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THERMOLYSIS OF SOME 6H-6-OXO-3-AMINOANTHRA[1,9-cd]ISOXAZOLES

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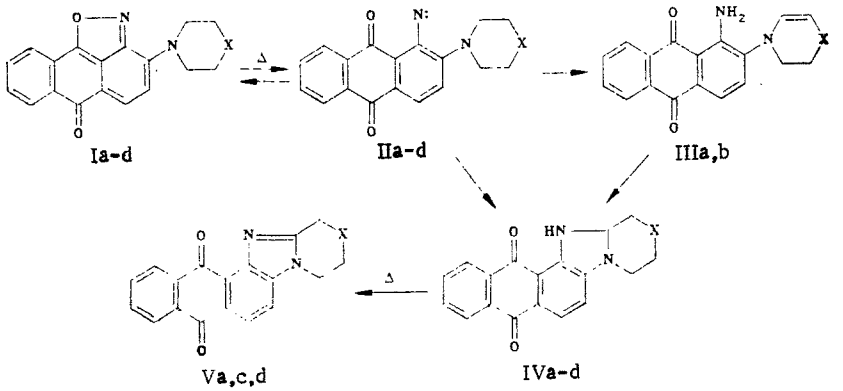
The thermolysis of 6H-6-oxo-3-alkylaminoanthra[1,9-cd]isoxazoles leads to derivatives of anthra[1,2-d]imidazole and 1-amino-9,10-anthraquinone.

In [1] it was demonstrated that 6H-6-oxo-3-morpholinoanthra[1,9-cd]isoxazole (Ia) is converted to 6H,11H,6,11-dioxoanthra[1,2-d]imidazole derivatives IVa and VA when it is heated in various solvents [dioxane, dimethylformamide (DMF), toluene], whereas 1-amino-2-dehydromorpholine-9,10-anthraquinone (IIIa) was isolated when starting Ia was maintained in refluxing pyridine.

In the present research we attempted to determine the structural requirements for substances that undergo this sort of conversion. We studied the transformations of various 6H-6-oxo-3-amino derivatives Ia-d in organic solvents. We found that 6H,11H,6,11-dioxoanthra[1,2-d]imidazoline derivatives IVa-d are the final or intermediate products in all of the investigated examples. Like the starting isoxazolones Ia,c,d, IVa,c,d undergo dehydrogenation to imidazoles Va,c,d at 135-180°C in various solvents.



a X=O; b X=N—C_6H_5; c X=CH_2; d X=$(CH_2)_2$

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TABLE 1. Products of the Thermolysis of 6H-6-Oxo-3-amino-anthra[1,9-cd]isoxazoles

Compound	X	mp,* °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}		N found, %	Empirical formula	N calc., %	Yield, %
				NH-(NH)	C=O**				
IIIa	O	156—157	513 (3,99)	3450, 3300	1660, 1625	9.3	$C_{18}H_{14}N_2O_3$	9.1	78
IIIb	N—C_6H_5	196—197	560 (3,90)	3425, 3260	1650, 1625	10.7	$C_{24}H_{19}N_3O_2$	11.0	84
IVa	O	266—268	550 (4,08)	(3400)	1640 (1620)	8,8	$C_{18}H_{14}N_2O_3$	9,1	67
IVb	N—C_6H_5	237—239	555 (3,81)	(3300)	1640 (1615)	10,7	$C_{24}H_{19}N_3O_2$	11,0	60
IVc	CH_2	204—206	570 (4,01)	(3340)	1640 (1620)	8,9	$C_{19}H_{16}N_2O_2$	9,2	56
IVd	$(CH_2)_2$	282—283	560 (3,95)	(3358)	1635 (1615)	8,5	$C_{20}H_{18}N_2O_2$	8,8	96
Va	O	269—270	370 (3,92)	—	1650	8,9	$C_{18}H_{12}N_2O_3$	9,2	80
Vc	CH_2	217—218	380 (3,88)	—	1660	8,9	$C_{19}H_{14}N_2O_2$	9,3	65
Vd	$(CH_2)_2$	290—291	376 (3,95)	—	1665	8,6	$C_{20}H_{16}N_2O_2$	8,9	69

*The compounds were crystallized: IIIa and IVa, c from chloroform, IIIb and IVb,d from benzene, Va,d from methanol, and Vc from acetone. At 140-150°C the crystals of IVa,c,d changed their form and melted at the temperatures cited.

**The position of the lower-frequency band of stretching vibrations of the carbonyl group is indicated in parentheses.

The thermolysis of 3-(4-phenylpiperazino)anthra[1,9-cd]-6-isoxazolone (Ib) in refluxing benzene leads to 1-amino-2-(4-phenyl-2,3-dehydropiperazino)-9,10-anthraquinone (IIIb). 3-Morpholinoanthra[1,9-cd]-6-isoxazolone was also similarly converted in refluxing pyridine [1]. Nitrenes IIa,b, which are formed as a result of the thermolysis of Ia,b, evidently then dehydrogenate the o-oriented tetrahydroazine ring and are converted to amines IIIa, b. We confirmed the possibility of the III → IV transformation experimentally. When amine IIIb is heated to 130°C in o-dichlorobenzene, it undergoes cyclization to imidazoline IVb in 86% yield. Moreover, imidazolines IVc, d were isolated directly from isoxazolones Ic,d under similar or more severe conditions. This may constitute evidence in favor of the direct incorporation of the nitrene in the C—H bond in the latter cases. Considering the structural peculiarities of the cyclic substituent in the 3 position of starting isoxazolones Ia-d, it might be noted that dehydrogenation by the nitrene and the formation of amines III are observed in those cases in which fragment X contains an unshared electron pair. It is known [2] that electron-pair donors are capable of affecting the multiplicity and reactivity of nitrenes. It is possible that this is why the thermolysis of isoxazolones Ia-d proceeds differently.

Imidazoles V are formed in rather high yields in the thermolysis of starting isoxazolones Ia,c,d (Table 1). It is known [3] that, in the benzene series, the yields of the corresponding benzimidazoles often exceed 50%, as, for example, in the thermolysis of o-piperidinophenyl azide in nitrobenzene or in the photolysis of such substances in acetophenone. This may be associated both with the participation of nitrobenzene as an oxidizing agent in the first case and, evidently, with photolytic oxidation of the intermediate imidazolines by acetophenone in the second case.

In the anthraquinone series the dehydrogenation of imidazolines to imidazoles may be facilitated, probably by the quinoid system itself. Thus, for example, the thermal cyclization of 1-piperidino-2-azido-9,10-anthraquinone to the corresponding imidazole in refluxing o-dichlorobenzene proceeds in 73-80% yield [4]. In this reaction, as in the reactions that we studied, the anthraquinoid system of the molecules of IV and V can accept hydrogen from imidazolines of the IV type, and the resulting anthradihydroquinone derivatives, under the influence of air oxygen, can again undergo oxidation to substances of the IV and V types. Data on the products of thermolysis of isoxazolones Ia-d are presented in Table 1.

The structures of III-V are confirmed by the results of molecular spectroscopy. Amines IIIa,b differ from the saturated 1-amino-2-cycloalkylaminoanthraquinones VIa-d that we obtained for comparison, with respect to a bathochromic shift of the long-wave band of the UV

spectra. Doublet signals of "olefin protons" are present in the PMR spectra of amines IIIa, b at 5.58 and 6.33 ppm and at 5.50 and 6.23 ppm; the appearance of multiplet signals of protons of methylene groups is observed at 3.27-3.61 and 3.83-4.17 ppm for IIIa and at 3.44-3.83 ppm for IIIb. The ratios of the integral intensities of the protons of III-V correspond to the proposed structures.

The IR spectra of imidazolines IV in the region of carbonyl absorption contain two bands of different intensity, viz., a strong band at 1640 cm^{-1} and a medium band at 1615-1620 cm^{-1}, and NH stretching vibrations are observed at 3300-3400 cm^{-1}. The presence of a lower-frequency carbonyl band is evidently associated with the development of an intramolecular hydrogen bond. Let us note that, according to the data in [5], an intramolecular hydrogen bond is absent in 2,2-pentamethyleneanthra[1,2-d]imidazolines because of the unfavorable geometrical orientation of the NH and carbonyl fragments. It is known that there is a strong intramolecular hydrogen bond between the NH fragment in the 1 position and the carbonyl group in the 9 position in tetrahydroanthraquinonepyrazine derivatives; the NH stretching vibrations appear at 3280 cm^{-1} (chloroform), and two bands of stretching vibrations of carbonyl groups are found at 1622 and 1642 cm^{-1}. Comparing these results with the data that we obtained for imidazolines IV, particularly taking into account the higher-frequency position of the band of NH stretching vibrations (3400 cm^{-1} for IVa in chloroform), as well as the appearance of two bands of stretching vibrations of carbonyl groups with different intensities, it may be assumed that the presence of an intramolecular hydrogen bond that is substantially weaker than in tetrahydroanthraquinonepyrazine is possible in imidazolines IVa-d [5, 6]. The presence in IVa-d of a cyclic saturated fragment (piperidine, morpholine, etc.) evidently facilitates the formation of a weak hydrogen bond in them.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-Vis spectrophotometer. The IR spectra of suspensions in mineral oil were obtained with a Specord 75-IR spectrometer. The mass spectrum of Vc was obtained with an MS-902 AEI spectrometer; the ionizing-electron energy was 70 eV, and the temperature of the direct-inlet system was 150°C. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Bruker WH-90 (90 MHz) and Tesla BS- 467A (60 MHz) spectrometers. The chemical shifts were measured relative to the signal of hexamethyldisiloxane (HMDS). The course of the reaction in all cases was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates; preparative chromatography was carried out on silica gel. The melting points were determined with a Boetius microheating stage.

Starting isoxazolones Ia,c were obtained by the method in [7].

6H-6-Oxo-3-(4-phenylpiperazino)anthra[1,9-cd]isoxazole (Ib). A mixture of 2.56 g (10 mmole) of 6H-6-oxo-3-chloroanthra[1,9-cd]isoxazole, 6.48 g (40 mmole) of N-phenylpiperazine, and 100 ml of methanol was stirred at 50°C for 12 h. The reaction product crystallized from the hot solution. The mixture was cooled, and the crystals were separated by filtration and recrystallized from benzene–heptane (10:1) to give 3.1 g (81%) of a product with mp 152-153°C. UV spectrum, λ_{max} (log ε): 530 nm (4.50). IR spectrum: 1625, 1665 cm^{-1} (C=N, C=O). Found, %: N 10.9. $C_{24}H_{19}N_3O_2$. Calculated, %: N 11.0.

6H-6-Oxo-3-hexamethyleneaminoanthra[1,9-cd]isoxazole (Id). This compound was obtained by the method indicated above from 2.5 g (10 mmole) of 6H-6-oxo-3-chloroanthra[1,9-cd]isoxazole and 5 g (50 mmole) of hexamethyleneamine in methanol. The yield of Id, with mp 141-142°C (from ethanol), was 2.43 g (78%). UV spectrum, λ_{max} (log ε): 546 nm (4.62). IR spectrum: 1626, 1666 cm^{-1} (C=N, C=O). Found, %: N 8.7. $C_{20}H_{18}N_2O_2$. Calculated, %: N 8.8.

1-Amino-2-dehydromorpholine-9,10-anthraquinone (IIIa). A 1.5 g (5 mmole) sample of isoxazolone Ia was refluxed with stirring in 10 ml of pyridine, after which the mixture was cooled, and the resulting precipitate was removed by filtration, washed with ether, and crystallized from chloroform (see Table 1). PMR spectrum (d_6-DMSO): 7.08-8.33 (8H, m, aromatic and NH_2 protons); 5.58; 6.33 (2H, two d, olefinic protons); 3.27-3.61; 3.83-4.17 ppm (4H, two m, CH_2CH_2).

1-Amino-2-(4-phenyl-2,3-dehydropiperazino)-9,10-anthraquinone (IIIb). A 0.95 g (2.5 mmole) sample of isoxazolone Ib was refluxed in 20 ml of benzene for 4 h, after which the mixture was cooled and treated with 10 ml of heptane, and the resulting precipitate was removed by filtration and washed with ether to give 0.80 g (84%) of the product (see Table 1).

PMR spectrum ($CDCl_3$): 6.83-8.20 (11H, m, aromatic and NH_2 protons); 5.50; 6.23 (2H, two d, olefinic protons); 3.44-3.83 ppm (4H, m, CH_2CH_2).

3,4,8,13,14,14a-Hexahydro-1H-anthra[1',2'-5,4]imidazo[2,3-c]-2,5-oxazin-8,13-dione (IIa). A 1.53 g (5 mmole) sample of isoxazolane Ia was refluxed in 20 ml of dioxane for 30 min, after which the mixture was cooled, and the resulting precipitate was removed by filtration and crystallized from chloroform to give 1.03 g (67%) of the product (see Table 1).

3,4,8,13,14,14a-Hexahydro-1H-anthra[1',2'-5,4]imidazo[2,3-c]-2-phenyl-2,5-pyrazine-8,13-dione (IVb). A 1 g (2.6 mmole) sample of isoxazolone Ib was heated with stirring in 20 ml of o-dichlorobenzene at 130°C for 30 min, after which the mixture was cooled and treated with 10 ml of heptane. The resulting precipitate was removed by filtration and washed with ether. The dried precipitate was chromatographed on silica gel by elution with benzene. The principal blue zone was collected, the benzene was evaporated, and product IVb was recrystallized from benzene (see Table 1). Compound IVb was obtained by heating 0.58 g (1.5 mmole) of IIIb in 10 ml of o-dichlorobenzene at 130°C for 30 min, followed by cooling and treatment of the reaction mixture with 10 ml of heptane. The resulting precipitate was removed by filtration, dried, chromatographed on silica gel by elution with benzene, and recrystallized from benzene to give 0.46 g (80%) of a product with mp 238-239°C. UV spectrum, λ_{max} (log ε): 555 nm (3.8). IR spectrum: 3300 (NH), 1640 cm^{-1} (C=O). Found, %: N 10.7. $C_{24}H_{19}N_3O_2$. Calculated, %: N 11.0.

Anthra[1,2-d]imidazoline-2,3-tetramethylene-6,11-dione (IVc). A 0.5 g (1.6 mmole) sample of isoxazolone Ic was maintained at 120°C for 1 h in 25 ml of dimethylformamide (DMF), after which the mixture was cooled and diluted to 200 ml with water. The aqueous mixture was treated with 20 g of NaCl, and the precipitate was removed by filtration, dried, and chromatographed on silica gel by elution with benzene–acetone (10:0.6) to give 0.28 g (56%) of the product (see Table 1).

Anthra[1,2-d]imidazoline-2,3-pentamethylene-6,11-dione (IVd). A 0.5 g (1.6 mmole) sample of isoxazolone Id was dissolved in 10 ml of DMF, and the solution was maintained at 125°C for 30 min. Compound IVd was then isolated and purified by the method set forth above (see Table 1).

3,4,8,13-Tetrahydro-1H-anthra[1',2'-5,4]imidazo[2,3-c]-2,5-oxazine-8,13-dione (Va). A 1.5 g (4.9 mmole) sample of imidazoline IVa was refluxed in 15 ml of o-dichlorobenzene for 30 min, after which the mixture was cooled to 20°C, and the yellow precipitate was removed by filtration, washed with ether, and recrystallized from methanol (Table 1).

Anthra[1,2-d]imidazole-2,3-tetramethylene-6,11-dione (Vc). A 1 g (3.3 mmole) sample of isoxazolone Ic was maintained in 10 ml of DMF at 135°C for 2.5 h, after which the mixture was cooled to 20°C, and the yellow precipitate was removed by filtration, washed with ether, recrystallized from acetone, and rewashed with ether (see Table 1). The molecular mass was determined by mass spectrometry and was in agreement with the calculated value. Molecular-ion peak M^+ 302, which was the maximum peak in the spectrum, was present in the mass spectrum of Vc. Elimination of a carbonyl group, as evidenced by the presence of fragment ion M^+ 274, evidently occurs in the first stage of the fragmentation of molecular ion M^+.

Anthra[1,2-d]imidazole-2,3-pentamethylene-6,11-dione (Vd). A 0.3 g (0.94 mmole) sample of isoxazolone Id was maintained in 5 ml of N,N-dimethylacetamide at 135°C for 20 min, after which the yellow precipitate was removed by filtration, washed with ethanol, and recrystallized from methanol (see Table 1).

1-Amino-2-morpholino-9,10-anthraquinone (VIa). A 1 g (3.3 mmole) sample of isoxazolone Ia was hydrogenated at atmospheric pressure in 150 ml of ethanol over 0.5 g of 0.2% palladium on carbon for 16 h at 50°C. The hot solution was removed from the catalyst by filtration, concentrated in vacuo to a volume of 40 ml. Water (50 ml) was added to the concentrate, and the aqueous mixture was cooled and filtered to give 0.8 g (79.5%) of a product with mp 178°C. UV spectrum, λ_{max} (log ε): 487 nm (3.97). IR spectrum: 3450, 3300, 1640, 1620 cm^{-1} (NH_2, C=O). Found, %: N 9.0. $C_{18}H_{16}N_2O_3$. Calculated, %: N 9.0.

1-Amino-2-(4-phenylpiperazino)-9,10-anthraquinone (VIb). A 0.26 g (5.2 mmole) sample of hydrazine hydrate and 0.3 g of 0.2% palladium on carbon were added to a suspension of 0.5 g (1.3 mmole) of isoxazolone Ib in 30 ml of ethanol, after which the mixture was maintained at 60°C for 5 h. The hot solution was filtered, the filtrate was diluted with 100 ml of water, and the precipitate was removed by filtration to give 0.32 g (64%) of a product with

mp 260-261°C. UV spectrum, λ_{max} (log ε): 495 nm (3.69). IR spectrum: 3415, 3295, 1640, and 1620 cm^{-1} (NH_2, C=O). Found, %: N 10.6. $C_{24}H_{21}N_3O_2$. Calculated, %: N 11.0.

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SYNTHESIS OF 3-AMINO-6-METHYL-5-ETHOXYCARBONYL-4,7-DIHYDROTHIENO[2,3-b]PYRIDINE DERIVATIVES

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The alkylation of piperidinium salts of substituted 1,4-dihydropyridine-2-thiols with chloroacetonitrile or iodoacetamide gave 2-cyanomethylthio- and 2-carbamoylmethylthio-substituted 6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridines, which undergo intramolecular cyclization in basic media to give 3-amino-6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-2-cyano(carbamoyl)-4,7-dihydrothieno[2,3-b]pyridines.

3-Aminothieno[2,3-b]pyridines are of theoretical interest, since their molecules simultaneously contain π-surplus thiophene and π-deficient pyridine rings [1]. These compounds have recently become widely used as synthones for the synthesis of complex condensed heterocyclic systems [2-6] and as biologically active compounds [7].

For the first time we have shown that 3-cyano-3,4-dihydropyridine-2(1H)-thiones are readily alkylated by alkyl halides to give 2-alkylthio-3-cyano-1,4-dihydropyridines [8]. 2-Alkylthio-3-cyano-1,4-dihydropyridines that contain an active methylene group in the 2-alkylthio substituent readily form a thiene ring in basic media to give 3-amino-4,7-dihydrothieno[2,3-b]pyridines — a new class of partially hydrogenated nitrogen- and sulfur-containing heterocycles [9, 10].

The goal of the present research was to synthesize 3-amino-6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-2-cyano(carbamoyl)-4,7-dihydrothieno[2,3-b]pyridines and to investigate their properties.

2-Cyanomethylthio- and 2-carbamoylmethylthio-substituted 6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridines II are obtained in high yields by brief heating of piperidine salts of substituted 1,4-dihydropyridine-2-thiols I [11] in absolute ethanol with chloroactonitrile or iodoacetamide.

It is more convenient to obtain 2-carbamoylmethylthio derivatives II without isolation of piperidinium salts I, i.e., it is more convenient to carry out the reaction of benzyli-

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