CONVERSION OF 2,1-BENZISOXAZOLINIUM IONS TO ANTHRANILS BY TREATMENT WITH HYDROHALIC ACIDS

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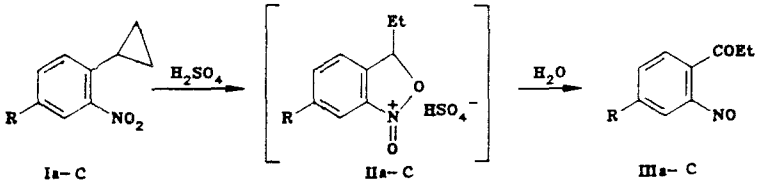
2,1-Benzisoxazolinium ions, obtained from o-nitrophenylcyclopropanes, react with hydrobromic and hydrochloric acids to give halo-substituted benzo[c]isoxazoles.

Isomerization of the o-nitrophenylcyclopropanes (Ia-c) by treatment with sulfuric acid, followed by treatment of the reaction mixture with water [1, 2] results in rapid removal by base (water) of a proton from the 2,1-benzisoxazolinium ions (IIa-c) formed in the first stage of the reaction to give quantitative yields of the nitrosoketones (IIIa-c). The presence of the ions (IIa-c) has been shown by ^1H and ^{13}C NMR spectroscopy [3].

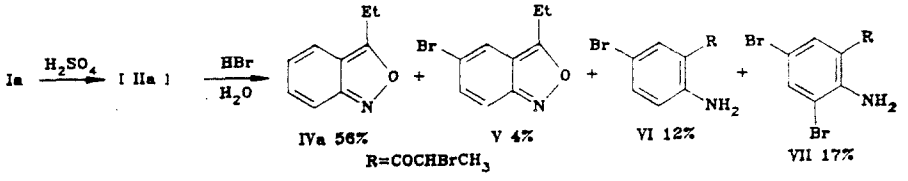


I—III a R=H, b R=*t*-C_4H_9, c R=NO_2

In order to establish the mode of stabilization of the ions (IIa-c) and the possibility of utilizing the reactions involved in organic synthesis, we have now examined the reactions of the heterocyclic ions (IIa-c) with hydrobromic and hydrochloric acids.

Unlike water, hydrobromic acid does not show pronounced basic properties, so that, in this case, the reaction might be expected to proceed other than by rearrangement to the nitrosoketones (IIIa-c).

For example, treatment of the unsubstituted N-oxo-2,1-benzisoxazolinium bisulphate (IIa) with concentrated HBr gives a mixture of compounds (IVa) and (V-VII).



The formation of 3-ethylbenzo[c]isoxazole (IVa) may be rationalized by the initially formed nitrosoketone (IIIa) undergoing intermolecular reduction by hydrogen bromide. The formation of 5-bromobenzo[c]isoxazole (V) could occur either by rearrangement of the cation of (IIa) to the nitrosoketone and reaction of the latter with HBr as in [4], or by direct reaction of (IIa) with HBr, as proposed by Andrews et al. [5, 6]

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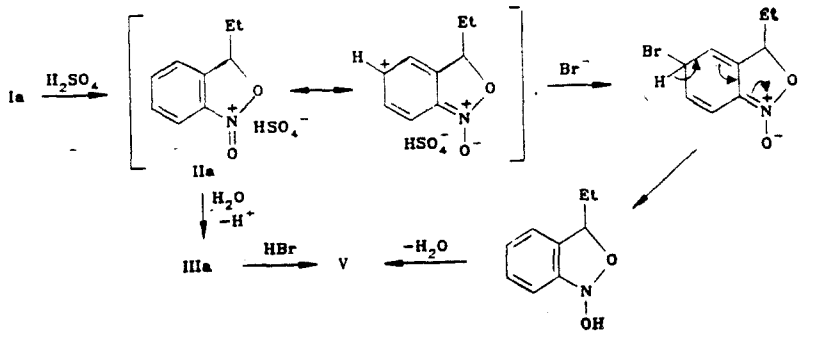
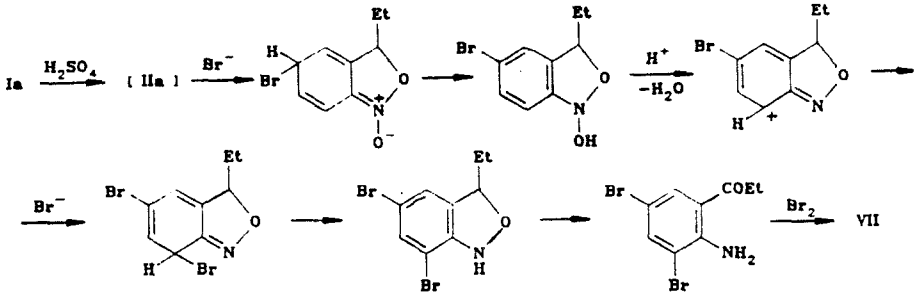
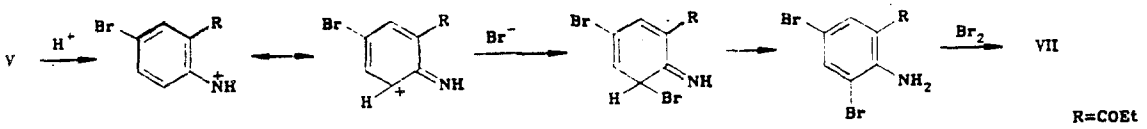


The aminopropiophenone (VI) is probably formed by subsequent reactions of the isoxazole (IVa), as suggested in [4] for the reaction of the nitrosopropiophenone (IIIa) with gaseous HBr in benzene.

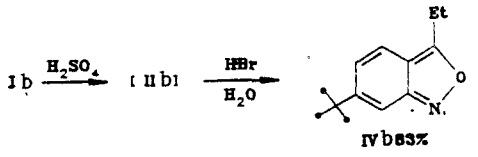
The formation of the tribromoaminopropiophenone (VII) in all likelihood results from several successive reactions. It could either be formed directly from the benzylisoxazolinium ion (IIa) by double nucleophilic replacement,



or from the isoxazole (V), as proposed for the conversion of the anthranil (IVa) into (VI).

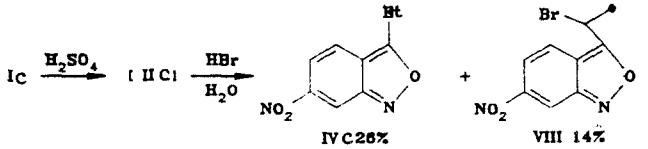


Reaction of the cyclic ion of (IIb), formed from 4-tert-butyl-2-nitrophenylcyclopropane (Ib), with hydrobromic acid gives 6-tert-butyl-3-ethylbenzo[c]isoxazole (IVb) as the sole reaction product.



The selectivity of this reaction could clearly be due to the steric influence of the tert-butyl group. The bulky nature of this group prevents nucleophilic attack of the bromide ion on the (IIb) anion, so that the Br^- functions solely as a reducing agent.

The reaction of the bisulfate (IIc) with HBr proceeds similarly, except that in this case substantial amounts of the side chain-substituted benzo[c]isoxazole (VIII) are obtained in addition to the anthranil (IVc).



The formation in this reaction of the isoxazoles (IVc) and (VIII) only, indicates that, like the tert-butyl radical, the nitro-group prevents nucleophilic attack of the bromide anion on positions 5 and 7 of the cyclic ion (IIc). This results in stabilization by loss of the benzyl proton on treatment with water giving the nitrosoketone (IIIc), which in turn is converted into the isoxazoles (IVc) and (VIII).

TABLE 1. Properties of Compounds (IV-XI) and (XIII)

Compound*	mp, °C	n_D^{20}	PMR spectrum, δ, ppm (J, Hz)	IR spectrum, cm^{-1}	Mass spectrum, m/z (I, %)	Yield, %	Literature
IVa**		1,5666				56	[9]
IVb***		1,5440				83	[9]
IVc	47...49					26	[9]
V		1,5721				4	[6]
VI	107...108		1,92 (3H, d, J=7, $-CH_3$); 5,24 (1H, q, $-CHBr$); 6,3 (2H, br.s, NH_2); 6,54 (1H, d, J_o=9, 3-H); 7,38 (1H, dd, J_o=9, J_m=2, 4-H); 7,85 (1H, d, J_m=2,6-H)	3510, 3360 (NH_2), 1660 (C=O)	M+ 305, 307, 309 (39%); [M−Br]+ 326, 328 (5); [M−CH_3CHBr]+ 198, 200 (100); [M−$COCHBrCH_3$]+ 170, 172 (18); [C_5H_4Br]+ 143, 145 (9)	12	
VII	103...104		1,86 (3H, d, J=7, $-CH_3$); 5,22 (1H, q, $-CHBr$); 6,9 (2H, br.s, NH_2); 7,68 (1H, d, J_m=2); 7,85 (1H, d, J_m=2)	3490, 3340 (NH_2), 1660 (C=O)	M+ 383, 385, 387, 389 (100); [M−Br]+ 304, 306, 308 (5); [M−CH_3CHBr]+ 276, 278, 280 (88); [M−$COCHBrCH_3$]+ 248, 250, 252 (21)	17	
VIII	95		2,35 (3H, d, J=7, $-CH_3$); 5,78 (1H, q, $-CHBr$); 7,60 (1H, d, J_o=9, 4-H); 7,80 (1H, d, J_m=2, 7-H); 8,30 (1H, dd, J_o=9, J_m=2, 5-H)	1540, 1350 (NO_2)	M+ 270, 272 (75); [M−Br]+ 191 (100); [M−Br−NO]+ 161 (8); [M−Br−NO_2]+ 145 (20); [M−Br−NO_2−NO]+ 115 (29); [M−$CH_3CHBr-NO_2H$]+ 116 (19)	14	
IXa		1,5672				64	[11]
IXc	78...79					32	[7]
X		1,5420				4	[6]
XI		1,5948				3	[11]
XIII	102...103					17	[7]

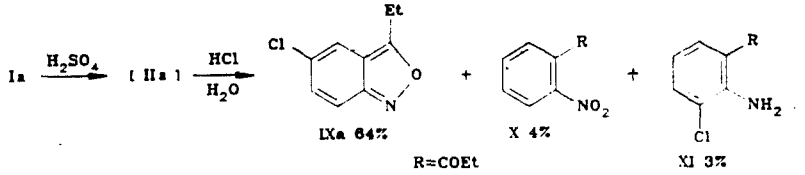
*The elemental analyses for (VI) and (VII) were in agreement with the calculated values.

** bp90-92°C (2 mm).

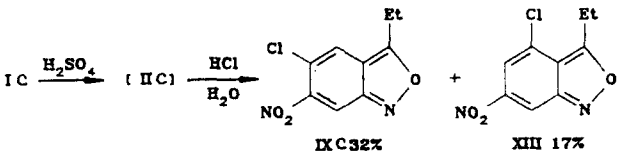
***bp 122-123°C (2 mm).

The preferential formation in all these cases of 5(7)-unsubstituted benzo[c]isoxazoles (IVa-c) from the N-oxo-3-ethyl-2,1-benzoisoxazolinium ions (IIa-c) is clearly due to the reducing properties of hydrobromic acid.

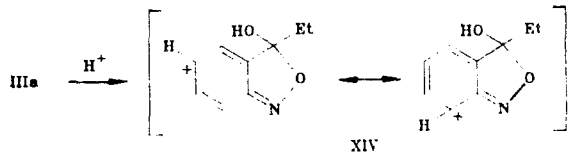
As is well known, hydrogen chloride does not possess any significant reducing properties, unlike hydrogen bromide. For this reason, we expected that the reaction of the 2,1-benzisoxazolinium bisulfates with hydrochloric acid would be more selective; at least, it was assumed that no intermolecular reduciton products (unsubstituted anthranils) would be formed. In fact, on treatment of the unsubstituted N-oxo-2,1-benzoisoxazolinium ion (IIa) with hydrochloric acid, the main product isolated was 5-chloro-3-ethylbenzo[c]isoxazole (IXa), apparently formed in a similar way to the conversion of the ion (IIa) to the isoxazole (V). The formation of small amounts of (X) and (XI) is probably due to an intermolecular redox reaction between the initially formed o-nitrosopropiophenone (IIIa) and 7-chloro-3-ethylbenzo[c]isoxazole (XII).



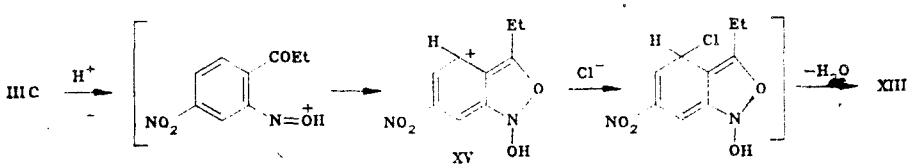
The presence of an electron-acceptor substituent (the nitro-group) in the aromatic ring of the five-membered cyclic ion has a marked effect on the course of its reaction with hydrochloric acid. In additon to 5-chloro-6-nitro-3-ethylbenzo[c]isoxazole (IXc), the ion (IIc) gives substantial amounts of 4-chloro-6-nitro-3-ethylbenzo[c]isoxazole (XIII).



The 4-substituted chloroanthranil (IXc) was first obtained from 2-nitrosopropiophenone by treatment with gaseous hydrogen chloride in benzene [7]. Its formation, albeit in only trace amounts, was attributed by the authors to the acceptor influence of the substituent (the nitro-group). Usually, in o-nitrosopropiophenones which do not bear electron-acceptor substituents in the benzene ring, the cyclization to anthranils commences with protonation of the carbonyl oxygen, followed by attack of the nitroso-oxygen on the incipient carbenium center to give the cyclic intermediate (XIV), which is predisposed to nucleophilic attack at the 5- and 7-positions.



The introduction of an electron acceptor substituent such as the nitro-group into the position para- to the acyl substituent in the initial nitroso-compound has the consequence that the basicity of the carbonyl oxygen is reduced, and protonation of the oxygen of the nitroso-group becomes competitive. This results in the formation of the cyclic ions of (XV), in which the 4-position is activated toward nucleophilic attack, thus giving rise to the 4-substituted anthrnail (XIII).



Hence, the reactions of benzisoxazolinium bisulfates with hydrohalic acids are largely dependent on the nature of the substituents present in the benzene ring, and on the reactant used. Reaction of the ions with hydrobromic acid gives predominantly the 5(7)-unsubstituted benzo[c]isoxazoles. Reaction of the ions with hydrochloric acid results in insertion of the nucleophilic chloride anion into the electron-deficient position of the benzene ring.

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-467 (60 MHz), internal standard TMS, solvents CCl_4 and $CDCl_3$. IR spectra were recorded in thin films or Vaseline grease on a UR-20 instrument. Mass spectra were obtained on a Varian MAT-44S quadrupole mass spectrometer and a Variant MAT-212 quadrant magnet instrument with direct introduction of the sample into the ion source. The ionizing electron energy was 70 eV.

The purity of the starting materials and products was established, and the reaction mixtures examined, by TLC on plates.

The properties of the compounds obtained are shown in Table 1.

The starting materials (Ia-c) were obtained by standard methods [8-10]; (Ia), bp 109°C (9 mm); (Ib), bp 153-154°C (8 mm); (Ic), mp 50°C.

Reaction of N-Oxo-3-ethyl-2,1-benzisoxazolinium Bisulfates (IIa-c) with Hydrobromic and Hydrochloric Acids. General Method. To 8 ml of concentrated sulfuric acid was added 100 mmoles of the appropriate o-nitrophenylcyclopropane at the required temperature, and the mixture stirred at this temperature for 1 h. The reaction mixture was then poured slowly with vigorous stirring into concentrated hydrohalic acid cooled to –20°C, taking care that the temperature did not rise. The resulting mixture was neutralized with sodium carbonate and extracted with chloroform. The chloroform extracts were dried over $MgSO_4$, the solvent removed, and the residue chromatographed on Silufol plates using the system ether–pentane (1:2).

Reaction of N-Oxo-3-ethyl-2,1-benzisoxazolinium Bisulfate (IIa) with HBr. Using the general method, 1.00 g (6 mmoles) of o-nitrophenylcyclopropane (Ia) at –20°C gave 0.50 g of 3-ethylbenzo[c]isoxazole (IVa), 0.056 g of 5-bromo-3-ethylbenzo[c]isoxazole (V), 0.22 g of α,5-dibromo-2-aminopropiophenone (VI), and 0.39 of α,3,5-tribromo-2-aminopropiophenone (VII).

Reaction of N-Oxo-6-tert-butyl-3-ethyl-2,1-benzisoxazolinium Bisulfate (IIb) with HBr. Using the general method, 1.50 g (7 mmoles) of (Ib) at –30°C gave 1.15 g of (IVb).

Reaction of N-Oxo-6-nitro-3-ethyl-2,1-benzisoxazolinium Bisulfate (IIc) with HBr. Using the general method, from 0.85 g (4 mmoles) of 2,4-dinitrophenylcyclopropane (Ic) at 0°C there were obtained 0.20 g of 6-nitro-3-ethylbenzo[c]isoxazole (IVc) and 0.15 g of 6-nitro-3-(1-bromoethyl)benzo[c]isoxazole (VIII).

Reaction of N-Oxo-3-ethyl-2,1-benzisoxazolinium Bisulfate (IIa) with Concentrated HCl. Using the general method, from 1.00 g (6 mmoles) of 2-nitrophenylcyclopropane (Ia) at –20°C there were obtained 0.71 g of 5-chloro-3-ethylbenzo[c]isoxazole (IXa), 0.03 g of 2-amino-3-chloropropiophenone (XI) and 0.04 g of 2-nitropropiophenone (X).

Reaction of N-Oxo-6-nitro-3-ethyl-2,1-benzisoxazolinium Bisulfate (IIc) with HCl. Using the general method, from 1.00 g (5 mmoles) of (Ic) at 0°C there were obtained 0.35 g of 5-chloro-6-nitro-3-ethylbenzo[c]isoxazole (IXc) and 0.19 g of 4-chloro-6-nitro-3-ethylbenzo[c]isoxazole (XIII).

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