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2-BENZOPYRYLIUM SALTS.

40*. ADDITION OF AZOMETHINES TO 2-BENZOPYRYLIUM SALTS – NEW METHOD FOR THE SYNTHESIS OF ISOQUINOLINIUM SYSTEMS

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UDC 547.814.1+547.833.07

The addition of azomethines to 2-benzopyrylium salts, which leads to derivatives of 3,4-dihydroisoquinolinium salts, was observed. An assumption regarding the mechanism of the reaction is expressed on the basis of its stereoselectivity. Dehydrogenation of the compounds obtained to completely aromatic isoquinolinium salts and reduction to tetrahydroisoquinolines were realized.

The reaction of monocyclic pyrylium salts with azomethines, which hypothetically proceeds via a four-center mechanism, concludes with the simple exchange of an oxygen atom for the amino fragment of the Schiff base, i.e., with the formation of pyridinium salts and the elimination of an aldehyde [2, 3]. With the same reagents, 2-benzopyrylium salts with a methyl group in the 1 position add the residue of an aromatic aldehyde at this substituent and form, with retention of the oxonium atom, 1-styryl-substituted derivatives [4].

We have observed the stereoselective addition of azomethines to 2-benzopyrylium salts that do not contain an alkyl substituent in the 1 position, as a result of which trans isomers of 3,4-dihydroisoquinolinium salts IVa-d are formed in quantitative yields. The configuration of the compounds obtained can be judged from the spin-spin coupling constants (SSCC) of the methylidine protons, viz., $J_{3,4} = 0$ Hz, while this value should be on the order of 6 Hz for the cis isomers [5].

As compared with the well-known conversion of 2-benzopyrylium salts to completely aromatic isoquinolinium salts under the influence of primary amines [6], which proceeds via the ANRORC scheme [7], a fundamentally different recyclization mechanism, viz., cycloaddition of the C=N bond of the azomethine to the 1 and 4 positions of the pyrylium fragment of salts Ia, b with subsequent opening of the ring containing the onium heteroatom in intermediates IIIa-d, is, in our opinion, realized in the case being described here.

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*See [1] for Communication 39.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1177-1180, September, 1990. Original article submitted November 11, 1988; revision submitted November 23, 1989.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp,* °C	IR spectrum, cm⁻¹	PMR spectrum,** δ, ppm	Yield, %
IVa	$C_{32}H_{30}ClNO_9$	159	1650, 1632, 1600, 1100	3,47 (3H, s, OCH_3); 3,52 (3H, s, OCH_3); 3,57 (6H, s 2 OCH_3); 5,25 (1H, s, 3-H); 5,65 (1H, s, 4-H); 6,72...7,22 (15H, arom., m); 8,90 (1H, s, 1-H)	96
IVb	$C_{38}H_{34}ClNO_9$	164	1650, 1595, 1100	3,32 (3H, s, OCH_3); 3,52 (3H, s, OCH_3); 3,57 (6H, s, 2 OCH_3); 5,20 (1H, s 3-H); 5,27 (1H, s, 4-H); 6,57...7,10 (20H arom., m)	88
IVc	$C_{33}H_{32}ClNO_{10}$	191	1650, 1632, 1600, 1100	3,69 (3H, s OCH_3); 3,81 (3H, s, OCH_3); 3,82 (H, s, OCH_3); 3,87 (6H, s, 2 OCH_3); 5,55 (1H, s 3-H); 6,18 (1H, s 4-H); 6,87...8,01 (14H arom, m,; 9,21 (1H, s, 1-H)	96
IVd	$C_{39}H_{28}ClNO_{10}$	161	1660, 1600, 1100	3,55 (3H, s, OCH_3); 3,52 (12H, s, 4 OCH_3); 5,25 (2H, br.s. , 3-H & 4-H); 6,52...7,32 (19H, arom, m)	85
VII	$C_{32}H_{28}ClNO_9$	272	1640, 1605, 1585, 1100	3,47 (6H, s 2 OCH_3); 3,60 (3H, s, OCH_3); 3,75 (3H, s, OCH_3); 6,57...7,15 (15H, arom., m); 9,07 (1H, s, 1-Harom)	60
VIII	$C_{32}H_{31}NO_9$	177	1675, 1590, 1015	3,70 (3H, s, OCH_3); 3,82 (3H, s, OCH_3); 3,84 (3H, s, OCH_3); 3,90 (3H, s, OCH_3); 4,28 (1H, d, $J = 14$ Hz 1-H); 4,64 (1H, d, $J = 14$ Hz 1-H); 4,98 (1H, d, $J = 1,4$ Hz, 3-H); 5,46 (1H, d, $J = 1,4$ Hz 4-H); 6,48...7,78 (15H, arom, m)	84

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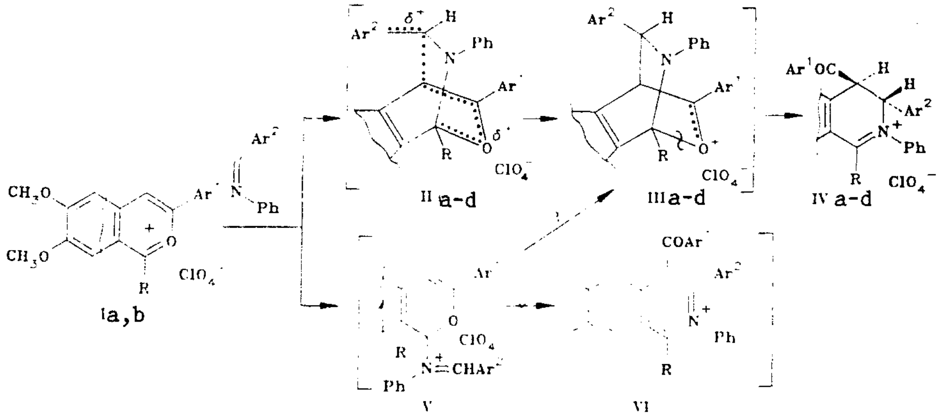
*Salts IVa, b, d were purified by reprecipitation from solution in acetic acid by the addition of ether, IVc was recrystallized from methanol, VII was recrystallized from acetic acid, and VIII was recrystallized from ethanol.

**The PMR spectra of salts IVa, b, d and VII were recorded in CF_3COOH (in CD_3CN for IVc and in $CDCl_3$ for VIII).

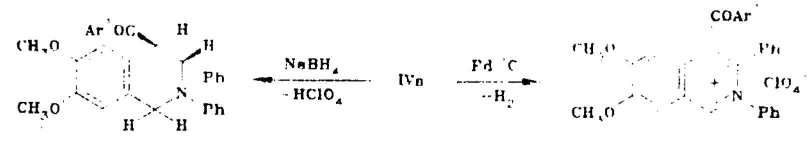


I—IV Ar^1=3,4-$(CH_3O)_2C_6H_3$; I a R=H, b R=Ph; II—IVa,c R=H, b,d R=Ph, a,b Ar^2=Ph, c,d Ar^2=4-$CH_3O—C_6H_4$

The alternative (to the proposed scheme) ANRORC mechanism is unlikely in this reaction since, first, it should include electrocyclic opening of adducts V to give the thermodynamically unfavorable o-quinoid intermediates VI and, second, the thermal six-electron cyclization of the latter, in accordance with the rules of retention of orbital symmetry, would lead to the cis isomers of salts IVa-d.

We have previously reported the similar (to the described addition) reaction of 2-benzopyrylium salts with vinyl ethyl ether [1] and the analogy between this process and the Bradsher–Falk reaction – the concerted [4 + 2]-cycloaddition of variously substituted olefins to isoquinolinium salts [8]. In analogy with the latter, the stereoselectivity of the cycloaddition of azomethines can be explained by the maximal separation of the delocalized charges in intermediates of the II type [8], and one can thus regard it as a confirmation of the concerted character of the reaction. However, a stepwise process with the participation of intermediates of the V type is less likely, since it would lead to mixtures of diastereomers of salts IVa-d due to free rotation about the =N⁺– bond of the isochromene ring.

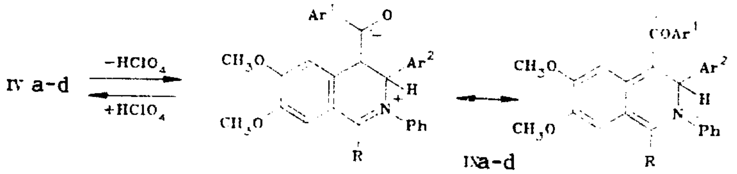
For an additional confirmation of the structures of the 3,4-dihydroisoquinolinium salts IVa-d obtained and expansion of the synthetic possibilities of the observed transformation we dehydrogenated salt IVa to isoquinolinium salt VII and reduced it to tetrahydroisoquinoline VIII, the structure of which was confirmed by data from the IR and PMR spectra and from mass spectrometry.



VIII VII

VII, VIII Ar'=3,4-$(CH_3O)_2C_6H_3$

Treatment of salts IVa-d in organic solvents with bases leads to the formation of colored labile products that are easily protonated to give the starting compounds; these colored labile products can be isolated only in the form of amorphous precipitates upon precipitation with water. The presence of a maximal intense MH^+ ion peak with m/z 508 in the chemical-ionization mass spectrum of this derivative of salt IVa provides evidence for splitting out of perchloric acid from the starting salt without any addition of the nucleophile. Deprotonation of the 4 position of salts IVa-d with the formation of o-quinoid structures IXa-d, which are stabilized by the contribution of dipolar resonance forms, is most likely. Unfortunately, we have not yet been able to satisfactorily purify these compounds and confirm their structures convincingly by other methods.



IX a–d Ar^1=3,4-$(CH_3O)_2C_6H_3$; a,c R=H; b,dR=Ph; a,b Ar^2=Ph, c,d Ar^2=4-$CH_3O—C_6H_4$

With respect to the results obtained, our new method for the synthesis of 3,4-dihydroisoquinolinium salts recalls the well-known condensation of homophthalic anhydride with azomethines that is used in the synthesis of some alkaloids [5, 9], but, in contrast to the latter, it has a different mechanism and a much more extensive choice of accessible starting compounds.

In conclusion, let us note that the ability of benzo[c]-annelated pyrylium salts – 2-benzopyrylium salts – to undergo transformations that lead to the formation of bridged intermediates of the III type, which were also described in the reaction with vinyl ethyl ether [1], is evidently due to the greater fixation of the double bonds in the hetero fragment of the starting cations as compared with their monocyclic analogs. One cannot exclude the possibility that the new type of reaction of 2-benzopyrylium salts that we have discovered may find extensive synthetic application that is comparable to the diversity of their transformations via the ANRORC scheme [1, 6, 10, 11].

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Specord IR-75 spectrometer. The PMR spectra were obtained with Tesla 487 C (80 MHz) and Tesla 567 A (100 MHz) spectrometers at 20°C with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with chemical ionization (with isobutane as the reactant gas) with a Finnigan MAT-4615 spectrometer.

The results of elementary analysis for C, H, Cl, and N were in agreement with the calculated values.

2,3-Diphenyl-4-(3,4-dimethoxybenzoyl)-3,4-dihydro-6,7-dimethoxyisoquinolinium Perchlorate (IVa). A 0.22-g (1.2 mmoles) sample of benzalaniline was added to a suspension of 0.43 g (1 mmole) of salt Ia in 5 ml of acetic acid, and the mixture was heated until the salt dissolved. After cooling, the solution was diluted with 30 ml of ether, and the resulting precipitate was separated (see Table 1).

Salts IVb-d were similarly obtained.

2,3-Diphenyl-4-(3,4-dimethoxybenzoyl)-6,7-dimethoxyisoquinolinium Perchlorate (VII). A mixture of 0.3 g (0.5 mmole) of salt IVa and 0.5 g of 2% Pd/C in 5 ml of acetic acid was heated for 2 h. After separation of the catalyst, the cooled mother liquor was diluted with ether until crystallization began. After crystallization was complete, the precipitate was removed by filtration.

1,2,3,4-Tetrahydro-2,3-diphenyl-4-(3,4-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (VIII). A solution of 0.2 g (0.33 mmole) of salt IVa in 2 ml of DMF and 1 ml of CH_3OH was cooled to 0°C and treated with 0.02 g (0.5 mmole) of sodium borohydride. Immediately after decolorization of the mixture, it was diluted with water, and the resulting precipitate was separated. Mass spectrum, m/z (I_{rel}, %): $[MH]^+$ 510 (100), M^+ 509 (16), 418 (8), $[M - C_6H_5NH]^+$ 417 (40), $[MH - C_6H_5N{=}CHC_6H_5]^+$ 329 (6), 281 (7), 191 (11), $[ArCO]^+$ 165 (25).

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