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2-BENZOPYRYLIUM SALTS.

33.* 4-1'-DIMERIZATION OF 2-BENZOPYRYLIUM SALTS. FORMATION OF BENZ[*a*]ANTHRACENES

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The conversion of 2-benzopyrylium salts to benz[*a*]anthracenes, which proceeds through prior dimerization of a new type, was observed. An intermediate dimer was isolated, its properties were studied, and assumptions regarding the mechanisms of its formation and conversion to benz[*a*]anthracenes, cenes were expressed.

We have recently described the formation of chrysenes from 1-(α)-methyl-2-benzopyrylium salts [2, 3]; it was shown [3] that in the presence of bases the reaction proceeds via prior α-1'-dimerization. Under these conditions the 2-benzopyrylium salt, acting as a CH acid, is deprotonated with the formation of the anhydro base, the unshielded (by substituents) nucleophilic exo-methylene group of which reacts with the cation of the unchanged salt. The anhydro base molecule can be regarded as a cyclic divinyl ether in which the reaction center is the exocyclic double bond; the endocyclic fragment of the vinyl ether does not participate in this reaction.

If, however, the 2-benzopyrylium salt is not deprotonated but adds a nucleophile, the vinyl ether fragment that develops in the resulting adduct is capable of participating in dimerization of a new type. However, only opening of the heteroring with the subsequent occurrence of intramolecular recyclization reactions has thus far been observed in adducts of the II type under the conditions used to realize the electrophilic-nucleophilic reaction of 2-benzopyrylium salts [4, 5].

We have observed that a product of new 4-1'-dimerization (IIIa) is formed in quantitative yield when 1-phenyl-3-methyl-2-benzopyrylium perchlorate Ia is maintained in the two-phase 10% aqueous alkali—ether system at 20°C (on top of following page).

The presence of two asymmetric centers in dimer IIIa molecule leads to its isolation from the reaction in the form of a mixture of two diastereomers in a ratio of ~1:1, from which one diastereomer (monitoring by means of the PMR spectra) was obtained after three recrystallizations from acetonitrile.

Absorption bands of two carbonyl groups at 1650 and 1725 cm^{-1} are present in the IR spectrum of this diastereomer. The weak-intensity band at 1675 cm^{-1} is related to the vibrations of the C=C bond of the vinyl ether of the isochromene ring. The retention of the isochromene ring is also confirmed by the weak splitting of the methyl group in the 3 position of the heteroring ($J = 0.8$ Hz), which is due to allylic coupling of the methyl group with the vinyl proton, the signal of which is also somewhat broadened.

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*See [1] for Communication 32.

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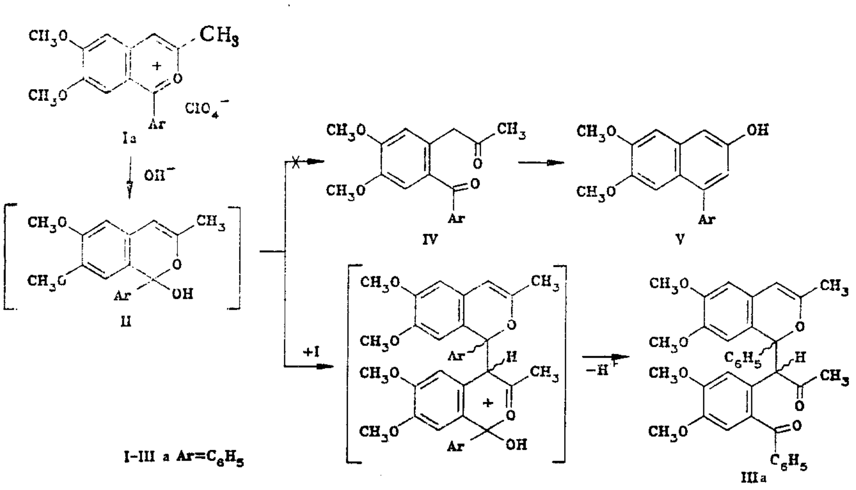
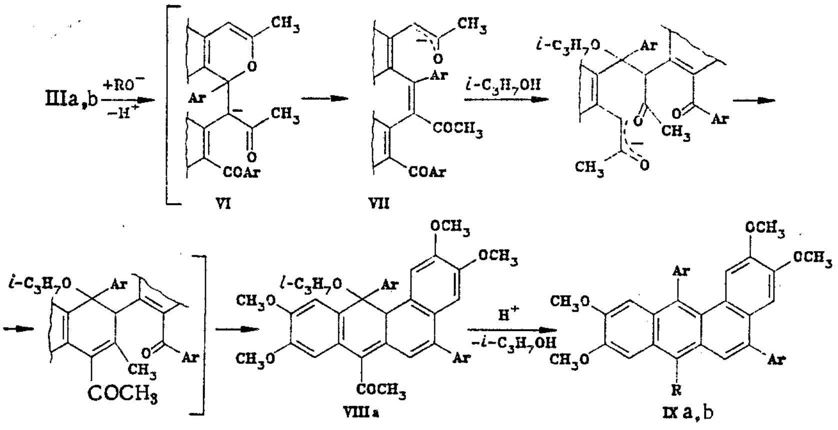


The signal of the methylidyne proton of the diketone fragment is shifted to weak field (5.75 ppm), and the signals of the CH_3O groups are recorded in the form of four singlets.

Dimerization of heteroaromatic cations, which proceeds similarly, is known for flavylium salts [6] and their nitrogen analogs [7]; however, the dimers formed in these cases are not capable to undergoing intramolecular transformations.

In contrast to this, dimer IIIa readily undergoes intramolecular condensation on heating in a mixture of aqueous alkali and isopropyl alcohol; like the transformations of the α-1'-dimerization product [3], dihydro derivative VIIIa is initially formed in quantitative yield.

Scheme



III, VI—IX a Ar=C_6H_5, b Ar=4-$CH_3OC_6H_4$; IX R=$COCH_3$, H

As in [3], in the crystallization of VIIIa from acetic acid a molecule of isopropyl alcohol is split out, and a completely aromatic benz[*a*]anthracene is formed.

The absorption band of a carbonyl group at 1700 cm^{-1} was recorded in the IR spectrum of this compound, while singlets of one methyl group and four methoxy groups, as well as a multiplet of 15 aromatic protons, were recorded in the PMR spectrum. The molecular ion (m/z 542) also corresponds to the proposed structure.

The spectral characteristics of VIIIa and IXa are extremely similar. However, a doublet of methyl groups of an isopropyl substituent is also present in the PMR spectrum of VIII, and the multiplet signal of the methylidyne proton at 3.50-3.90 ppm is partially overlapped by the signals of the methoxy groups. The signal of the proton in the α position relative to the isopropyl group shows up in the form of a singlet at 3.2 ppm. The hypsochromic shift of the long-wave absorption band in the electronic spectrum of VIIIa as compared with the spectrum of benz[*a*]anthracene IXa confirms partial disruption of the conjugation system in the VIII molecule.

Treatment of IXa (R = $COCH_3$) with strong acids as in [3] leads to ipso substitution of the acetyl group (IXa, R = H).

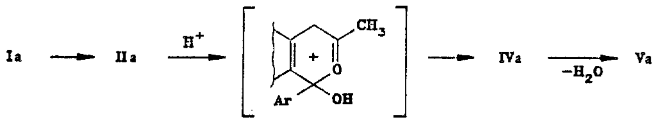
The formation of VIII and IX implies obligatory opening of the isochromene ring in dimer IIIa, which can be regarded as the product of reaction of the 2-benzopyrylium salt with a C-nucleophile. It must be noted that the possibility of the direct opening of the heteroring in such C-adducts is questionable [8], since a thermodynamically unfavorable intermediate with a dearomatized annelated benzene ring is formed in this case. Not deeming this evidence to be sufficiently convincing, especially since instances of photochemical opening of the ring in such C-adducts are known [9], let us note that the formation of the undesired intermediate can be avoided under the condition of prior deprotonation of the added C-substituent in dimer IIIa (see the scheme).

The anionic intermediate VI that develops upon deprotonation promotes opening of the heteroring [10] and the formation of the fragment of α,β-unsaturated ketone VII, the double bond of which is covalently solvated under the reaction conditions, and its carbonyl group participates in aldol condensation. A second aldol condensation leads to the formation of four-ring compound VIIIa.

By heating salt Ia in a solution of isopropyl alcohol with sodium isopropoxide one can obtain anthracene IXa (R = $COCH_3$) in 40% yield without isolation of dimer III.

In this case, in addition to dimerization of the intermediate pseudobase of the II type, there is a possibility of its opening to give diketone IVa, which, as a result of intermolecular condensations, is capable of forming anthracene IXa. However, the complete conversion of specially isolated diketone IVa to naphthol Va excludes this assumption.

In contrast to 1-methyl-2-benzopyrylium salts, which form chrysenes in both alkaline and acidic nucleophilic media [2], salt Ia at pH ≤ 7 is converted, depending on the heating time, to either diketone IVa or β-naphthol Va. Pseudobase IIa is probably also formed in this case in the first step of the reaction, but the reacting electrophile is not the starting salt but rather the proton.



The same unique 1,4-addition of the elements of water to 1-(CH_2-R)-2-benzopyrylium cations (R ≠ H) in an acidic medium evidently ensures their smooth recyclization to α-naphthols [11]. The decomposition of dimer IIIa to starting salt Ia or diketone IVa on treatment with acids can also most likely be explained by initial protonation of the vinyl fragment of the isochromene ring.

As expected, 2-benzopyrylium salt Ib, the electrophilicity of the 1 position of which is partially cancelled by the effect of the donor CH_3O group in the para position of the aryl substituent, undergoes 4-1'-dimerization somewhat less readily. Thus anthracene IXb can be obtained directly from salt Ib only in trace amounts, while its yield does not exceed 50% (based on starting salt Ib) when the reaction is carried out in successive fashion. Intermediate compounds could not be isolated and identified in this case.

Thus we have observed a new type of dimerization of 2-benzopyrylium salts that, in the case of salts Ia, b, results in the formation of benz[*a*]anthracenes, various representatives of which are widely used in the study of the mechanism of the development of cancer [12, 13]. The possibilities of the described type of dimerization are limited by structural requirements to a considerably smaller extent than the alternative α-1'-process [3]. In addition, the multiplicity and diversity of the reaction centers in the resulting dimers probably make it possible to realize various transformations of them.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Specord UR-71 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla BS-487C spectrometer (80 MHz) at 20°C with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with a Varian MAT-112 spectrometer at an ionization energy of 70 eV with direct introduction of the samples into the source. The UV spectra of solutions in MeOH were recorded with a Specord M-40 spectrophotometer. The purity of the products obtained was monitored by means of TLC on aluminum oxide in $CHCl_3$.

O-Benzoyl-α-(1-phenyl-3-methyl-6,7-dimethoxyisochromen-1-yl)-3,4-dimethoxyphenylacetone (IIIa). A suspension of 0.95 g (2.5 mmole) of perchlorate Ia [14] in a mixture of 3 ml of 10% aqueous NaOH solution and 4 ml of ether was stirred for 1 h at 20°C until the green color of the starting salt vanished. The precipitate was filtered, washed with water, and dried to give 0.71 g (98%) of colorless crystals with mp 152-154°C and R_f 0.55. IR spectrum: 1725, 1675, 1650, 1230 cm^{-1}. Signals of four methyl groups and eight OCH_3 groups were recorded in the PMR spectrum. Found, %: C 74.6, H 6.0. $C_{36}H_{34}O_7$. Calculated, %: C 74.7, H 5.9.

After three recrystallizations from CH_3CN, the product had mp 186°C. The IR spectrum and the results of elementary analysis did not change. PMR spectrum: 1.65 (s, CH_3), 2.05 (d, J = 0.8 Hz, CH_3), 3.49 (s, OCH_3), 3.59 (s, 2 OCH_3), 3.72 (s, OCH_3), 5.35 (broad s, 1 H), 5.75 (s, 1 H), 6.15 (s, 1 H_{arom}), 7.10-8.05 ppm (m, 13 H_{arom}).

5,12-Diphenyl-7-acetyl-12-isopropoxy-2,3,9,10-tetramethoxy-12,12a-dihydrobenz[*a*]anthracene (VIIIa). A suspension of 0.57 g (1 mmole) of IIIa in 15 ml of isopropyl alcohol and 0.5 ml of 10% aqueous NaOH solution was heated for 15 min. Dilution of the reaction solution with water and separation of the resulting precipitate gave 0.57 g (98%) of colorless crystals with mp 166°C (from isopropyl alcohol) and R_f 0.50. IR spectrum: 1700, 1610, 1600, 1570, 1255 cm^{-1}. PMR spectrum: 1.10 (d, 2 CH_3), 2.37 (s, CH_3), 3.12 (s, OCH_3), 3.33 (s, 1 H), 3.60-3.85 (m, 3 OCH_3, 1 H), 6.40 (s, 1 H), 6.67-7.50 ppm (m, 14 H_{arom}). UV spectrum, λ (log ε): 243.9 (4.4), 259.2 (4.5), 284 (4.4), 323 (4.2), 354.1 nm (3.9). Found, %: C 77.8, H 6.2. $C_{39}H_{38}O_6$. Calculated, %: C 77.7, H 6.5.

5,12-Diphenyl-7-acetyl-2,3,9,10-tetramethoxybenz[*a*]anthracene (IXa, R = $COCH_3$). A) In the recrystallization of 0.30 g (0.5 mmole) of VIIIa from 1 ml of glacial acetic acid, filtration after 24 h gave 0.21 g (77%) of light-yellow crystals with mp 249°C and R_f 0.85. Dilution of the filtrate with water gave an additional 0.05 g (20%) of IXa. IR spectrum: 1700, 1600, 1260, 1030 cm^{-1}. PMR spectrum: 2.72 (s, CH_3), 3.10 (s, OCH_3), 3.55 (s, OCH_3), 3.60 (s, OCH_3), 3.90 (s, OCH_3), 6.70 (s, 1 H_{arom}), 6.95 (s, 1 H_{arom}), 7.35 ppm (s, 13 H_{arom}). Found, %: C 79.7, H 5.6. $C_{36}H_{30}O_5$. Calculated, %: C 79.7, H 5.6.

B) A 0.03-g (1.3 mmole) sample of sodium was dissolved in 4 ml of isopropyl alcohol, 0.38 g (1 mmole) of perchlorate Ia was added, and the mixture was heated for 2 h. After 24 h, the mixture was filtered to give 0.11 g (40%) of IXa, which was completely identical to the product obtained by method A.

5,12-Diphenyl-2,3,9,10-tetramethoxybenz[*a*]anthracene (IXa, R = H). A solution of 0.27 g (0.5 mmole) of IXa (R = $COCH_3$) in 2 ml of CF_3COOH was allowed to stand for 2 days, after which it was evaporated, and the residue was purified by preparative column chromatography with collection of the fraction with R_f 0.8-0.9 ($Al_2O_3/CHCl_3$). Evaporation of the solvent gave 0.2 g (80%) of beige crystals with mp 221°C (from alcohol) and R_f 0.9. IR spectrum: 1620, 1600, 1170, 1020 cm^{-1}. PMR spectrum: 3.23 (s, OCH_3), 3.50 (s, OCH_3), 3.65 (s, OCH_3), 3.93 (s, OCH_3), 6.65-8.10 ppm (m, 16 H_{arom}). Found, %: C 81.4, H 5.8. $C_{34}H_{28}O_4$. Calculated, %: C 81.6, H 5.6.

5,12-Bis(4-methoxyphenyl)-7-acetyl-2,3,9,10-tetramethoxybenz[*a*]anthracene (IXb, R = $COCH_3$). A suspension of 0.41 g (1 mmole) of perchlorate IIb [15] in 15 ml of ether and 5 ml of 50% aqueous KOH solution and stirred for 5 h at 20°C, after which the ether layer was separated, and the solvent was removed by distillation. The residue was treated with 10 ml of isopropyl alcohol and 0.3 ml of 10% aqueous NaOH solution, and the mixture was refluxed for 15 min. It was then diluted with water, and the precipitate was separated and recrystallized from 2 ml of glacial acetic acid to give 0.15 g (50%) of light-yellow crystals with mp 204°C and R_f 0.75. IR spectrum: 1700, 1605, 1250,1030 cm^{-1}. PMR spectrum: 2.28 (s, CH_3), 3.38 (s, OCH_3), 3.67 (s, OCH_3), 3.70 (s, OCH_3), 3.83 (s, OCH_3), 3.85 (s, OCH_3), 3.95 (s, OCH_3), 6.83-7.45 ppm (m, 13 H_{arom}). Found, %: C 75.6, H 5.7. $C_{38}H_{34}O_7$. Calculated, %: C 75.7, H 5.7.

O-Benzoyl-3,4-dimethoxyphenylacetone (IV). Two drops of 96% sulfuric acid were added to a suspension of 0.20 g (0.5 mmole) of perchlorate Ia in 2 ml of alcohol and 2 ml of water, and the mixture was heated until the solid material dissolved. The mixture was then cooled and diluted with cold water, and the resulting precipitate was extracted with

$CHCl_3$ (three 3 ml portions). Evaporation gave 0.14 g (94%) of a colorless product with mp 127°C (from alcohol) and R_f 0.53. IR spectrum: 1700, 1640, 1600, 1250 cm^{-1}. PMR spectrum: 2.11 (s, CH_3), 3.69 (s, OCH_3), 3.85 (s, OCH_3, 2 H), 6.70 (s, 1 H_{arom}), 6.85 (s, 1 H_{arom}), 7.33-7.75 ppm (m, 5 H_{arom}). Found, %: C 72.3, H 6.2. $C_{18}H_{18}O_4$. Calculated, %: C 72.5, H 6.1.

1-Phenyl-6,7-dimethoxy-3-naphthol (V). A solution of 0.15 g (0.5 mmole) of IV in 3 ml of alcohol and two drops of 10% aqueous NaOH solution was refluxed for 15 min, after which it was acidified with 25% aqueous HCl solution, and the resulting precipitate was extracted with ether (three 5-ml portions). Drying and evaporation of the solvent gave 0.13 g (92%) of a light-brown oil with R_f 0.2. IR spectrum: 3380, 1600, 1250, 1010 cm^{-1}. PMR spectrum: 3.68 (s, OCH_3), 3.83 (s, OCH_3), 6.89-7.33 ppm (m, 9 H_{arom}). Found, %: C 77.5, H 5.9. $C_{18}H_{16}O_3$. Calculated, %: C 77.3, H 5.7.

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