

2-BENZOPYRYLIUM SALTS

X.* REACTION WITH NITROGEN BASES AND AROMATIC ALDEHYDES

G. N. Dorofeenko, E. I. Sadekova,
and V. M. Goncharova

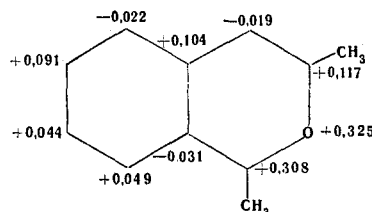
UDC 547.814+547.833

The properties of 1,3-dimethyl-6,7-dialkoxy-2-benzopyrylium salts were studied. The heterocyclic oxygen atom is readily replaced by nitrogen by reaction of the 2-benzopyrylium salts with primary amines, hydrazine, phenylhydrazine, glycine ethyl ester, and hydroxylamine; reaction with secondary amines leads to naphthalene derivatives. The activities of the methyl groups in the 1 and 3 positions of the heterocyclic ring are compared.

It is well known that monocyclic pyrylium salts are highly reactive: they form various compounds of the heterocyclic and aromatic series on reaction with nucleophilic reagents [1]. At the same time, the properties and reactions of 2-benzopyrylium salts remain virtually unstudied except for the reaction with ammonia, which leads to the formation of the corresponding isoquinolines [2-5] or alkaloids of the isoquinoline series [6].

In order to fill this gap we have investigated the chemical properties of 2-benzopyrylium salts in the case of condensation of 1,3-dimethyl-6,7-dimethoxy-2-benzopyrylium perchlorate (I) with several primary (methylamine, aniline, p-phenylenediamine, and glycine ethyl ester) and secondary (diethylamine, morpholine) amines, hydrazine derivatives, hydroxylamine, and aromatic aldehydes.

According to the results of quantum-mechanical calculations the positive charge in the 1 position of 2-benzopyrylium salts is higher by a factor of approximately three than in the 3 position, as is apparent from the following molecular diagram†:

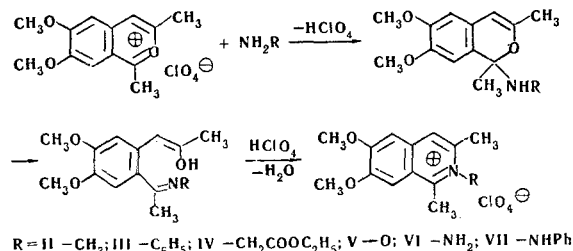


In accordance with this, attack on the 2-benzopyrylium salts by nucleophilic reagents should occur at the site with the highest electron deficit, i.e., the 1 position of the heterocycle.

We have shown that the reaction of I with primary amines and hydrazine derivatives proceeds via the following scheme:

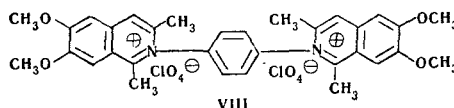
*For Communication IX, see [6].

†The quantum-mechanical calculation of the 2-benzopyrylium cation was carried out by V. I. Minkin using the MO LCAO method.



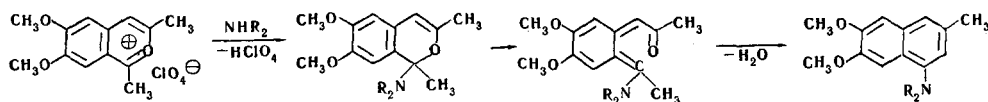
Quaternary isoquinoline salts II and III are formed in high yields in the reaction of I with primary amines.

Reaction of I with p-phenylenediamine proceeds similarly at both amino groups; 1,4-diphenylenebis-2,2'-(1,3-dimethyl-6,7-dimethoxy)isoquinolinium diperchlorate (VIII) is formed in the process:



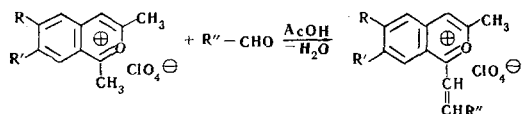
2-Benzopyrylium salt I, like monocyclic pyrylium salts [4], reacts readily with glycine ethyl ester to form quaternary salt IV in high yields.

Reaction of salt I with hydroxylamine proceeds in a manner similar to the reaction with the common pyrylium salts [7] to form an intermediate product - 2-hydroxylisoquinoline perchlorate - which on treatment with a solution of alkali gives the N-oxide (V) of the substituted isoquinoline. The reaction of the pyrylium salts with secondary amines, which leads to the synthesis of aromatic amino compounds [1, 8], is of considerable interest. In this connection, one might expect that dialkylamines of the naphthalene series, which are difficult to synthesize by other methods, should be obtained on reaction of perchlorate I with secondary amines. Investigation of the reaction of I with morpholine and diethylamine confirmed this assumption.



It turned out that 1-(N-morpholino)-3-methyl-6,7-dimethoxynaphthalene was obtained in quantitative yield on brief heating of the starting materials in ethanol, while 1-diethylamino-3-methyl-6,7-dimethoxynaphthalene is formed in 59% yield since another nitrogen-containing product is obtained along with it, the structure of which was not established.

In order to study the reactivity of the methyl group in the 2-benzopyrylium salt we studied the condensation of I and 1,3-dimethyl-6,7-methylenedioxy-2-benzopyrylium perchlorate (IX) with various aldehydes of the aromatic and heterocyclic series. It turned out that the reaction of 2-benzopyrylium salts with the aldehydes proceeded just as readily as in the case of α - and γ -alkylpyrylium salts with various structures [9] via the scheme



It could be assumed that the presence of active methyl groups in the 1 and 3 positions might lead to the formation of a mixture of two products as well as condensation products containing two styryl substituents. However, only one product (as shown by chromatography) is always isolated as a result of this reaction, viz., the 2-benzopyrylium salt with a styryl substituent in the 1 position. These data are also satisfactorily confirmed by the above-presented results of quantum-mechanical calculation, according to which the methyl group in the 1 position should have considerably higher activity than the methyl group in the 3 position of the heterocycle.

In fact, only the starting pyrylium salt was isolated in an attempt to condense 1-phenyl-3-methyl-6,7-dimethoxy-2-benzopyrylium perchlorate with benzaldehyde in glacial acetic acid; this is also proof of the inertness of the methyl group in the 3 position.

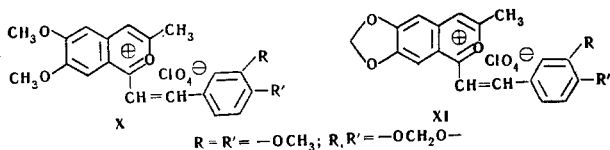
TABLE 1. 1-Styryl-Substituted 2-Benzopyrylium Salts

R'	R''	R'''	mp °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	Cl	C	H	Cl	
OCH ₃	OCH ₃	3',4'-Dimethoxyphenyl	306	C ₂₂ H ₂₂ ClO ₉	55,80	5,26	8,02	56,59	4,93	7,60	54
OCH ₃	OCH ₃	3',4'-Methylenedioxyphenyl	298— —302	C ₂₁ H ₁₉ ClO ₉	55,66	4,31	7,90	56,93	4,22	7,88	53
OCH ₃	OCH ₃	p-Hydroxy-m-methoxyphenyl	296 (dec.)	C ₂₁ H ₂₁ ClO ₉	54,99	4,91	7,74	55,69	4,64	7,84	50
OCH ₃	OCH ₃	o-Hydroxy-m-methoxyphenyl	267	C ₂₁ H ₂₁ ClO ₉	56,32	4,33	8,58	55,69	4,64	7,84	46
OCH ₃	OCH ₃	m-Nitrophenyl	272— —273	C ₂₀ H ₁₈ ClNO ₉	52,94	4,08	7,26	53,16	3,77	7,86	55
OCH ₃	OCH ₃	Styryl	252	C ₂₂ H ₂₁ ClO ₇	62,07	5,05	7,97	61,40	4,85	8,20	48
OCH ₃	OCH ₃	Thienyl*	>280 (dec.)	C ₁₈ H ₁₇ ClISO ₇ *	51,92	4,15	8,60	52,36	4,12	8,60	82
OCH ₂ O		3',4'-Dimethoxyphenyl	292	C ₂₁ H ₁₉ ClO ₉	55,38	4,15	7,18	55,94	4,22	7,51	55
OCH ₂ O		3',4'-Methylenedioxyphenyl	310 (dec.)	C ₂₀ H ₁₅ ClO ₉	55,34	3,65	8,24	55,23	3,45	8,17	61
OCH ₂ O		Phenyl	306— —308	C ₁₉ H ₁₅ ClO ₇	58,46	4,24	8,57	58,38	3,84	9,09	55
OCH ₂ O		m-Nitrophenyl	278— —280	C ₁₉ H ₁₄ ClNO ₉	52,22	3,52	7,79	52,35	3,22	8,15	71
OCH ₂ O		α-(5'-Bromofuryl)	289 (dec.)	C ₁₇ H ₁₂ BrClO ₈	44,85	2,63	24,71	44,30	2,52	25,29	78

*Found %: S 7.31. Calculated %: S 7.75.

It should also be noted that, according to the literature [10], 1,3-dimethylisoquinoline and its quaternary salt form only 1-styryl-substituted isoquinolines on reaction with aldehydes.

The 1-styryl-substituted 2-benzopyrylium salts obtained with methoxy and methylenedioxy groups in the benzene ring attached to the heterocycle by a vinyl group (X, XI) are close structural analogs of isoquinoline alkaloids and are readily converted to isoquinolinium salts on heating of I with methylamine in acetone:



The structures of the compounds obtained were confirmed from the IR spectroscopic data. Thus the absorption bands at 1620 and 1550 cm^{-1} , characteristic for quaternary isoquinoline derivatives, and at 1600, 1580, and 1500 cm^{-1} , specific for aromatic systems, are present in the spectra of all the isoquinolinium salts.

The IR spectra of the 1-(N-morpholino)- and 1-diethylamino-3-methyl-6,7-dimethoxynaphthalenes are characterized by intense vibrational bands at 1602 and 1580 cm^{-1} and still more intense bands at 1500 and 1450 cm^{-1} ; this is typical for the stretching vibrations of condensed benzene rings [11].

The presence in the IR spectra of the products of condensation of 2-benzopyrylium salts with aldehydes of groups of bands in the intervals 1656-1648, 1584-1539, 1468-1418, 1280-1250, and 1050-1000 cm^{-1} attests to the fact that these compounds are 2-benzopyrylium salts [3]. However, in this case the frequencies of the symmetrical valence vibrations of the hetero ring (the 8a band in the Wilson classification [12]) are shifted by 8-14 cm^{-1} as compared with the analogous frequencies of the 1,3-dimethyl-2-benzopyrylium salts. Thus the introduction of styryl substituents into the 1 position of 2-benzopyrylium salts leads to a long-wave shift of the 8a band.

EXPERIMENTAL

1,3-Dimethyl-6,7-dimethoxy-2-benzopyrylium perchlorate (I) and 1,3-dimethyl-6,7-methylenedioxy-2-benzopyrylium perchlorate were obtained by acetylation of 3,4-dimethoxyphenylacetone [2].

1,2,3-Trimethyl-6,7-dimethoxyisoquinolinium Perchlorate. Methylamine (0.2 ml of a 20% solution) was added to a suspension of 0.1 g of I in acetone, the mixture was refluxed for 5 min, and the precipitated pale-yellow crystals were filtered to give 60% of a product with mp 261° (acetone-alcohol). IR spectrum: 1642, 1620, 1524, 1514, 1225, 1104 cm^{-1} . Found %: C 50.03; H 5.22; Cl 10.31. $\text{C}_{14}\text{H}_{18}\text{ClNO}_6$. Calculated %: C 50.67; H 5.42; Cl 10.70.

1,3-Dimethyl-2-phenyl-6,7-dimethoxyisoquinolinium Perchlorate. A mixture of 0.2 g of I and 1 ml of aniline was refluxed in 4 ml of ethanol on a water bath for 1.5 h. The precipitated, colorless crystals were filtered and washed with ether to give 66% of product with mp 298° (ethanol-water). IR spectrum: 1640, 1616, 1584, 1518, 1274, 1106 cm^{-1} . Found %: C 57.28; H 5.23; Cl 9.30. $\text{C}_{19}\text{H}_{20}\text{ClNO}_6$. Calculated %: C 57.97; H 5.09; Cl 9.02.

1,3-Dimethyl-2-amino-6,7-dimethoxyisoquinolinium Perchlorate. Hydrazine hydrate (0.3 ml) was added to 0.64 g of I in 5 ml of ethanol. Dissolving of I with heating and slow precipitation of a colorless substance was observed. Work-up gave 0.59 g (89%) of long, fine needles with mp 254° (ethanol). IR spectrum: 1620, 1570, 1524, 1500, 1380, 1270, 1100, 1000 cm^{-1} . Found %: C 47.30; H 5.23; Cl 11.05. $\text{C}_{13}\text{H}_{17}\text{ClN}_2\text{O}_6$. Calculated %: C 46.91; H 5.11; Cl 10.97.

1,3-Dimethyl-2-benzalamino-6,7-dimethoxy-2-isoquinolinium Perchlorate. This compound was obtained by refluxing a mixture of 0.25 g of 1,3-dimethyl-2-amino-6,7-dimethoxyisoquinolinium perchlorate, 0.2 ml of benzaldehyde, and 5 ml of glacial acetic acid for 1 h. On cooling 0.31 g (99%) of a light-colored product with mp 246° (ethanol) precipitated. IR spectrum: 1630, 1618, 1576, 1518, 1384, 1270, 1240, 1100 cm^{-1} . Found %: C 57.18; H 5.29; Cl 8.22. $\text{C}_{20}\text{H}_{21}\text{ClN}_2\text{O}_6$. Calculated %: C 57.07; H 4.99; Cl 8.44.

1,3-Dimethyl-2-phenylamino-6,7-dimethoxyisoquinolinium Perchlorate. This compound was obtained by refluxing a mixture of 0.2 g of I, 0.1 g of phenylhydrazine, and 3 ml of absolute ethanol for 1 h on a water bath. The product began to precipitate from the hot solution. On work-up 0.2 g (80%) of product with mp 245° (acetic acid) was obtained. IR spectrum: 1620, 1600, 1572, 1510, 1370, 1264, 1100, 1000 cm^{-1} . Found %: C 56.19; H 5.36; Cl 8.91. $\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}_6$. Calculated %: C 55.88; H 5.14; Cl 8.69.

1,4-Phenylenebis-2,2'-(1,3-dimethyl-6,7-dimethoxyisoquinolinium) Perchlorate. This compound was similarly obtained from 0.64 g of I, 0.11 g of phenylenediamine, and 5 ml of ethanol. The yield was 0.43 g (60%) and the melting point was above 380°. IR spectrum: 1636, 1620, 1576, 1520, 1378, 1270, 1100, 1006 cm^{-1} . Found %: C 54.04; H 4.93; Cl 9.57; N 3.68. $\text{C}_{32}\text{H}_{34}\text{Cl}_2\text{N}_2\text{O}_{12}$. Calculated %: C 54.16; H 4.79; Cl 10.01; N 3.94.

1,3-Dimethyl-2-carbethoxymethyl-6,7-dimethoxyisoquinolinium Perchlorate. Compound I (0.64 g) was mixed with an equimolecular amount of an alcohol solution of excess glycine ethyl ester and heated for 1 h. An oil separated on cooling which crystallized completely on addition of ether to give 0.7 g (87%) of a product with mp 206° (from ethanol). IR spectrum: 1726, 1642, 1620, 1576, 1520, 1502, 1380, 1278, 1100, 1012 cm^{-1} . Found %: C 51.15; H 5.74; Cl 9.04. $\text{C}_{17}\text{H}_{22}\text{ClNO}_8$. Calculated %: C 50.53; H 5.44; Cl 8.79.

1,3-Dimethyl-6,7-dimethoxyisoquinoline N-Oxide. Hydroxylamine hydrochloride (0.69 g) in 5 ml of absolute ethanol with a drop of phenolphthalein was placed in a three-necked flask equipped with a stirrer and a dropping funnel, and an alcoholic solution of sodium ethoxide was added dropwise with water cooling for 30 min until a color developed. The precipitate was filtered, 0.64 g of I was added to the alcoholic solution of hydroxylamine, and the mixture was refluxed for 1 h. The solution was cooled, and the filtered product was dissolved in a dilute solution of alkali and extracted with chloroform. A colorless product [0.42 g (90%)] with mp 155° (from ethanol) was obtained after drying and removal of solvent. IR spectrum: 1620, 1600, 1514, 1370, 1246, 1186, 1154, 1004 cm^{-1} . Found %: C 66.56; H 6.23. $\text{C}_{13}\text{H}_{15}\text{NO}_3$. Calculated %: C 66.94; H 6.43.

1-N-Morpholino-3-methyl-6,7-dimethoxynaphthalene. A mixture of 0.64 g of I, 0.44 ml of morpholine, and 3 ml of ethanol was refluxed for 1 h. The reaction mixture was diluted with a solution of alkali; and 0.56 g (98%) of a colorless product with mp 164° (from ethanol) was filtered off. IR spectrum: 1610, 1580, 1506, 1374, 1260, 1110, 1030, 980 cm^{-1} . Found %: C 71.58; H 7.45; N 5.20. $\text{C}_{17}\text{H}_{21}\text{NO}_3$. Calculated %: C 71.08; H 7.31; N 4.87.

1-Diethylamino-3-methyl-6,7-dimethoxynaphthalene. This compound was similarly obtained from 0.64 g of I and 0.8 ml of diethylamine in 5 ml of ethanol. Purification was carried out in a column filled

with aluminum oxide (chloroform solvent). The first fraction with bp 277° (according to Sivolobov) was collected. IR spectrum: 1604, 1580, 1498, 1370, 1240, 1136, 1010 cm^{-1} . Found %: C 74.16; H 8.49. $\text{C}_{17}\text{H}_{23}\text{NO}_2$. Calculated %: C 74.72; H 8.42.

1-Styryl-3-methyl-6,7-dimethoxy-2-benzopyrylium Perchlorate. A mixture of 0.2 g of I and 0.1 ml of freshly distilled benzaldehyde was refluxed for 2-3 h in glacial acetic acid. Red crystals precipitated during the refluxing period were filtered from the hot solution and washed with hot acetic acid and ether to give 0.12 g (50%) of a product with mp 290-293° (from acetic acid). IR spectrum: 1650, 1612, 1546, 1506, 1308, 1104 cm^{-1} . Found %: C 59.32; H 4.26; Cl 8.08. $\text{C}_{20}\text{H}_{19}\text{ClO}_7$. Calculated %: C 59.04; H 4.67; Cl 8.73.

1-(3',4'-Dimethoxystyryl)-2,3-dimethyl-6,7-dimethoxyisoquinolinium Perchlorate. A mixture of 0.47 g of I, 0.5 ml of aqueous methylamine, and 5 ml of acetone was refluxed on a water bath for 15 min. Cooling precipitated 0.43 g (89%) of yellow crystals with mp 260° (from acetic acid). IR spectrum: 1620, 1592, 1562, 1508, 1380, 1270, 1090, 1016 cm^{-1} . Found %: C 56.87; H 5.44; Cl 6.86. $\text{C}_{23}\text{H}_{26}\text{ClNO}_8$. Calculated %: C 57.44; H 5.51; Cl 7.39.

LITERATURE CITED

1. K. Dimroth, *Angew. Chem.*, **72**, 331 (1960).
2. S. V. Krivun, V. I. Dulenکو, L. V. Dulenکو, and G. N. Dorofeenko, *Dokl. Akad. Nauk SSSR*, **166**, 359 (1966).
3. G. N. Dorofeenko, A. D. Semenov, V. I. Dulenکو, and S. V. Krivun, *Zh. Obshch. Khim.*, **36**, 1492 (1966).
4. Yu. A. Zhdanov, A. N. Narkevich, and G. N. Dorofeenko, in: *Synthesis of Natural Compounds [in Russian]* (1965), p. 160.
5. A. N. Narkevich, G. N. Dorofeenko, and Yu. A. Zhdanov, *Zh. Obshch. Khim.*, **36**, 819 (1966).
6. G. N. Dorofeenko, E. I. Sadekova, S. V. Krivun, and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR*, **181**, 345 (1968).
7. E. Schmitz, *Chem. Ber.*, **91**, 1488 (1958).
8. G. N. Dorofeenko, V. V. Mezheritskii, and B. I. Ardashev, *Zh. Obshch. Khim.*, 1855 (1967).
9. G. N. Dorofeenko, O. E. Shelepin, Z. N. Nazarova, V. N. Novikov, and G. P. Tikhonova, *Zh. Obshch. Khim.*, **35**, 570 (1965).
10. R. Elderfield (editor), *Heterocyclic Compounds*, Wiley (1961).
11. K. Nakanishi, *Infrared Spectra and Structure of Organic Compounds*, Practical Holden-Day, San Francisco (1957).
12. E. B. Wilson, *Phys. Rev.*, **45**, 706 (1934).