UNUSUAL REACTION BETWEEN 6H-6-OXO-5-HALOANTHRA[1,9-cd]-ISOXAZOLES AND QUINOLINE

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The reaction of 6H-6-oxo-5-haloanthra[1,9-cd]isoxazoles with quinolines leads to unexpected fragmentation of the quaternized quinoline ring to give xylidine or o-toluidine.

It is known that 6H-6-oxo-5-chloroanthra[1,9-cd]isoxazole (Ia) readily quaternizes pyridine bases [1]. Cleavage of the salts formed in this way, either by dilute alkali solution [1] or by an alkylamine [2] gives N-(anthra[1',9'-cd]isoxazole-6-one-5-yl)-5-amino-2,4-pentadienal-1 or its alkylimines.

We have studied the reaction of 6H-6-oxo-5-haloanthra[1,9-cd]isoxazoles (Ia-e) with quinolines. It was found that the isoxazolones Ia-d at 25° did not react with anhydrous quinoline; at higher temperatures, the reaction proceeded ambiguously. However, in the presence of a small quantity of water, compounds Ia-d reacted smoothly with quinoline at 25° to give high yields of compounds which, based on UV and IR spectroscopic data [3], were assigned the structure 6H-6-oxo-5-arylaminoanthra[1,9-cd]isoxazole.

Quinoline salts are known [4] to be cleaved by alkali to give N-substituted derivatives of o-aminocinnamic aldehyde, which exist in tautomeric equilibrium with 2-hydroxy-1,2-dihydroquinolines. It is therefore possible that the compounds IIa-d are formed in the reaction which we are studying. However, in the PMR spectra of the substances formed in the reaction of the isoxazoles Ia-d with quinoline, there are no signals corresponding to aldehyde group protons, or to "unsaturated" protons; at 2.2-2.3 ppm, compounds IIa-d give rise to two singlets.

It is probable that the products of the reaction of isoxazoles Ia-d with quinoline are 6H-6-oxo-5-xylidinoanthra[1,9-cd]isoxazoles. In the mass spectrum of one of these products, IIIa, obtained from isoxazolone Ia and quinoline, there is a strong peak at M-15; this is characteristic for dimethylbenzenes [5]. Reductive cleavage of compound IIIa does in fact give xylidine.

Fractional crystallization of acetylated xylidines gave 3,5-dimethylacetylaminobenzene, which on hydrolysis yielded 3,5-dimethylaniline; these compounds were identified by PMR spectroscopic data [6], and also by comparison with authentic material. Comparison of the PMR spectra of the xylidines obtained from compound IIIa with the PMR spectra of all the possible xylidine isomers indicates that the mixture, in addition to 3,5-dimethylaniline, contains 3,4-dimethylaniline. The two amines were present in the ratio 2:1.

The reaction of 6H-6-oxo-5-fluoroanthra[1,9-cd]isoxazole (Ie) with authentic samples of 3,5-dimethyl- and 3,4-dimethylaniline gave compounds IIIf, g.

The positions of the signals from the methyl-group protons of compounds IIIf, g agree with those of compound IIIa. Moreover, the PMR spectrum of the mixture of the products IIIf, g, obtained in the ratio 2:1, are completely identical with the PMR spectrum of compound IIIa. Signals at 2.2-2.3 ppm from the protons of the methyl groups of the reaction products suggest that isoxazolones Ib-d react with quinoline in the same way as compound Ia.

Thus, the reaction of 6H-6-oxo-5-haloanthra[1,9-cd]isoxazoles with quinoline occurs with an unusual fragmentation of the quinoline ring.

Compounds IIIa-d could not be separated by chromatography, and the data given in Table 1 are for unseparated compounds.

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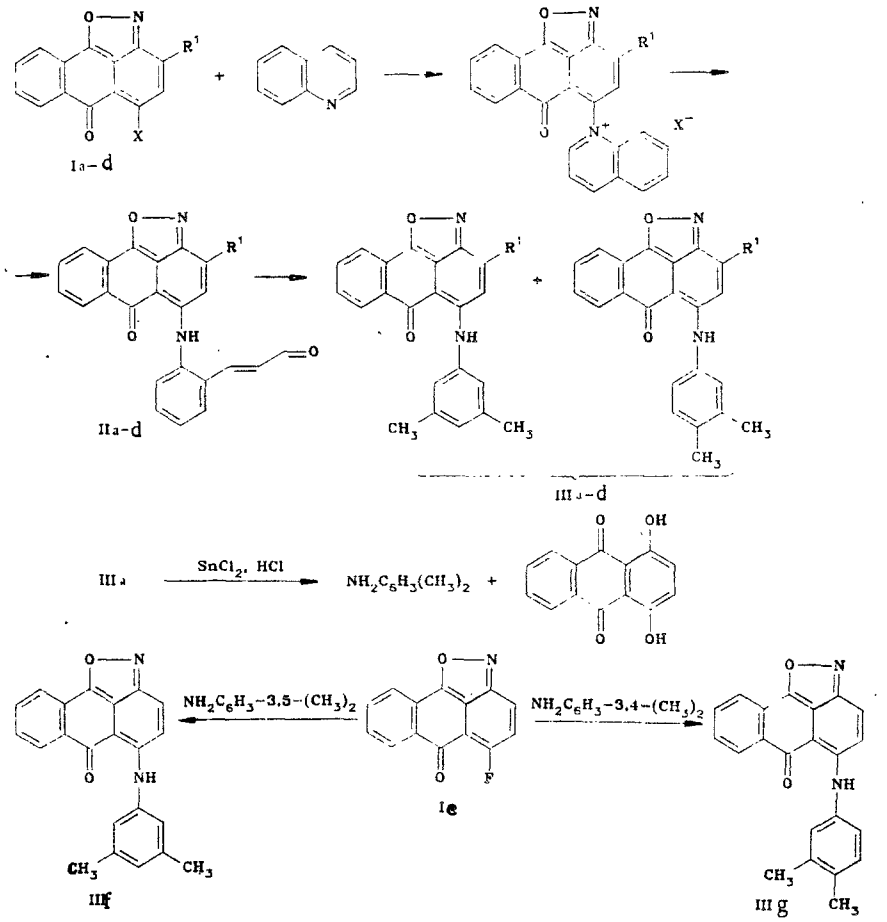


I a X=Cl, R^1=H; b X=R^1=Cl; c X=R^1=Br; d X=Br, R^1=CH_3; e X=F, R^1=H;
II, III a,e–g R^1=H; b R^1=Cl; c R^1=Br; d R^1=CH_3

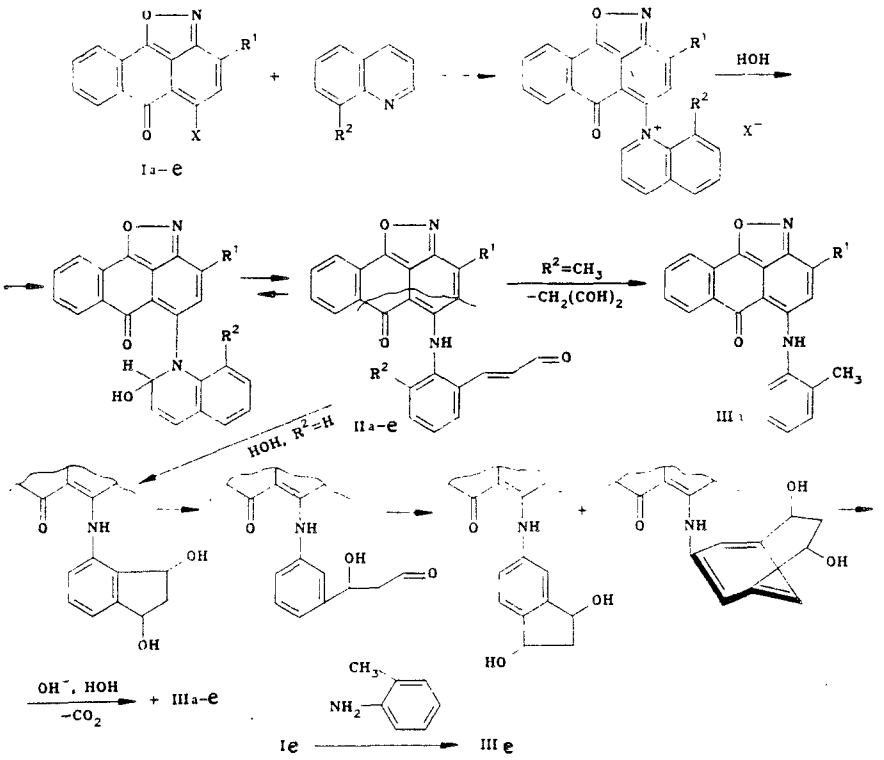
As noted above, the formation of compounds IIIa-d from the isoxazolones Ia-d was made possible by the presence of water in the quinoline. Assuming, based on this, that quinoline salts are formed first, and these then react to give the aldehydes IIa-d, we attempted to carry out this reaction in the presence of substances which are selective for aldehydes – an oxidizing agent (Ag_2O) and a reducing agent ($NaBH_4$). However, these reaction conditions give mainly compounds IIIa-d. Performing the reaction in a sealed tube in an atmospher of helium did not alter the course of the reaction, showing that oxygen does not take part in the reaction.

It is suggested that the sterically hindered position of the amino group in the aldehydes IIa-d, and also their low nucleophilic character prohibits their stabilization by cyclization to derivatives of 2-hydroxydihydroquinoline. In addition to this, by the direct and reverse reactions of hydroxyalkylation, hydration, and decarboxylation, the aldehydes IIa-d in fact can change to compounds IIIa-d:

TABLE 1. 6H-6-Oxo-5-xylidinoanthra[1,9-cd]isoxazoles IIIa-d

Compound	mp,* °C	UV spectrum, cm^{-1} λ_{max}, nm (log ε)	IR spectrum, cm^{-1}		Found, %		Empirical formula	Calculated, %		Yield, %
			C=O	C=N	N	Hal		N	Hal	
IIIa	180—196	500 (4,31) 526 (4,35)	1666	1620	8,0		$C_{22}H_{16}N_2O_2$	8,2		67
IIIb	176—186	505 (4,30) 530 (4,35)	1673	1620	7,3 7,4	9,5 9,3	$C_{22}H_{15}ClN_2O_2$	7,5	9,5	45
IIIc	196—215	505 (4,24) 530 (4,29)	1660	1615	6,3 6,1	18,4 18,5	$C_{22}H_{15}BrN_2O_2$	6,6	19,1	67
IIId	189—196	495 (4,30) 521 (4,36)	1673	1615	7,5 7,6		$C_{23}H_{18}N_2O_2$	7,9		70

*Recrystallized from a 1:2 mixture of benzene and heptane.



Under the reaction conditions employed, the 2-, 4-, 6-, 7-, and 8-methylquinolines did not react with the isoxazolones Ia-d.

The isoxazolone Ie with a fluorine atom, which is sensitive to nucleophilic attack, at position 5, reacts with 8-methylquinoline at 25°. Carrying out the reductive cleavage of the product of this reaction IIIe, we isolated o-toluidine. A compound, identical with compound IIIe, was obtained from the oxazolone Ie and o-toluidine. Apparently, in the absence of the above reaction between the oxazolones Ia-d and quinoline, the aldehyde group cannot migrate with the ring, and fragmentation of the quinoline ring with isolation of malonic dialdehyde occurs. In this case the transformation Ie → IIIe can be considered as a reverse Combes [7] reaction, or a modification of it [8].

Thus, the splitting of quinoline salts can occur in different ways, depending on the structural characteristics of both the quinoline ring, and the group attached to the nitrogen atom of the quinoline salt.

EXPERIMENTAL

Infrared spectra were recorded on a Specord 75-IR spectrophotometer (mineral oil); ultraviolet spectra were taken on a Specord UV-vis (in ethanol). The mass spectrum of compound IIIa was obtained on an MS-902 AEI at an ionization voltage of 70 eV and inlet source temperature of 150°. PMR spectra were recorded on a Bruker CXP-300 (300 MHz); samples were dissolved in $CDCl_3$, internal standard – HMDS. Purity of starting and final compounds, and also the course of the reaction were checked by TLC on Silufol UV-254 plates.

6H-6-Oxo-5-xylidinoanthra[1,9-cd]isoxazoles (IIIa-d). A mixture of 10 mmoles of isoxazolones Ia-d, 200 ml of quinoline, and 10 ml of water was stirred at 25° for 160 h. The reaction mixture was then poured into a mixture of 200 ml of HCl, 400 g of ice, and 400 ml of water. The dark-red compounds IIIa-d were filtered off. The dried compounds were chromatographed on silica gel (100 × 250), which had previously been treated with water [9] (eluant – benzene), and recrystallized from a 1:2 benzene–heptane mixture.

Reductive Cleavage of Compound IIIa. A mixture of 15 g (44 mmoles) of compound IIIa, 200 ml of concentrated HCl, and 50 g (220 mmoles) of $SnCl_2 \cdot 2H_2O$ was refluxed for 5 h. After cooling to 10°, the reaction mixture was diluted with an equal volume of water, and the precipitated material filtered off. Ice (500 g) was added to the filtrate and the solution made strongly alkaline with NaOH. The oily layer was extracted twice with benzene and the extract dried over KOH. The residue, after removal of the benzene, contained products which boiled at 200-225°. This mixture of xylidines (4 g) was acetylated with acetic anhydride

and after three recrystallizations from aqueous ethanol, pure 3,5-dimethyl-1-acetylaminobenzene was isolated. Evaporation of the filtrates gave a mixture of the acetyl derivatives of 3,5- and 3,4-dimethylaniline, which were characterized by comparison with authentic material.

6H-6-Oxo-5-(3,5-dimethylphenylamino)anthra[1,9-cd]isoxazole (IIIf). A solution of 0.1 g (0.42 mmole) of isoxazolone Ie in 3 ml of dioxane was maintained at 25° for 20 h with 1 g (0.83 mmole) of 3,5-dimethylaniline. After 20 h, 100 ml of water was added, and the precipitated material was filtered off to give 0.12 g (86%). mp 222-224° (from 1:2 mixture of benzene and heptane). PMR spectrum: 2.31 (6H, s, 3,5-dimethyl): 6.8-8.5 (9H, m, aromatic protons); 11.42 ppm (1H, s, NH). UV spectrum, λ_{max} (log ε): 500 (4.32), 526 nm (4.36) IR spectrum: 1620, 1670 cm^{-1} (C=N, C=O). Found, %: N 8.32. $C_{22}H_{16}N_2O_2$. Calculated, %: N 8.23.

6H-6-Oxo-5-(3,4-dimethylphenylamino)anthra[1,9-cd]isoxazole (IIIg) was obtained by the method given above in 86% yield with mp 195-196° (from a 1:2 mixture of benzene and heptane). PMR spectrum: 2.23 (6H, s, 3,4-dimethyl): 7.0-8.5 (9H, m, aromatic protons): 11.42 ppm (1H, s, NH). UV spectrum, λ_{max} (log ε): 500 (4.29), 526 nm (4.33). IR spectrum: 1610, 1660 cm^{-1} (C=N, C=O). Found, %: N 8.1. $C_{22}H_{16}N_2O_2$. Calculated, %: N 8.2.

6H-6-Oxo-5-(2-methylphenylamino)anthra[1,9-cd]isoxazole (IIIe). A mixture of 1.2 g (5 mmoles) of isoxazole Ie, 50 ml of 8-methylquinoline, and 1 ml of water was maintained at 25° for 30 h. The reaction mixture was poured into a mixture of 50 ml of concentrated HCl and 400 g ice, and the dark-red product filtered off. Recrystallization from a 1:2 mixture of benzene and heptane gave 1.55 g (93%) of IIIe. The crystals changed form at 140-160°, and melted at 172-174°. PMR spectrum: 2.32 (3H, s, CH_3); 7.0-8.5 (10H, m, aromatic protons); 11.32 ppm (1H, s, NH). UV spectrum, λ_{max} (log ε): 495 (4.24), 521 nm (4.29). IR spectrum: 1620, 1670 cm^{-1} (C=N, C=O). Found, %: N 8.1. $C_{21}H_{14}N_2O_2$. Calculated, %: N 8.6.

Reductive cleavage of isoxazolone (IIIe) was carried using 6.52 g (20 mmoles) of starting material by the action of $SnCl_2 \cdot 2H_2O$ in a mixture of concentrated HCl and AcOH as described in [10] to give 1.2 g (56%) of o-toluidine.

Reverse Synthesis of Isoxazolone (IIIe). A mixture of 0.6 g (25 mmoles) of compound Ie, and 1 g (9.3 mmoles) of o-toluidine in 10 ml of dioxane was mixed for 20 h at 25°. After dilution with 100 ml of water, the product was filtered off and recrystallized to give 0.74 g (95%) of material, completely identical with the material obtained from the isoxazolone Ie and 8-methylquinoline, as indicated above.

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