.7; Cl 7.6%. $C_{20}H_{19}O_9Cl$. Calculated: C 54.7; H 4.3; Cl 7.9%.

1-Ethyl-3-phenacyloxy-6,7-dimethoxy-2-benzopyrylium Perchlorate (IIb). This compound was similarly obtained in 78% yield with mp 175° (dec., from glacial acetic acid). IR spectrum, ν, cm^{-1}: 1710 s, 1628 s, 1534 weak (w), 1265 m, 1226 s, 1090 s, and 1008 w. Found: C 55.9; H 4.8; Cl 7.8%. $C_{21}H_{21}O_9Cl$. Calculated: C 55.7; H 4.6; Cl 7.8%.

2-Acetylhomoveratric Acid (IVa). A mixture of 1 g (5 mmole) of homoveratric acid, 1 ml of glacial acetic acid, and 10 g of PPA was heated at 90° for 10 min. The solution was diluted with cold water and allowed to stand in a refrigerator to crystallize. The precipitate was removed by filtration and dried. An additional amount of the keto acid was isolated from the mother liquor by bringing the pH of the solution to 7 to give an overall yield of 0.9 g (75%) of a product with mp 174° (from benzene). IR spectrum, ν, cm^{-1}: 1718 s, 1635 s, 1602 s, 1562 s, 1272 s, 1222 w, 1064 s, and 1028 m. Found: C 60.9; H 5.9%. $C_{12}H_{14}O_5$. Calculated: C 60.5; H 5.9%.

2-Phenylacetylhomoveratric Acid (IVb). A mixture of 1.96 g (10 mmole) of homoveratric acid, 1.5 g (11 mmole) of phenylacetic acid, and 35 g of polyphosphoric acid was heated at 90-95° for 10-15 min. It was then diluted with water (~100 ml) and allowed to stand in a refrigerator for crystallization. The precipitate was removed by filtration to give 3 g of crude material, which was purified by crystallization from benzene to give 2.55 g (81%) of colorless crystals with mp 141°. IR spectrum, ν, cm^{-1}: 1707 s, 1660 m, 1608 m, 1572 m, 1530 s, 1236 m, and 1022 m. Found: C 68.4; H 5.6%. $C_{18}H_{18}O_5$. Calculated: C 68.8; H 5.7%.

2-(p-Methoxyphenyl)acetylhomoveratric Acid (IVc). This compound was obtained as above in 97% yield as colorless crystals with mp 146° (from benzene). IR spectrum, ν, cm^{-1}: 1706 s, 1676 s, 1610 s, 1574 s, 1522 s, 1240 s, and 1018 m. Found: C 66.1; H 5.6%. $C_{19}H_{20}O_6$. Calculated: C 66.3; H 5.8%.

2-(3,4-Dimethoxyphenylacetyl)homoveratric Acid (IVd) [6]. A 2-g (10.2 mmole) sample of homoveratric acid was heated with 20 g of polyphosphoric acid at 95-98° for 13 min. The hot mixture was poured into 100 ml of ice water, and the mixture was allowed to stand for crystallization to give 1.81 g (95%) of colorless crystals with mp 153° (from propanol). IR spectrum, ν, cm^{-1}: 1704 s, 1608 m, 1520 s, 1237 s, and 1033 s. Found: C 63.7; H 6.0%. $C_{20}H_{22}O_7$. Calculated: C 64.2; H 5.9%.

1-Phenyl-3-(2-carboxymethylene-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium Perchlorate (VIIIa). A 3-g sample of crude IVb was refluxed in 5 ml of benzene, and the insoluble material was removed by filtration and washed with benzene and ether to give 0.45 g of phosphate VIIa. The product was dissolved in 3 ml of glacial acetic acid, the solution was heated to the boiling point, and 0.5 ml (5 mmole) of 70% $HClO_4$ was added dropwise to it. The mixture was then allowed to stand for crystallization. The orange crystalline precipitate was removed by filtration to give 0.35 g (6.1% based on homoveratric acid) of a product with mp 260° (dec., from glacial acetic acid–nitromethane). IR spectrum, ν, cm^{-1}: 1720 m, 1630 s, 1601 m, 1578 w, 1500 s, 1268 s, 1236 m, 1100 s, 1008 m. Found: C 58.6; H 4.5; Cl 5.8%. $C_{28}H_{27}O_{11}Cl$. Calculated: C 58.5; H 4.7; Cl 6.2%.

1-(3,4-Dimethoxybenzyl)-3-(2-carboxymethylene-3,4-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium Perchlorate (VIIIb). This compound was similarly obtained in 3.6% yield and had mp 245° (dec., from glacial acetic acid). IR spectrum, ν, cm^{-1}: 1702 s, 1600 s, 1530 w, 1512 w, 1270 s, 1225 s, 1083 s, and 1030 m. Found: C 56.5; H 5.0; Cl 5.9%. $C_{30}H_{27}O_{11}Cl$. Calculated: C 56.7; H 4.9; Cl 5.6%.

1-(3,4-Dimethoxybenzyl)-3-acetoxy-6,7-dimethoxy-2-benzopyrylium Perchlorate (Xb). A total of 0.5 ml of 72% $HClO_4$ (5 mmole) was added dropwise to 1 g (2.7 mmole) of homoveratrylhomoveratric acid (IVd) in 6 ml (60 mmole) of acetic anhydride. The mixture was cooled to precipitate 0.7 g (54%) of yellow crystals with mp 249° (from nitromethane). IR spectrum, ν, cm^{-1}: 1728 s, 1610 s, 1547 m, 1520 w, 1265 w, 1227 s, 1100 s, 1040 w, and 1010 w. Found: C 52.6; H 4.9; Cl 7.0%. $C_{22}H_{23}O_{11}Cl$. Calculated: C 52.9; H 4.6; Cl 7.1%.

1-Benzyl-3-acetoxy-6,7-dimethoxy-2-benzopyrylium Perchlorate (Xa). This compound was similarly obtained in 74% yield and had mp 168° (dec., from nitromethane). IR spectrum, ν, cm^{-1}: 1718 s, 1610 s, 1516 s, 1270 s, 1232 m, 1098 s, 1016 w. Found: C 55.1; H 4.6; Cl 7.8%. $C_{20}H_{19}O_9Cl$. Calculated: C 54.7; H 4.3; Cl 8.1%.

1-Benzyl-3-oxo-6,7-dimethoxy-4H-isoquinoline (Vb). A mixture of 0.5 g (1.6 mmole) of 2-phenylacetylhomoveratric acid, 1.3 g (14 mmole) of anhydrous ammonium acetate, and 7 ml of glacial acetic acid was refluxed for 1.5 h. The cooled solution was poured into water, and the resulting precipitate was removed by filtration to give 0.4 g (85%) of yellow crystals with mp 232° (dec., from ethanol). IR spectrum, ν, cm^{-1}: 1660 s, 1566 s, 1490 s, 1232 s, 1011 m. Found: C 73.4; H 6.0; N 4.6%. $C_{18}H_{17}NO_3$. Calculated: C 73.2; H 5.8; N 4.7%.

1-(p-Methoxybenzyl)-3-oxo-6,7-dimethoxy-4H-isoquinoline (Vc). This compound was similarly obtained in 97% yield and had mp 220° (dec., from alcohol). IR spectrum, ν, cm^{-1}: 1643 s, 1560 s, 1500 s, 1225 m, and 1015 s. Found: C 70.5; H 5.7; N 4.4%. $C_{19}H_{19}NO_4$. Calculated: C 70.2; H 5.8; N 4.3%.

1-(3,4-Dimethoxybenzyl)-3-oxo-6,7-dimethoxy-4H-isoquinoline [6] (Vd). This compound was similarly obtained in 85% yield as yellow crystals with mp 232° (from nitromethane). IR spectrum, ν, cm^{-1}: 1670 s, 1595 w, 1520 w, 1240 m, and 1040 m. Found: C 67.7; H 6.1; N 3.7%. $C_{20}H_{21}NO_5$. Calculated: C 67.7; H 5.9; N 3.9%.

1-(3,4-Dimethoxybenzyl)-3-acetoxy-6,7-dimethoxyisoquinoline (3-Acetoxypapaverine) (XII). A mixture of 0.5 g (1.4 mmole) of XI and 4 ml of acetic anhydride was heated on a water bath at 60-70° for 30 min. The mixture was cooled and diluted with water, and the precipitate was removed by filtration and

dried to give 0.52 g (94%) of colorless crystals with mp 71° (from alcohol). IR spectrum, ν, cm^{-1}: 1750 s, 1620 w, 1600 w, 1570 m, 1520 s, 1255 s, 1220 m, and 1030 s. Found: C 66.1; H 5.9%. $C_{22}H_{23}NO_6$. Calculated: C 66.5; H 5.8%.

Complex of 1-Methyl-3-acetoxy-6,7-dimethoxyisoquinoline with Acetic Anhydride. A mixture of 1 g (4.6 mmole) of 1-methyl-3-oxo-6,7-dimethoxy-4H-isoquinoline (Va) [1] and 3 ml (28 mmole) of acetic anhydride was heated for 30 min. Cooling of the mixture precipitated 0.8 g (66%) of colorless crystals with mp 114° (from acetic anhydride). IR spectrum, ν, cm^{-1}: 1755 s, 1710 s, 1620 m, 1570 m, 1510 s, 1260 m, 1200 m, 1170 m, 1140 m, and 1080 m. Found: C 59.8; H 5.9%. $C_{18}H_{21}NO_7$. Calculated: C 59.5; H 5.8%.

1-(3,4-Dimethoxybenzyl)-3-ethoxy-6,7-dimethoxyisoquinoline Hydrochloride (XIII). Concentrated HCl (1 ml) was added dropwise to a mixture of 0.5 g (1.4 mmole) of XI and 4 ml of ethyl orthoformate to precipitate 0.55 g (90%) of a colorless precipitate with mp 213° (from methanol). IR spectrum, ν, cm^{-1}: 1640 s, 1600 w, 1540 w, 1500 s, 1260 s, 1220 m, 1140 m, and 1020 s. Found: C 60.2; H 6.3; Cl 8.3%. $C_{22}H_{25}NO_5 \cdot HCl \cdot H_2O$. Calculated: C 60.3; H 6.4; Cl 8.1%.

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