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2-BENZOPYRYLIUM SALTS.

45.* INTERACTION OF 2-BENZOPYRYLIUM SALTS AND THEIR MONOCYCLIC ANALOGS WITH IMINES OF KETONES

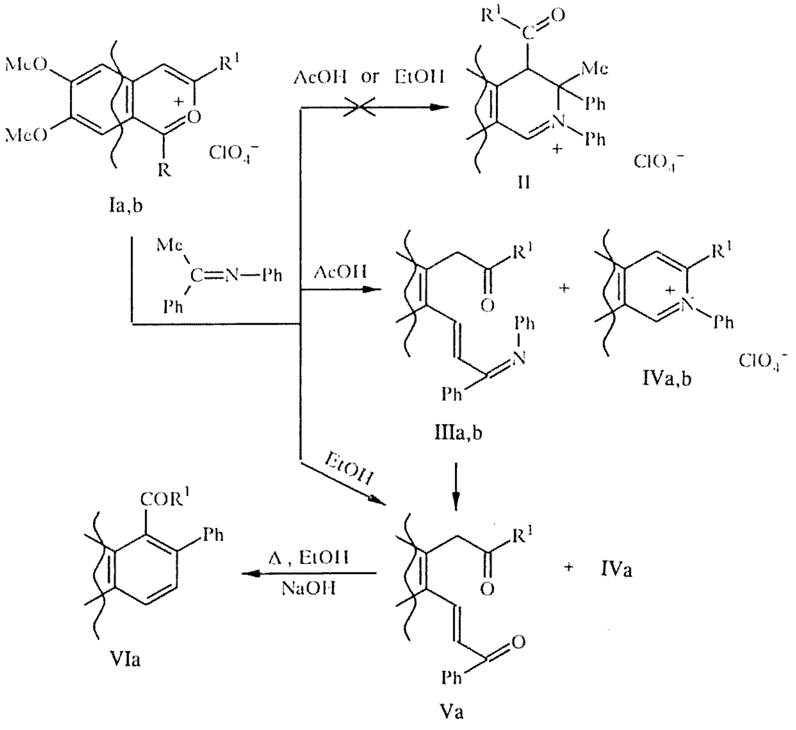
D. É. Tosunyan, S. V. Verin, and E. V. Kuznetsov

It was shown that ketonimines, which can have imine–enamine tautomerism, react with pyrylium salts in the enamine form. In such reactions, the 2-benzopyrylium salts are transformed into unsaturated ketones, and their monocyclic analogs are transformed into either quinolizinium salts or pyridinium salts depending on the structure of the initial imine.

We previously found that the reaction of 2-benzopyrylium salts, not containing an alkyl substituent at the position 1, with azomethines leads to the formation of 3,4-dihydroisoquinolinium salts in quantitative yield [1].

For the purpose of expanding the synthetic possibilities of this conversion, an attempt was made to introduce imines of ketones into the analogous reaction for the isolation of 3,3-disubstituted dihydroisoquinolinium salts (II).

Scheme 1



I—VIa, b R = H; a R¹ = 3,4-(MeO)$_2$C$_6$H$_3$; b R¹ = Ph

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*For the Communication 44, cf. [1].

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However, only the isoquinolinium salt (IVa) – the product of the usual interaction of the 2-benzopyrylium salt with the aniline, evidently formed as a result of hydrolysis of the imine, by the ANRORC scheme – was found as the result of the reaction of the salt (Ia) with the anil of benzophenone in acetic acid. At the same time, the reaction of the same salt with the anil of acetophenone led to the isolation of a compound not having the structure of a salt, which has the structure (IIIa) judging from the data of IR, PMR, and mass spectroscopy, together with the isoquinolinium salt (IVa).

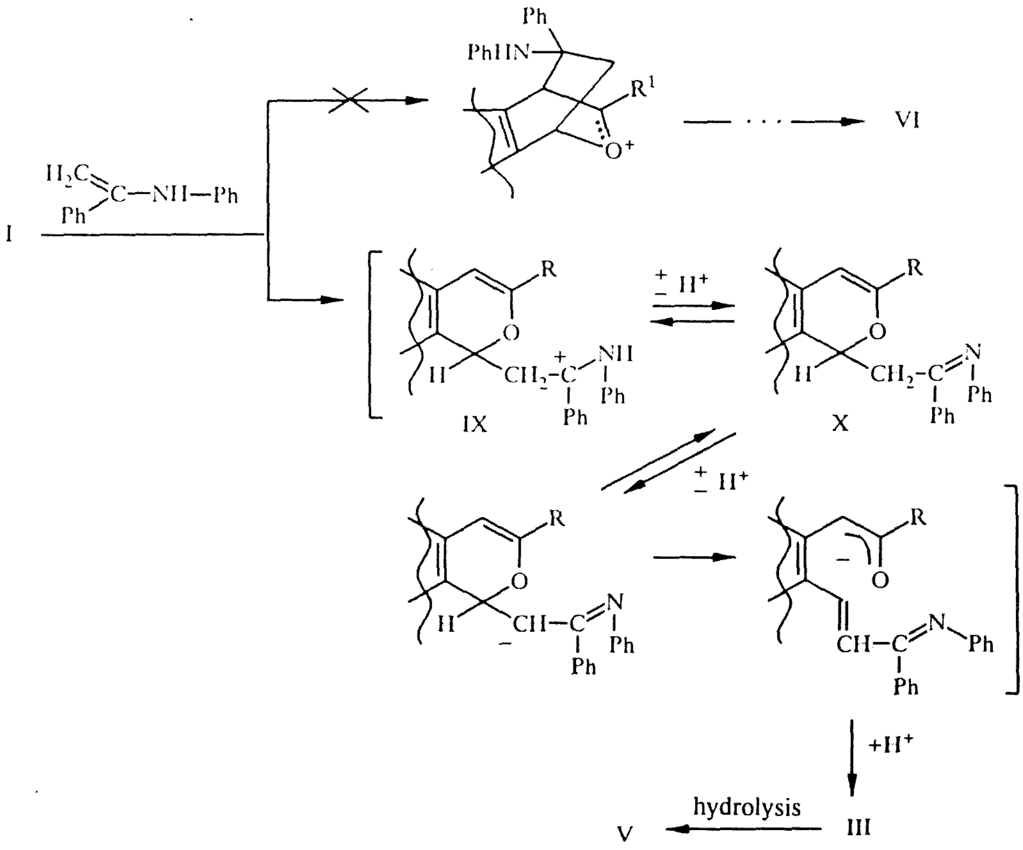
The brief heating of (IIIa) in aqueous ethanol leads to the hydrolysis of the C=N bond and the formation of the unsaturated ketone (Va), which can also be obtained directly by the reaction of the initial salt (Ia) with the anil of acetophenone in alcohol. If the diketone (Ba) is heated with alkali, the naphthalene (VIa) is formed as the result of intramolecular condensation. The analogous imine (IIIb) was obtained by the interaction of the 3-phenyl-6,7-dimethoxy-2-benzopyrylium salt (Ib) with the imine of acetophenone.

We explain the formation of the open-chain compounds of the type (III) and (V) by the realization of the classical imine–enamine tautomerism [2], as a result of which the enamine (VIII) becomes the reagent, emerging not as a π-excess dienophile [the direct formation of the naphthalene (VIa)] but as a C-nucleophile.

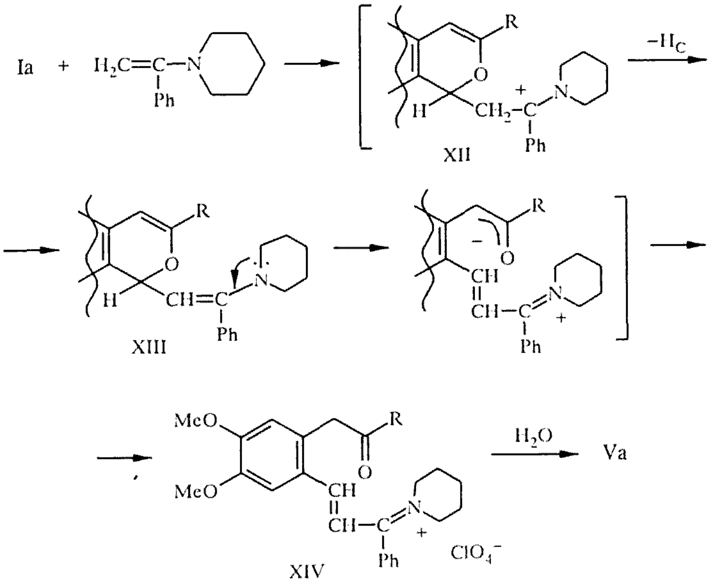
VII VIII

Evidently, the initial attack of the methylene group of the enamine at the position 1 of the 2-benzopyrylium cation leads to the formation of the charged adduct (IX), the stabilization of which occurs due to the loss of the available proton of the NH group. The subsequent opening of the heterocycle in the adduct (X) proceeding, as in the reaction of 2-benzopyrylium salts with methylene-active compounds [5], by the action of a base, which is evidently provided by the excess of the initial imine, leads to the formation of the anil (III). The last is converted by hydrolysis to the unsaturated ketone (V).

Scheme 2

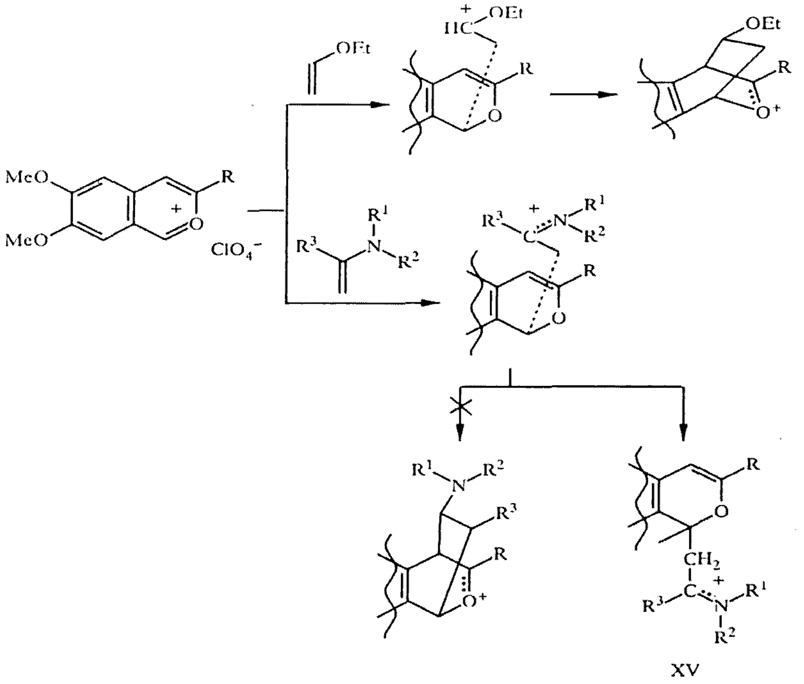


In order to confirm the fact that the imine of acetophenone enters into the reaction in the enamine form, we investigated the interaction of the salt (Ia) with the true piperidine enamine of this ketone not containing the available proton of the NH group [3]. In the given case, the charged adduct (XII) formed at the first stage, which is only capable of C-deprotonation, is converted to the adduct (XIII). The opening of the heterocycle in it, due to the disintegrating action of the free electron pair of the nitrogen atom along the chain of conjugation, results in the formation of the perchlorate (XIV).* Its hydrolysis in aqueous ethanol gives the desired diketone (Va).



Therefore, the behavior of enamines in reactions with 2-benzopyrylium salts differs strikingly from the character of reaction of vinyl ethers with the same salts [5], although it is known that both types of compounds are classical dienophiles in the Diels–Alder reaction with reversed electronic requirements [6].

It can be seen that this difference is explained by the different degree of delocalization of the positive charge arising in the unsymmetrical transition state:



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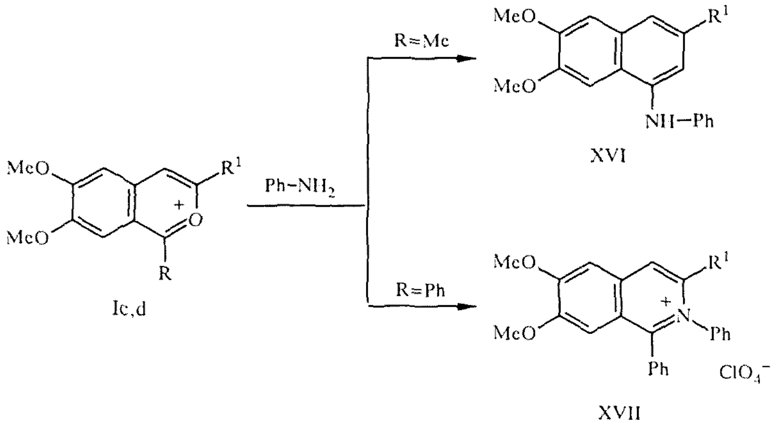
*In contrast to the reaction of the salt (Ia) with N-cyclohexenylmorpholine [4], we did not detect the process of dimerization and subsequent disproportionation in the case under consideration.

In the case of the application of the vinyl ether, the possibility of the delocalization of the positive charge with the participation of the oxygen atom is low; on the whole, this increases the probability of the formation of a bridge intermediate by the path of 4 + 2-cycloaddition or with the involvement of a bridging mechanism. The free electron pair of the nitrogen atom participates in the delocalization of the positive charge developing in the reaction with enamines. This naturally lowers its activity and, on the whole, the probability of the formation of a new C−C bond. Therefore, this stage of the reaction results in the formation of the adduct (XV), which cannot react by the bridging mechanisms and undergoes either N-deprotonation (R^1 or R^2 = H), or C-deprotonation (R^1, $R^2 \neq$ H).

The answer to the other question as to why the enamines react smoothly by the path of the 4 + 2-cycloaddition with the formation of bridge intermediates with isoquinolinium and acridizinium salts [7], and with 2-benzopyrylium salts with the formation of compounds of open-chain structure, is probably explained by the varying degree of the ease of the opening of the heterocycle: the breaking of the C−O bond in isochromenes of the type (X) requires significantly lower energy outlay than in the case of the C−N bond in 1,2-dihydroisoquinolines. As a consequence, the tendency for recyclization reactions by the ANRORC scheme is significantly higher for 2-benzopyrylium salts than for isoquinolinium salts [8].

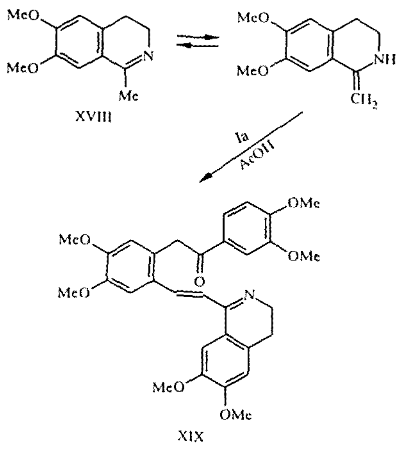
It should be stressed that acetophenone, in contrast to its enamines, does not enter into the reaction with the salt (Ia) either under conditions of interphase catalysis, or under traditional conditions of the reaction of pyrylium salts with methylene-active compounds [5]. Therefore, the classical activation of the alkyl group of the ketone is available for electrophilic substitution reactions by means of its conversion into the corresponding enamine [9].

The appearance of a substituent at the position 1 of the 2-benzopyrylium salt evidently prevents its reaction with the imine of acetophenone for steric reasons and leads to the hydrolysis of the last. The resulting aniline gives the naphthylamine (XVI) with the 1-methyl-substituted salt (Ic) by analogy with [10], and it correspondingly gives the isoquinolinium salt (XVII) with the 1-phenyl-substituted salt (Id).



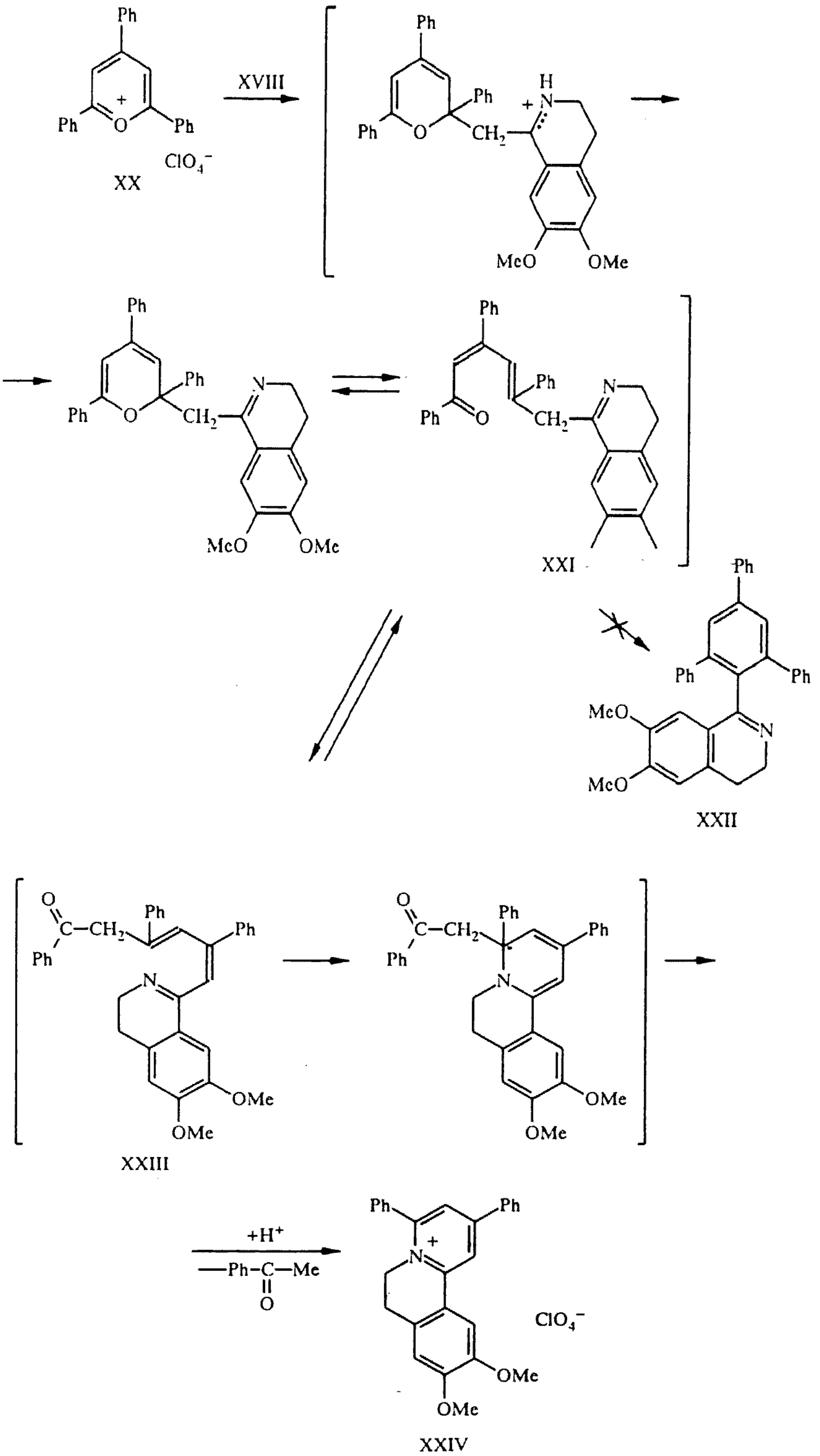
R^1 = 3,4-$(MeO)_2C_6H_3$, c R = Me, d R = Ph

In the case of 1-methyl-3,4-dihydroisoquinoline, which can be considered correspondingly as a cyclic anil of the substituted acetophenone, the salt (Ia) reacts with the formation of the unsaturated ketone (XIX), i.e., by the same scheme as with the anil of acetophenone.



The reaction of monocyclic pyrylium salts with enamines not having the available proton of the NH group, which results in the formation of a substituted benzene due to the electrocyclic cyclization of the hexatriene intermediate, was described in the literature [11]. Such reactions were not studied with imines of ketones capable of imine–enamine tautomerism.

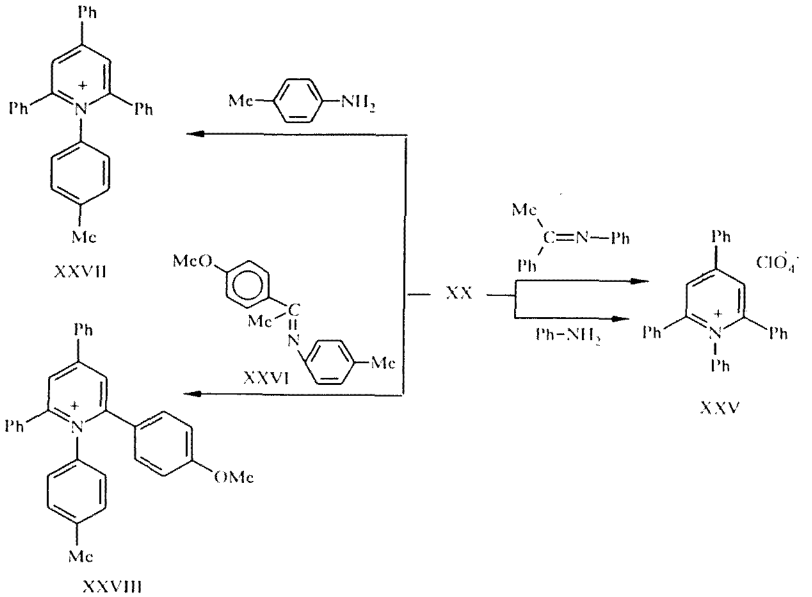
The data described above led one to believe that the presence of the available proton of the NH group in such enamines does not allow the reactions to proceed by the known scheme [11].



It seemed more probable that the reaction proceeded by a path analogous to the reaction of pyrylium salts with methylene-active compounds [12], i.e., with the formation of the substituted benzene (XXII) as a result of the intramolecular condensation at the active methylene group of the intermediate (XXI). However, it was found that the quinolizinium salt (XXIV) appears due to the reaction of the triphenylpyrylium salt (XX) with the 1-methyl-3,4-dihydroisoquinoline. Its formation is explained most logically by the preliminary shift of the proton in the intermediate (XXI) with the formation of the azatriene (XXIII), the electrocyclic cyclization of which, with the subsequent cleavage of acetophenone, also leads to the perchlorate (XXIV).

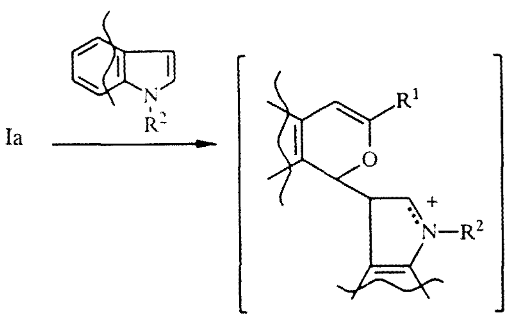
The reaction of the same pyrylium salt (XX) with the linear imine resulted, as expected, in the formation of the usual N-phenylpyridinium salt (XXV). However, taking into account the results of the reaction of the 2-benzopyrylium salts (Ic, d) with this imine, when its complete hydrolysis occurred, it was impossible to exclude the possible formation of the pyridinium salt precisely due to the appearance of aniline in the reaction mixture.

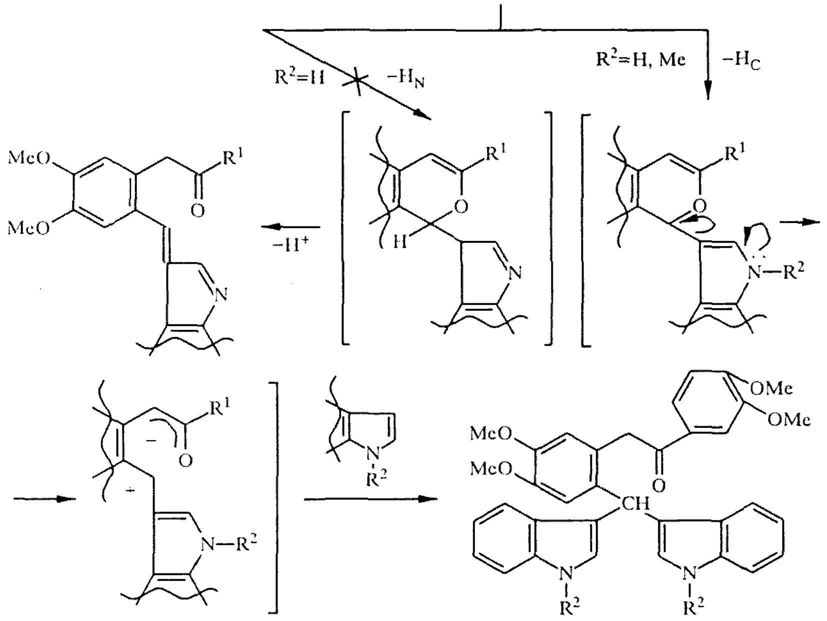
In order to explain a workable scheme for the process described in a series of monocyclic pyrylium salts with the α-position occupied, the imine (XXVI), the structure of which allows both reaction paths to be distinguished, was introduced into the reaction with the same pyrylium salt (XX).



The analysis of the PMR spectrum of the compound obtained showed that a mixture of two salts is formed as a result of the reaction: one of them (XXVII) is formed due to the reaction of the initial pyrylium salt (XX) with p-methylaniline, and the second (XXVIII) is formed by the scheme presented above. The integral data show that the ratio of the amounts of the salts (XXVII):(XXVIII) is 4:1.

Analogous results were also obtained in another control experiment by the reaction of the imine of acetophenone with 2,6-ditolyl-4-anisylpyrylium perchlorate. Therefore, monocyclic pyrylium salts of the type (XX), in contrast to 1-substituted 2-benzopyrylium salts, nevertheless react with linear imines of the type (VII) or (XXVI) without preliminary hydrolysis, although also to an insignificant degree.





XXX XXXIa,b

XXXI a $R^2 = H$, b $R^2 = Me$

It was interesting to investigate the behavior of compounds being potential enamines in reactions with pyrylium salts. Thus, the presence of the enamine fragment with a sufficiently available NH proton in the molecule of indole allowed us to accept the possibility of its reaction with the 2-benzopyrylium salt (Ia) with the formation of the compound (XXIX), i.e., by a path analogous to that described in the Schemes 1 and 2. However, it was shown that the final product here is the compound (XXXIa) – a unique derivative of triarylmethane. It can be seen that the cleavage of a proton occurred from the CH group instead of the expected NH deprotonation, and only the bipolar form (XXX) is capable of addition of the second molecule of indole in the intermediate, occurring in the form of several resonance forms, which is formed after the opening of the ring. The N-methylindole also naturally behaves analogously, forming the derivative (XXXIb).

EXPERIMENTAL

The IR spectra were taken on the Specord IR-75 spectrometer using mineral oil. The PMR spectra were taken on the Tesla 487 C (80 MHz), Tesla 567 A (100 MHz), and Unity 300 instruments at 20°C with $CDCl_3$ as the solvent; the internal standard was HMDS. The mass spectra were obtained with chemical ionization using isobutane as the gas reactant and the Finnigan MAT-4615 instrument.

The data of the elemental analysis for C, H, Cl, and N correspond with the calculated data.

3,4′,4,4′-Tetramethoxy-6-(2-iminophenyl-2-phenylpropenyl)desoxybenzoin (IIIa) ($C_{33}H_{31}NO_5$). To the suspension of 0.43 g (1 mmole) of the salt (Ia) in 5 ml of acetic acid is added 0.4 g (2 mmole) of the anil of acetophenone, and the mixture is heated until the solution of the salt is effected. After cooling the mixture, 40 ml of ether are added, and the precipitated residue is isolated, washed with 10 ml of ether, dried, and separated on a chromatographic column of Al_2O_3 with chloroform as the eluent. The fraction with the R_f 0.8 is collected and evaporated prior to the isolation of yellow crystals with the mp 168°C (from ethanol); the yield is 41%. The IR spectrum was as follows: 1673, 1580, 1140 cm^{-1}. The PMR spectrum was as follows: 3.72 ppm (3H, s, OCH_3), 3.80 ppm (3H, s, OCH_3), 3.82 ppm (3H, s, OCH_3), 3.9 ppm (3H, s, OCH_3), 4.1 ppm (2H, s, CH_2CO), and 6.50-7.65 ppm (17H, m, $15H_{arom} + 2H_{vinyl}$). The mass spectrum was as follows: 52(7), 51(21), 137(3.6) Ar^+; 165(26) $ArCO^+$. The isoquinolinium salt (IVa) remaining at the start is washed out with the 2:1 mixture of chloroform–ethanol; the yield is 35%.

3,3′,4,4′-Tetramethoxy-6-(2-iminophenyl-2-phenylpropenyl)desoxybenzoin (IIIb) ($C_{31}H_{27}NO_3$). This compound is obtained analogously. The yield is 40%. The mp is 160°C (from ethanol). The IR spectrum was as follows: 1660, 1580, and 1135 cm^{-1}. The PMR spectrum was as follows: 3.79 ppm (3H, s, OCH_3), 3.84 ppm (3H, s, OCH_3), 3.92 ppm (2H, s, CH_2CO), and 6.6-7.45 ppm (19H, m, $17H_{arom} + 2H_{vinyl}$).

3,3,4,4-Dimethoxy-6-(2-benzoyl-1-ethenyl)desoxybenzoin (Va) ($C_{27}H_{26}O_6$). A. To the suspension of 0.43 g (1 mmole) of the salt (Ia) in 10 ml of ethyl alcohol is added 0.4 g (2 mmole) of the anil of acetophenone, and the mixture is heated for 10 min. The mixture is cooled, and the precipitated isoquinolinium salt (IVa) (0.08 g) is filtered off. The mother liquid is diluted with 40 ml of ether prior to the isolation of 0.2 g (44%) of the diketone (Va) with the mp 188°C (from acetonitrile). The IR spectrum was as follows: 1673, 1660, and 1140 cm^{-1}. The PMR spectrum was as follows: 3.81 ppm (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.9 (3H, s, OCH_3) 4.38 ppm (2H, s, CH_2CO), and 6.66-8.34 ppm (12H, m, $10H_{arom}$ + $2H_{vinyl}$).

B. After the heating of the imine (IIIa) for 5 min in aqueous ethyl alcohol, the diketone (Va) is obtained in quantitative yield.

C. The diketone (Va) is formed with the yield of (72%) as the result of heating the perchlorate (XIV) in aqueous ethyl alcohol for 20 min.

1-(3,4-Dimethoxybenzoyl)-2-phenyl-6,7-dimethoxynaphthalene (VIa) ($C_{27}H_{24}O_5$). The suspension of 0.3 g (0.67 mmole) of the diketone (Va) in the mixture, consisting of 10 ml of ethyl alcohol and 1-2 drops of the 25% solution of NaOH, is boiled until the solution is effected and the dark blue color disappears. The mixture is cooled, and 40 ml of water are added. The precipitated residue is separated, washed with water, dried, and purified on a column with Al_2O_3 using chloroform as the eluent. The colorless fraction with the R_f 0.75 is collected; its evaporation leads to the isolation of 0.15 g (54%) of colorless crystals with the mp 142°C (from ethanol). The IR spectrum was as follows: 1665, 1633, and 1120 cm^{-1}. The PMR spectrum was as follows: 3.75 ppm (9H, s, $30CH_3$), 3.99 ppm (3H, s, OCH_3), and 6.45-7.86 ppm (12H, m, $12H_{arom}$). The mass spectrum was as follows: 137(7) Ar^+, 165(69) $ArCO^+$, 291(36) $[M-Ar]^+$, and 428(100) $[M]^+$.

1-Phenyl-1-(N-piperidyl)-3-[3,4-dimethoxy-6-(3,4-dimethoxyphenacyl)phenyl]propenylium Perchlorate (XIV) ($C_{32}H_{36}NO_5^+\ ClO_4^-$). To the suspension of 0.43 g (1 mmole) of the salt (Ia) in 5 ml of acetonitrile is added 0.4 ml (2 mmole) of the enamine of piperidine, and the mixture is heated until the solution of the salt is effected (2-3 min). The solution is cooled, and 50 ml of ether are added. To the oil which is formed in the course of 20 min, after the decantation of the ether layer, are added 2 ml of methyl alcohol, and the mixture is brought to boiling. The crystals of yellow color, which were precipitated on cooling, are separated to give the yield of 0.12 g (21%) and the mp 205°C. The IR spectrum was as follows: 1686, 1593, and 1100 cm^{-1}. The PMR spectrum was as follows: 1.65-1.69 ppm (4H, m), 2.1 ppm (3H, m), 3.62 ppm (2H, t), 3.85 ppm (3H, s, OCH_3), 3.95 ppm (3H, s, OCH_3), 4.00 ppm (3H, s, OCH_3), 4.05 ppm (5H, s, OCH_3 + CH_2CO), 4.20 ppm (2H, t), and 6.64-7.60 ppm (12H, m, $10H_{arom}$ + $2H_{vinyl}$).

3,3′,4,4′-Tetramethoxy-[2-(3,4-dimethoxydihydroisoquinolin-1-yl)ethen-1-yl]desoxybenzoin (XIX) ($C_{31}H_{33}NO_7$). To the suspension of 0.43 g (1 mmole) of the salt (Ia) in 3 ml of acetic acid is added 0.2 g (1 mmole) of the dihydroisoquinoline (XVIII), and the mixture is heated for 10 min. The mixture is cooled, and the precipitated yellow crystals are separated and washed with 10 ml of ether prior to the isolation of 0.5 g (74%) with the mp 195°C (from acetic acid). The IR spectrum was as follows: 1673, 1580, and 1153 cm^{-1}. The PMR spectrum was as follows: 2.64 ppm (2H, t, CH_2-), 3.6-3.87 ppm (20H, m, 2H, $-CH_2-$ + $60CH_3$), 4.32 ppm (2H, s, $-CH_2-$), and 6.33-7.65 ppm (9H, m, $7H_{arom}$ + 2H). The mass spectrum was as follows: 137(7) Ar^+, 165(100) $ArCO^+$, 166(14), and 198(28).

2,3-Dimethoxy-5,6-dihydro-8,10-diphenylbenzo[a]quinolizinium Perchlorate (XXIV) ($C_{27}H_{24}NO_2^+ClO_4^-$). To the suspension of 0.4 g (1 mmole) of the salt (XX) in 10 ml of methyl alcohol is added 0.9 g (4.5 mmole) of the isoquinoline (XVIII), and the mixture is heated for 10 min. When the mixture is cooled, 0.36 g (76%) of crystals of a bright yellow color is precipitated; the crystals are separated and washed with 5 ml of methyl alcohol. The mp is 250°C (from methanol). The IR spectrum was as follows: 1620, 1220, and 1100 cm^{-1}. The PMR spectrum was as follows: 3.06 ppm (2H, t, $-CH_2-$), 3.92 ppm (3H, s, OCH_3), 3.96 ppm (3H, s, OCH_3), 4.42 ppm (2H, t, $-CH_2-$), and 6.86-7.86 ppm (14H, m, $14H_{arom}$).

Di-3-indolyl-2-(3,4-dimethoxyphenacetyl)-4,5-dimethoxyphenylmethane (XXXIa) ($C_{35}H_{32}N_2O_5$). To the suspension of 0.43 g (1 mmole) of the salt (Ia) in 10 ml of ethyl alcohol is added 0.23 g (2 mmole) of indole, and the mixture is heated until the solution of the salt is effected. The mixture is cooled, and 100 ml of water are added; the precipitated residue is separated and washed with 50 ml of water. The yield of 0.45 g (54%) of the colorless crystals, with the mp 156°C (from ethanol) is obtained. The IR spectrum was as follows: 3580, 3366, 1660, and 1500 cm^{-1}. The PMR spectrum was as follows: 3.5 ppm (3H, s, OCH_3), 3.78 ppm (3H, s, OCH_3), 3.82 ppm (3H, s, OCH_3), 3.88 ppm (3H, s, OCH_3), 4.26 ppm (2H, s, CH_2CO), 5.86 ppm (1H, s, $-CH-$), 6.6-7.46 ppm (15H, m, $15H_{arom}$), and 8.86 ppm (2H, broad s, $2-NH-$).

Di-3-N-methylindolyl-2-(3,4-dimethoxyphenacetyl)-4,5-dimethoxyphenylmethane (XXXIb) ($C_{37}H_{36}N_2O_5$). This compound is obtained analogously. After cooling the mixture for 1 h, the precipitated crystals are separated and purified on a column with Al_2O_3 using chloroform as the eluent. The fraction with the R_f 0.8 is collected. The yield of 0.33 g (56%) of colorless crystals, with the mp 199°C (from propan-2-ol), is obtained. The IR spectrum was as follows: 1673, 1580, and 1440 cm^{-1}. The PMR spectrum was as follows: 3.58 ppm (3H, s, CH_3), 3.67 ppm (6H, s, 2 OCH_3), 3.84 ppm (3H, s, CH_3), 3.93 ppm (6H, s, 2 OCH_3), 4.26 ppm (2H, s, $-Ch_2-$), 5.94 ppm (1H, s, $-CH-$), and 6.47-7.42 ppm (15H, m, $15H_{arom}$).

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