2-BENZOPYRYLIUM SALTS

XXIII.* SYNTHESIS OF SUBSTITUTED 6-OXODIBENZO[*a*,g]QUINOLIZINIUM SALTS AND THEIR ESTERS

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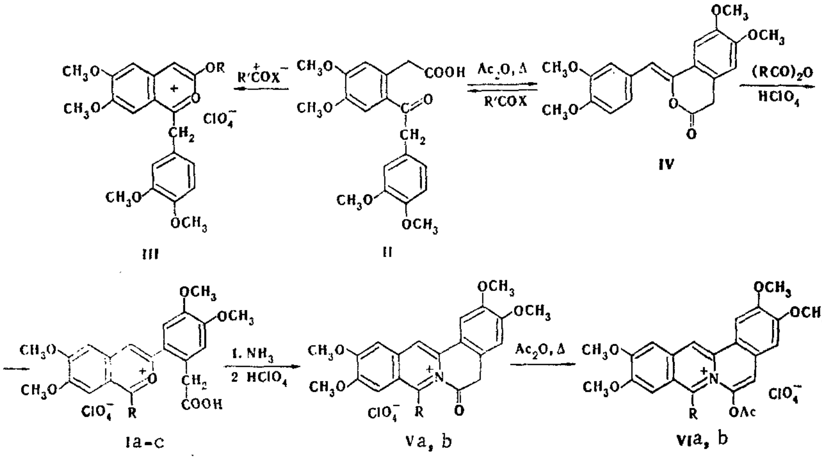
The synthesis of berberine analogs — substituted dibenzo[*a*,g]quinolizinium salts — was worked out on the basis of 2-benzopyrylium salts.

It has been recently demonstrated [2] that quinolizinium derivatives [3] related to the alkaloid berberine have strong antileukemia activity; this has stimulated the publication of several new methods for the synthesis of compounds of this type [4-7].

2-Benzopyrylium salts of the I type are extremely promising intermediates for the synthesis of dibenzo-[*a*,g]quinolizinium salts and analogs of berberine alkaloids. Two such salts [$R = CH_2C_6H_5$ or $3,4\text{-}(CH_3O)_2C_6H_3$] were recently obtained as secondary products in the acylation of homoveratric acid in 6 and 3% yields, respectively [8]. The reaction in this case undoubtedly proceeds through the intermediate formation of keto acid II. However, all of our attempts to obtain salts I by direct acylation of keto acid II led only to 3-hydroxy-(acyloxy)-2-benzopyrylium salts (III) [8] or to the starting acid.

In a previous paper [1] we showed that carboxy-2-benzopyrylium salts can be obtained by acylation of veratrylidene phthalide, a cyclic enol acetate.

Isochromenone IV, which is readily obtained [9] by dehydration of keto acid II, is also a cyclic vinyl ester, and we found that similar acylation methods are also applicable to it.



I a $R = CH_3$; b $R = C_2H_5$; c $R = C_3H_7$; III $R = H$, R'CO

Thus brightly colored high-melting salts Ia-c are formed in 30-40% yields in the acylation of IV with aliphatic acid anhydrides in the presence of 70% $HClO_4$. A mixed anhydride with the carboxyl group formed in salt I (ν_{CO} 1800 cm^{-1}) is evidently obtained initially in the acylation of IV with acetic anhydride; this product then undergoes hydrolysis when it is refluxed with 70% $HClO_4$ in nitromethane. The IR spectrum of salt Ia, like the spectra of Ib, c, contains absorption bands at 3500 and 1700 cm^{-1} (free carboxyl group) and a number of bands characteristic for 2-benzopyrylium salts [8].

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*See [1] for communication XXII.

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Integration of the PMR spectrum of salt Ia indicates the presence of a methylene group at 3.6-3.8 ppm covered by the absorption of four methoxy groups.

It was found that the formation of a new ring occurs along with replacement of the oxygen heteroatom by nitrogen in the reaction of salts Ia, b with a saturated alcohol solution of ammonia under pressure or when ammonia is passed through a suspension of these salts in refluxing alcohol. The easily identifiable perchlorates were isolated after dilution of the reaction mixture with water and acidification with 70% $HClO_4$.

The PMR spectrum of Va, which indicates the presence of five aromatic protons (four aromatic protons for benzo[c]phenanthridine), makes it possible to make a choice between the quinolizinium and alternative benzo[c]phenanthridine structures in favor of the former.

It is interesting to note that the signal of a methylene group in the PMR spectrum of Va is shifted to strong field and shows up separately from the signals of the methoxy groups.

The IR spectra of Va, b contains absorption at 1665 cm^{-1} (amide carbonyl), which is replaced by a strong absorption band at 1785 cm^{-1} (ester) after they are refluxed briefly in acetic anhydride.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord 711R spectrometer. The PMR spectra of CF_3COOH solutions of the compounds at 20 deg C were recorded with a Tesla spectrometer with hexamethyldisiloxane as the internal standard.

1-Methyl-3-(2-methylenecarboxy-3,4-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium Perchlorate (Ia). A 0.1-ml sample of 70% $HClO_4$ was added with cooling to 0.36 g (0.001 mole) of isochromenone IV in 3 ml of acetic anhydride, after which the mixture was heated cautiously at 50 deg C for 10 min. It was then cooled, and ether was added until crystallization commenced. After 24 h, the precipitated salt was removed by filtration, washed with ether, dried, and dissolved by heating in the minimum volume of nitromethane containing two to three drops of 70% $HClO_4$. The solution was refluxed for 2 h, after which it was cooled, and salt Ia was precipitated with ether to give 0.2 g (40%) of orange crystals with mp 232 deg C (from acetic acid). IR spectrum: 3500, 1710, 1580, 1500, and 1080 cm^{-1}. PMR spectrum, δ: 2.90 (s, CH_3); 3.63, 3.80, 3.88 (CH_2 and four OCH_3); 6.78-7.78 ppm (m, 5H). Found: C 52.8; H 4.6; Cl 7.2%. $C_{22}H_{23}ClO_{11}$. Calculated: C 52.9; H 4.6; Cl 7.1%.

1-Ethyl-3-(2-methylenecarboxy-3,4-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium Perchlorate (Ib). A 0.1-ml sample of 70% $HClO_4$ was added with cooling to 0.36 g (0.001 mole) of isochromenone IV in 3 ml of freshly distilled propionic anhydride. After 15 min, the mixture was diluted with a large amount of ether, and the liberated oil was separated by decantation and washed several times with ether. It was then treated with 2 ml of alcohol and two to three drops of 70% $HClO_4$, and ether was added until crystallization commenced. The mixture was allowed to stand overnight in the cold, after which it was worked up to give 0.15 g (30%) of orange crystals with mp 207 deg C (from acetic acid). IR spectrum: 3500, 1705, 1600, 1530, 1500, and 1090 cm^{-1}. Found: C 53.6; H 4.9; Cl 6.9%. $C_{23}H_{25}ClO_{11}$. Calculated: C 53.8; H 4.9; Cl 6.9%.

1-Propyl-3-(2-methylenecarboxy-3,4-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium Perchlorate (Ic). This compound, with mp 146 deg C (from acetic acid), was similarly obtained in 32% yield. Found: C 54.7; H 5.0; Cl 6.7%. $C_{24}H_{27}ClO_{11}$. Calculated: C 54.6; H 5.1; Cl 6.7%. IR spectrum: 3500, 1705, 1590, 1535, 1505, 1080 cm^{-1}.

8-Methyl-2,3,10,11-tetramethoxy-5,6-tetrahydro-6-oxodibenzo[*a*,g]-quinolizinium Perchlorate (Va). A) A suspension of 0.5 g (0.001 mole) of salt Ia in 5 ml of ethanol in an ampul was cooled to −10 deg C and saturated with ammonia. The sealed ampul was then heated at 100 deg C for 6 h, after which it was cooled, and the resulting precipitate was removed by filtration and purified by recrystallization from ethanol containing three to four drops of 70% $HClO_4$. Workup gave colorless acicular crystals with mp 258 deg C in quantitative yield. IR spectrum: 1665, 1635, 1595, 1500, 1250, and 1080 cm^{-1}. PMR spectrum: 2.80 (s, CH_3), 3.37 (s, CH_2); 3.55, 3.60 (two OCH_3); 3.80 (s, two OCH_3); 6.80-7.65 (m, 5H) ppm. Found: C 55.1; H 4.6; N 3.0; Cl 7.6%. $C_{22}H_{22}NClO_9$. Calculated: C 55.0; H 4.6; N 2.9; Cl 7.5%.

B) A product identical to the product described in method A with respect to its IR spectrum and melting point was obtained in quantitative yield by passing ammonia through a suspension of salt Ia in refluxing ethanol in the course of 30 min, cooling the solution, diluting it with water, and adding excess 70% $HClO_4$.

8-Ethyl-2,3,10,11-tetramethoxy-5,6-tetrahydro-6-oxobenzo[*a*,g]quinolizinium Perchlorate (Vb). This compound, with mp 166-168 deg C (from ethanol), was similarly obtained in quantitative yield. IR spectrum:

1660, 1630, 1590, 1500, 1260, and 1085 cm^{-1}. Found: C 55.9; H 4.9; N 2.8; Cl 7.2%. $C_{23}H_{24}NClO_9$. Calculated: C 55.9; H 4.9; N 2.8; Cl 7.2%.

8-Methyl-2,3,10,11-tetramethoxy-6-acetoxydibenzo[*a*,g]quinolizinium Perchlorate (VIa). A 0.5-g (0.001 mole) sample of salt Va was refluxed for 10 min in 3 ml of acetic anhydride, during which a precipitate formed. The mixture was cooled, and the precipitate was removed by filtration, washed with ether, and dried to give 0.43 g (88%) of orange-red crystals with mp 248 deg C (from acetic acid). IR spectrum: 1785, 1600, 1545, 1500, and 1080 cm^{-1}. Found: C 55.4; H 4.5; N 2.7; Cl 6.8%. $C_{24}H_{24}NClO_{10}$. Calculated: C 55.2; H 4.6; N 2.7; Cl 6.6%.

8-Ethyl-2,3,10,11-tetramethoxy-6-acetoxydibenzo[*a*,g]quinolizinium Perchlorate (VIb). This compound, with mp 260-262 deg C (from acetic acid), was similarly obtained in 85% yield from salt Vb. IR spectrum: 1785, 1595, 1540, 1490, and 1090 cm^{-1}. Found: C 56.9; H 4.6; N 2.7; Cl 6.9%. $C_{25}H_{26}NClO_{10}$. Calculated: C 56.7; H 4.8; N 2.6; Cl 6.7%.

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PYRYLIA[2,3-d]PYRIMIDINE SALTS

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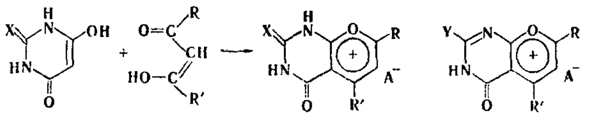
The condensation of 2-amino- and 2-methylthio-4,6-dihydroxypyrimidines and barbituric and thiobarbituric acids with β-diketones in strong acids leads to pyrylia[2,3-d]pyrimidine salts, which on treatment with ammonia or aniline are converted to pyrido[2,3-d]pyrimidines or to 8-phenylpyrido[2,3-d]pyrimidinium salts, respectively.

The reaction of 4-hydroxypyrimidines that have electron-donor substituents in the 2 and 6 positions with β-keto acids and malonic acids and their derivatives leads to pyrano[2,3-d]pyrimidinones [1, 2]. In the present research we studied the condensation of 2-amino- and 2-methylthio-4,6-dihydroxypyrimidines and barbituric and thiobarbituric acids with β-diketones in strong acids. As a result we obtained the previously unknown pyrylia[2,3-d]pyrimidine salts (I and II). The latter, which have a methyl substituent in the pyrylium ring, form blue polymethine dyes when they are heated in acetic anhydride with p-dimethylaminobenzaldehyde or ethyl orthoformate.



I II

X=O, S; R, R'=CH_3, C_6H_5; A=ClO_4^-, $H_2PO_4^-$, CF_3COO^-; Y=NH_2, SCH_3

Compounds with methyl groups in the 5 and 7 positions initially react with p-dimethylaminobenzaldehyde to give a dye involving the methyl group in the 5 position; this was proved by the PMR spectra, in which the signal of the unchanged methyl group in the 7 position (2.53 ppm) is observed. The assignment of the signals of the

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