2-BENZOPYRYLIUM SALTS. 44.* FORMATION OF 4-ACYL-3,4-DIHYDROISOQUINOLINIUM SALTS FROM THE REACTION OF 2-BENZOPYRYLIUM SALTS WITH AZOMETHINES AND THE CYCLOADDITION OF MALEIMIDES TO THE PRODUCT OF THEIR DEPROTONATION, THE 2,3-DIHYDROISOQUINOLINES

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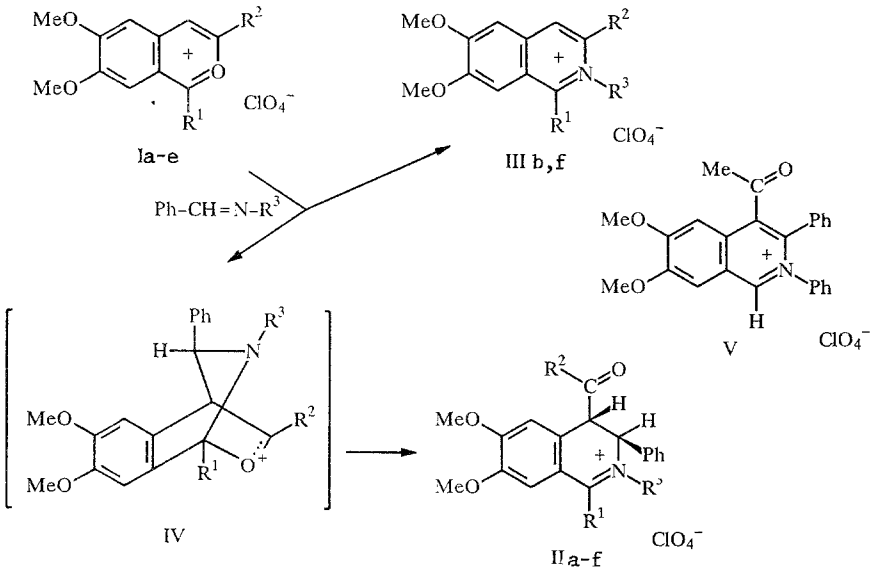
The effect of substituents in the 2-benzopyrylium cation and in the azomethines on the character of their reaction in various solvents has been clarified. It was shown that the 4-acyl-3,4-dihydroisoquinolinium salts resulting after deprotonation form compounds with an ortho-quinonoid structure which then react with maleimides by cycloaddition.

We showed previously that, depending on the nature of the substituent in position 1, the 2-benzopyrylium salts (Ia, e) react with arylidenanilines either by a [4+ 2] cycloaddition ending with the formation of 2-acyl-3,4-dihydroisoquinolinium salts (IIa, g) [2], or are converted, when R^1 = Me, into the 1-styryl-substituted analogs [3].

While continuing investigations in this direction we found that varying the substituent in position 3 of the 2-benzopyrylium cation, which usually affects the direction of its conversion [4], did not affect the course of the reaction of salts (Ib, c) with benzaldehyde and the products were also isoquinolinium derivatives (IIc, d).



Ia–d R^1 = H, e R^1 = Ph a, e R^2 = 3,4-$(MeO)_2C_6H_3$, b R^2 = Ph, c R^2 = Me, d R^2 = Me; IIa —f R^1 = H, g R^1 = Ph, a, h; g R^2 = 3,4-$(MeO)_2C_6H_3$, c R^2 = Ph, d R^2 = Me e, f R^2 = Me, a, c–e, g R^3 = Ph, b, f R^3 = =Me, III f R^2 =OH, R^3 = Me

*For Communication 43 see [1].

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TABLE 1. Physicochemical Characteristics of Salts (IIb-f), (IIIf), and (V)

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}	PMR spectrum (δ, ppm.) in $CDCl_3$**	Yield, %
IIIf	$C_{12}H_{14}ClNO_7$	248	3553, 1660, 1100	3,65 (3H, s, CH_3); 3,70 (3H, s, OCH_3); 3,32 (3H, s, OCH_3); 6,80 ($1H_{ar}$, s) 8,30 ($1H_{ar}$, s)	31
V	$C_{25}H_{22}ClNO_7$	175	1725, 1633, 1100	2,15 (3H, s, CH_3); 3,70 (3H, s, OCH_3); 3,90 (3H, s, OCH_3); 7,30...7,10 ($11H_{ar}$, s); 7.75 ($1H_{ar}$, s); 8,75 ($1H_{ar}$, s)	—
IIb	$C_{27}H_{28}ClNO_9$	207	1677, 1660, 1606, 1100	3,02 (3H, s, CH_3); 3,12 (3H, s, OCH_3); 3,20 (6H, s, $2OCH_3$); 3,25 (3H, s, OCH_3); 4,67 (1H, s, 3-H); 4,80 (1H, s, 4-H); 6,30...7,22 ($11H_{ar}$, m); 8,32 (1H, , 1-H)	66 (A), 69 (B)
IIc	$C_{30}H_{26}ClNO_9$	152	1680, 1594, 1100	3,35 (3H, s, OCH_3); 3,35 (3H, s, OCH_3); 5,15 (1H, s, 3-H); 5,62 (1H, s, 4-H); 6.50...7,75 ($17H_{ar}$, m); 8,57 (1H, s, 1-H)	47
IId	$C_{25}H_{24}ClNO_7$	195	1706, 1633, 1100	2,07 (3H, s, CH_3); 3,7 (3H, s, OCH_3); 3,77 (3H, s, OCH_3); 4,37 (1H, s, 3-H); 6,07 (1H, s, 4-H); 7,05...7,92 ($12H_{ar}$, m); 8,77 (1H, s, 1-H)	40
IIe	$C_{25}H_{24}ClNO_8$	157	1740, 1560, 1100	3,65 (3H, s, OCH_3); 3,87 (6H, s, $2OCH_3$); 4,37 (1H, s, 3-H); 6,12 (1H, s, 4-H); 6,95...7,82 ($12H_{ar}$, m); 9,27 (1H, s, 1-H)	63
IIf*	$C_{20}H_{24}ClNO_8$	102 (decomp.)	1753, 1660, 1609, 1100 (in $CHCl_3$)	3,76 (6H, s, CH_3, OCH_3); 3,87 (6H, s, $2OCH_3$); 4,16 (1H, s, 3-H); 5,50 (1H, s, 4-H); 6,87 ($1H_{ar}$, s); 7,05...7,37 ($7H_{ar}$, m); 7,62 ($1H_{ar}$, s); 9,25 (1H, s, 1-H)	64 (A)

*Compounds (IIc, e, f) were purified by reprecipitation with ether from acetic acid, (IIb) was crystallized from ethanol, (IId) was triturated in methanol in the cold, (IIIf) and (V) were crystallized from acetic acid.

**The spectra of compounds (IIIf) and (V) were taken in CF_3COOH.

***Reaction in absolute acetonitrile.

Even the poorly stable perchlorate (Id) was converted in good yield into the dihydroisoquinolinium salt (IIe), analogs of which have been successfully used previously in the synthesis of phenanthridine alkaloids [5].

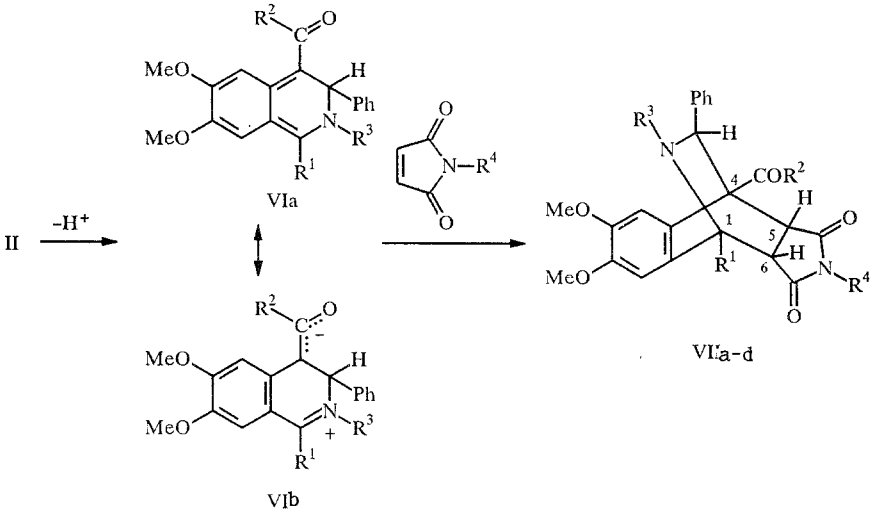
The reaction of 2-benzopyrylium salts (Ia, d) with benzalmethylamine proceeds less unequivocally. On reaction in acetic acid, i.e., under the conditions used previously in [2], the aromatic derivatives (IIIb, f) were formed in addition to the dihydroisoquinolinium salts (IIb, f). The compounds (IIIb, f) were identical to the products of the classical ANRORC recyclization of (Ia, d) with methylamine [6]. The mechanism of forming salts (II) undoubtedly includes a 1,4-cycloaddition with the participation of the bridge intermediate (IV). The second conversion may occur both by the four-center mechanism proposed previously for the analogous transformation of monocyclic pyrylium salts [7] and as a result of solvolytic fission of the C=N bond in the initial benzalmethylamine.

The reaction of salts (Ia, d) with benzalmethylamine was conducted in absolute dimethylformamide where the possibility of hydrolysis is excluded [7]. In this solvent the isoquinolinium salts (IIIb, f) were detected in only trace quantities, however the yields of dihydroisoquinolinium salts (IIb, f) were effectively unchanged. The competing reaction in this case proved to be dimerization of the 2-benzopyrylium salts [8]. Similar results were also obtained in acetonitrile.

It must be noted that a fourfold excess of the Schiff's base is required for a successful synthesis of the perchlorates (IIb, c, f).

The acyldihydroisoquinolinium salts (IIa-f) proved to be completely stable and were isolated as the trans isomers ($0 < J_{3,4} < 0.5$ Hz, while $J_{3,4}$ for the cis isomer must be of the order of 6 Hz [9]). Only the salt (IId) was oxidized to the aromatic salt (V) when plotting its PMR spectrum in CF_3COOH.

Labile colored products, which were not isolated in a pure state, were formed by the action of various bases on salts (IIb-f) as obtained previously for their analogues (IIa, g) [2]. The initial salts (II) are readily regenerated on treatment with perchloric acid. These salts differed from the initial (II) only by the absence of a molecule of this acid according to mass spectroscopy. Evidently this product must correspond to the ortho-quinonoid structure (VIa) stabilized by the contribution of the bipolar resonance form (VIb).



VIIa—e R^1=H; a-d R^2 = 3,4-$(MeO)_2C_6H_3$, e R^2= Ph; a,b,e R^3 = Ph c,d R^3 =Me; a,c,e R^4 = Ph, b,d R^4 = Me

In order to confirm the structure of the products (VI) we introduced them into a direct diene synthesis which is the most typical reaction for compounds with an ortho-quinonoid structure [10]. p-Quinone, acrylonitrile, acetylenedicarboxylic acid dimethyl ester, N-phenyl- and N-methylmaleimide were used as dienophiles. However, only the last two compounds reacted under the mild conditions used (heating in ethanol). It transpired that the reaction is more conveniently carried out directly with the salts in the presence of sodium acetate. The adducts (VIIa-e) were isolated directly from boiling alcohol or on cooling, it must be noted, as one diastereoisomer.

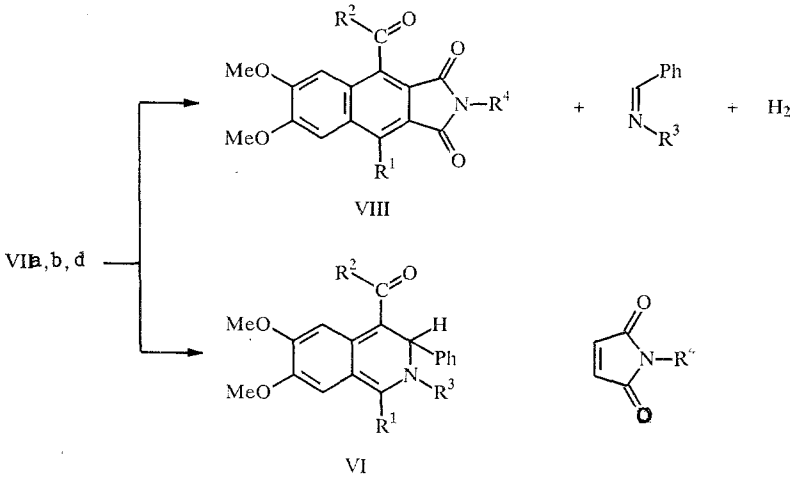
The PMR spectra of the compounds obtained were of a single type. The values of the spin—spin interaction constants $J_{1,6} \sim 3.5$ Hz and $J_{5,6} \sim 8.5$ Hz correspond to an angle between the 1-H/6-H protons of 50° and 5-H/6-H of 150° [9] and, according to the conclusions of [11] and of molecular models, point to the endo configuration for the adducts (VIIa-e).

TABLE 2. Physicochemical Characteristics of Adducts (VIIa-e)

Compound	Empirical formula	Boiling time, min	mp, °C	IR spectrum, cm^{-1}	PMR spectrum (δ, ppm) in $CDCl_3$					Yield, %
					arom (m)	H-1(d)	H-9(s)	H-5 (s)	H-6 · OCH_3, CH_3	
VIIa	$C_{42}H_{36}N_2O_7$	30	275	1713, 1686, 1593	7,29...6,30 (2OH)	5,58, $J_{1,6}$=3 Hz	4,92 (b)	4,59, $J_{5,6}$=9 Hz	3,84...3,75 (1OH, m); 3,24 (3H,br.s OCH_3)	54 (A), 56 (B)
VIIb	$C_{37}H_{34}N_2O_7$	90	207	1700, 1606, 1160	7,52...6,66 (15H)	5,52, $J_{1,6}$=4 Hz	4,86 (b)	4,42, $J_{5,6}$=8 Hz	3,86s (6H, Hz, $2OCH_3$); 3,78 (3H,s, OCH_3); 3,64 ($J_{6,5}$=8 Hz, $J_{6,1}$=4 Hz,q); 3,28 (3H,br.s, OCH_3); 2,4 (3H,s, CH_3)	62 (B)
VIIc	$C_{37}H_{37}N_2O_7$	150	298	1713, 1660, 1580	7,29...6,36 (15H)	4,41, $J_{1,6}$=4,5 Hz	3,99	4,17, $J_{5,6}$=9 Hz	3,9...3,78 (1OH,t);3,45 (3H, s,OCH_3); 2,34 (3H, s CH_3)	54 (B)
VIId	$C_{32}H_{32}N_2O_7$	40	264	1706, 1660, 1120	7,62...6,24 (1OH)	4,29, $J_{1,6}$=3 Hz	3,9	3,93, $J_{5,6}$=9 Hz	3,87 (3H,s,OCH_3); 3,81 (3H, s,OCH_3); 3,79 (3H,s,OCH_3); 3,66 ($J_{6,5}$=9 Hz, $J_{6,1}$=3 Hz,q); 3,45 (3H s, OCH_3); 2,37 (3H, s CH_3); 2,25 (3H, s CH_3)	50 (B)
VIIe	$C_{40}H_{32}N_2O_5$	40	290	1706, 1680, 1570	7,32...6,30 (22)	5,58, $J_{1,6}$=4,5 Hz	4,98 (b)	4,53, $J_{5,6}$=7,5Hz	3,93...3,75 (7H,m)	54 (B)

Note. Compounds (VIIa, b, e) were purified by crystallization from acetic acid, (VIIc) on a column (Al_2O_3) R_f = 0.5, (VIId) was washed out from ethanol.

In addition attention is drawn in the PMR spectrum of compounds (VIIa, b, e) to the broadening of the signals for the 3-H protons and for one methoxyl substituent in the annelated ring. This is probably linked with retardation of the inversion of the bridge nitrogen atom carrying a phenyl substituent, since this change was not observed for the corresponding signals in the spectra of adducts (VIIc, d) where R^3 = Me.



In spite of the fact that no M^+ ions were observed in the mass spectra of compounds (VIIa, b, d) obtained by electron impact, their structure was confirmed by the characteristic fragmentation to azomethine and the tricyclic system (VIII) and for compound (VIIa) by a parallel retrodecomposition.

EXPERIMENTAL

The IR spectra were taken on a Specord IR 75 spectrophotometer in Nujol and the PMR spectra on Tesla 487C 80 MHz and Tesla 567A 100 MHz instruments at 20°C, internal standard was HMDS. Mass spectra were obtained on a Finnigan MAT 4615 instrument with the energy of the ionizing radiation 70 eV and direct insertion of samples into the source.

The physicochemical characteristics of compounds (IIb-f), (IIIf), (V), and (VIIa-e) are given in Tables 1 and 2.

The data of elemental analysis for C, H, Cl, and N of all compounds obtained corresponded to calculated values.

3,6,7-Trimethoxy-2-benzopyrylium Perchlorate [(Id), $C_{12}H_{13}ClO_8$]. Aluminum chloride (10 g: 75 mmoles) was added with ice-cooling and stirring to a solution of methyl homoveratrate [12] (14 g: 66 mmoles) in dry chloroform (30 ml) and dichloromethyl butyl ether (10 ml: 66 mmoles) was added dropwise during 25 min. The mixture was stirred for 30 min more then poured onto pulverized ice (100 g). Ether (100 ml) was added to the mixture obtained and thoroughly mixed. The ether layer was separated off. Colorless crystals separated from it after 1 h and were filtered off and dried. The methyl ester of 1-formyl-4,5-dimethoxyphenylacetic acid (10 g: 62%) was obtained with mp 109°C. IR spectrum; 1726, 1686, 1566 cm^{-1}. PMR spectrum ($CDCl_3$): 3.40 (3H, s, OCH_3), 3.65 (6H, s, $2OCH_3$), 3.71 (2H, s, $-CH_2-$), 6.50 (1H-arom, s), 7.05 (1H-arom, s), 9.55 ppm (1H, s, CHO). A mixture (5 ml) prepared with cooling from acetic anhydride (24.4 ml) and 57% perchloric acid (6.8 ml) was added to a suspension of the product obtained above (2.4 g: 10 mmoles) in acetic anhydride (1 ml). After 10 min the light-yellow solid was filtered off and washed with acetic acid (10 ml) and with ether (50 ml). The salt (Id) (1.8 g: 56%) was obtained of mp 140°C (with decomposition). IR spectrum: 1641, 1620, 1100 cm^{-1}. PMR spectrum (CF_3COOD): 3.50 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.71 (1H-arom, s), 6.73 (1H-arom, s), 6.85 (1H-arom, s), 6.82 (1H-arom, s), 8.62 ppm (1H-arom, s).

2-Methyl-6,7-dimethoxy-4- (3,4-dimethoxybenzoyl)-3-phenyl-3,4-dihydroisoquinolinium Perchlorate (IIb). A. Benzalmethylamine (0.30 ml: 25.0 mmoles) was added to a suspension of the salt (Ia) (0.25 g: 5.8 mmoles) in acetic acid (3 ml). The mixture was heated until the salt dissolved, cooled, and after 1 h the isoquinolinium salt (IIIb) (0.07 g: 28%) had separated [6]. The mother liquor was diluted with ether (30 ml) and the precipitate of dihydroisoquinolinium salt (IIb) was filtered off. Salts (IIf) and (IIIf) were obtained analogously by method A, but on heating.

B. Salt (Ia) (0.25 g: 5.8 mmoles) was added to a solution of benzalmethylamine (0.30 ml: 25.0 mmoles) in absolute dimethylformamide (3 ml). The mixture was brought to boiling, cooled, and diluted with ether (30 ml). After reprecipitation of the resulting oily substance with ether (100 ml) from chloroform (25 ml) the solid salt (IIb) was filtered off.

Analogous results were obtained on carrying out the reaction in absolute acetonitrile.

4-Benzoyl-6,7-dimethoxy-2,3-diphenyl-3,4-dihydroisoquinolinium Perchlorate (IIc). Benzalaniline (0.40 g: 2.20 mmoles) was added to a suspension of salt (Ib) (0.25 g: 0.68 mmole) in acetic acid (3 ml) and the mixture boiled for 10 min. After cooling, the solution was diluted with ether (30 ml) and the precipitated salt (IIc) filtered off.

Salt (IIe) was obtained analogously, salt (IId) was formed without heating on leaving the mixture for 20 min at 20°C.

Adduct (VIIa). A. The salt (IIa) (0.20 g: 0.33 mmole) was dissolved in dimethylformamide (3 ml), 10% NaOH solution (0.5 ml) added, and the mixture diluted with water (25 ml). The blue solid which precipitated was filtered off and dried. Yield was 0.16 g (95%). The product obtained was suspended in ethanol (3 ml), N-phenylmaleimide (0.1 g: 0.57 mmole) added, and the mixture boiled for 30 min. After cooling, the colorless precipitate of adduct (VIIa) (0.13 g: 54%) was filtered off.

B. Fused sodium acetate (0.03 g: 0.36 mmole) and N-phenylmaleimide (0.1 g: 0.56 mmole) were added to a suspension of salt (IIa) (0.20 g: 0.33 mmole) in ethanol (3 ml). The mixture was boiled for 30 min and, after cooling, the product (0.14 g: 56%) was filtered off. It coincided in all characteristics with that obtained by method A.

Adducts (VIIb-e) were obtained similarly by method B.

Mass spectra of adducts: (VIIa): 137 (13) Ar^+, 165 (100) $ArCO^+$, 173 (3) $[maleimide]^+$, 181 (57) $[Ph-CH=N-Ph]^+$, 182 (68) $[Ph-CH=NH-Ph]^+$, 497 (23) $[VIII]^+$, 507 (3) $[VI]^+$. (VIIb): 137 (9) Ar^+, 165 (100) $ArCO^+$, 181 (43) $[Ph-CH=N-Ph]^+$, 182 (68) $[Ph-CH=N-Ph]^+$, 434 (25) [VIII−H]. (VIId): 120 (100) $[Ph-CH=NH-Me]^+$, 137 (5) Ar^+, 165 (46) $ArCO^+$, 434 (4) $[VIII-H]^+$.

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