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CYCLIZATION OF o-NITROSOACYLBENZENES TO ANTHRANILS

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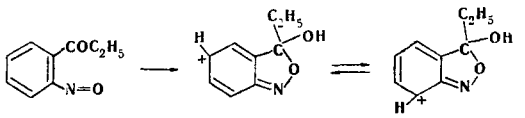
5-Bromo- and 5-methoxy-3-ethylanthranils, respectively, were obtained by cyclization of o-nitrosopropiophenone under the influence of hydrogen bromide in benzene and hydrogen chloride in methanol. In these reactions, the starting nitroso ketone undergoes redox transformations that also proceed readily in an inert solvent in the absence of any cyclizing reagents.

There have been previous reports of the synthesis of various anthranils by cyclization of substituted o-nitrosoacylbenzenes under the influence of zinc in glacial acetic acid [1], triphenylphosphine [2], and dry hydrogen chloride in benzene [3]. It was noted that in the latter case the introduction of a halogen atom in the 5 or 7 position of the resulting anthranilic system is always observed.

In [3] it was assumed that the conversion to an anthranil proceeds through a step involving the formation of benzenonium ions of the A and B type:



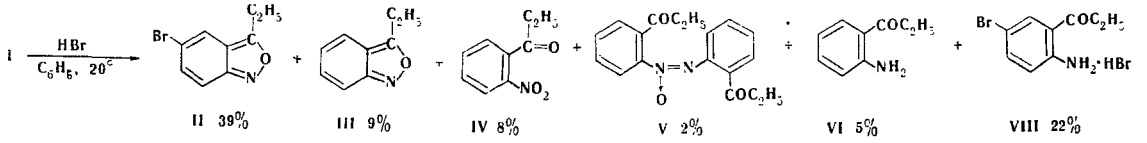
I A B

The latter on adding a nucleophile (chloride ion) gave hexadiene chloro derivatives, which were converted to the corresponding anthranils under the reaction conditions.

Using hydrogen bromide in benzene and hydrogen chloride in methanol as the cyclizing agents we hoped, first of all, to show the general character of this method for the synthesis of substituted anthranils, and, second, to obtain additional proof for a process occurring via the pathway proposed above.

M. V. Lomonosov Moscow State University, N. I. Pirogov Moscow State Medical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 886-890. July, 1976. Original article submitted June 10, 1975.

It was found that only 5-bromo-3-ethylanthranil (II) is formed on treatment of 2-nitrosopropiophenone (I) with hydrogen bromide gas in benzene; the 7-bromo-substituted anthranil was not detected in the reaction products.

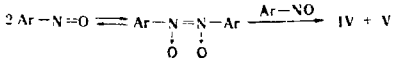


In addition to anthranil II, we isolated five other substances – 3-ethylanthranil (III), 2-nitropropiophenone (IV), 2,2'-dipropionylazoxybenzene (V), 2-aminopropiophenone (VI), and 2-amino-5-bromopropiophenone (VII) in the hydrobromide (VIII) form.

The fact that an appreciable amount of 7-halo-substituted anthranil was not formed in this case (whereas it was formed when hydrogen chloride was used for the cyclization) may be explained by steric hindrance associated with the large volume of the introduced (ion B) substituent – the bromine atom.

3-Ethylanthranil (III) and 2-nitropropiophenone (IV) are, in all likelihood, formed through intermolecular redistribution of oxygen. Evidence in favor of this assumption is the fact that in an oxygen-free medium and in the absence of a cyclizing agent, starting nitroso ketone I gave the same reaction products (III-VI) both in the light and in the dark when it was heated to 60° in benzene.

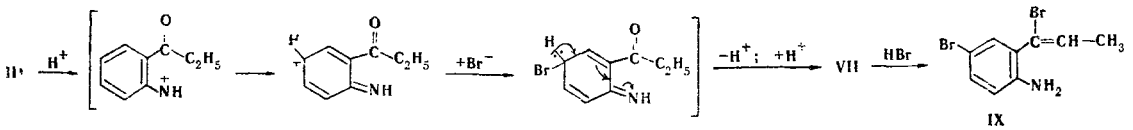
Azoxy compound V can be formed by deoxidation of the dimer of 2-nitrosopropiophenone (I), which is present in the reaction mixture as a result of the equilibrium



It is not possible to state anything definite as to how 2-aminopropiophenone (VI) is formed in the reaction, since the manner in which this sort of reduction could occur is not yet clear.

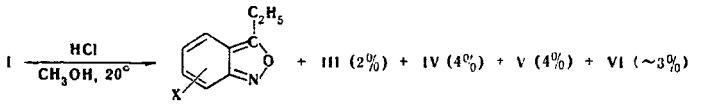
It was found that 2-amino-5-bromopropiophenone (VII) is the product of subsequent reduction of unsubstituted anthranil III under the influence of hydrogen bromide.

Confirmation of this was obtained by treatment of 3-ethylanthranil (III) with hydrogen bromide under the reaction conditions. As a result we isolated bromoaniline VII and, in addition to it, in all likelihood the product of its subsequent transformation – 1-(5-bromo-2-aminophenyl)-1-bromopropene (IX); bromoanthranil II was not changed when it was treated similarly. One cannot exclude the possibility that the conversion of 3-ethylanthranil (III) to the corresponding aniline may proceed via the following scheme:



The cyclization of I in methanol during continuous bubbling of hydrogen chloride through the mixture gave a mixture of 5-methoxy-3-ethylanthranil (X) and 5- and 7-chloro-3-ethylanthranils (XI and XII). In addition to these compounds, as in the case described above, we also found III-VI in the reaction products.

Assuming that the formation of considerable amounts of chloroanthranils XI and XII is due to the high concentration of hydrogen chloride in the reaction mixture, we carried out the reaction with a considerably smaller amount of hydrogen halide. It was found that in this case the formation of 5-methoxy-3-ethylanthranil (X) is slowed down markedly (the color of the nitroso ketone vanished only after 48 h), and substances formed as a result of redox conversion of starting nitroso compound I begin to predominate in the reaction products; anthranil X was isolated in only 11% yield.



X X = 5-OCH$_3$ (39%); XI X = 5-Cl (12%); XII X = 7-Cl (2%)

It should be noted that even in this case, the ratio of the amounts of chloroanthranils XI and XII and methoxyanthranil X was practically the same as in the case described above.

TABLE 1. PMR Spectra of the Compounds Obtained

Compound	Chemical shifts, δ, ppm*										J, Hz	
	CH_3	CH_2	OCH_3	NH_2	C=CH–	aromatic protons					J_{ortho}	J_{meta}
						3-H	4-H	5-H	6-H	7-H		
II	t, 1.41	q, 3,11	—	—	—	—	d, 7,48	—	dd, 7,24	d, 7,04	8,2	1
VI	t, 1,10	q, 2,82	—	s, 5.95	—	dd, 7,52	dt, 6,34	dt, 7,06	dd, 6,47	—	9	2
VII	t, 1,11	q, 2,79	—	s, 6,14	—	d, 7.60	—	dd, 7,12	d, 6,35	—	9	2
IX	d, 1,82	—	—	s, 6,15	q, 5,14	d, 6,48	dd, 7,18	—	d, 7,86	—	9	2
X	t, 1,32	q, 2.93	s, 3,65	—	—	—	d, 6.37	—	dd, 6,81	d, 7,24	8,6	2
XIII	t, 1.07	q, 2,82	s, 3,57	s, 5,75	—	d, 6,96	—	dd, 6.72	d, 6,38	—	8,4	2.4

*On the δ scale. Abbreviations: t is triplet, d is doublet, q is quartet, s is singlet, dd is doublet of doublets, and dt is doublet of triplets.

Reduction of anthranils II and X gave, respectively, 5-bromo-2-amino-(VII) and 5-methoxy-2-aminopropiophenone (XIII).

Thus 5-bromo- and 5-methoxy-3-ethylanthranils (II, X) can be obtained from 2-nitrosopropiophenone (I), but the yields of reaction products in this case are considerably lower than in the cyclization of nitroso ketones under the influence of hydrogen chloride in benzene [3], where cyclization proceeds quite rapidly and side processes are suppressed to a considerable degree.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were obtained with a JNM H-60 spectrometer with hexamethyldisiloxane as the internal standard.

Reaction of 2-Nitrosopropiophenone (I) with Hydrogen Bromide in Benzene. A stream of hydrogen bromide gas was bubbled with stirring in the course of 45 min into a suspension of 5 g (0.031 mole) of 2-nitrosopropiophenone (I) and 150 ml of dry benzene, after which the mixture was stirred for 1 h, and the resulting precipitate was removed by filtration, washed with ether, and dried to give 1.8 g (22%) of 2-propionyl-4-bromoaniline (VII) hydrobromide. The filtrate was washed with water to neutrality, dried with magnesium sulfate, and evaporated, and the residue was chromatographed with a column filled with activity II aluminum oxide in an ether-petroleum ether (40-70°) system (1:3). The following compounds were eluted successively: 0.3 g (9%) of 3-ethylanthranil (III), with n_D^{20} 1.5672 [1]; 2.5 g (39%) of 5-bromo-3-ethylanthranil (II),* with n_D^{20} 1.5721. Found: C 47.7; H 3.4%. C_9H_8BrNO. Calculated: C 47.8; H 3.5%; 0.23 g (5%) of 2-aminopropiophenone (VI), with mp 45-46° (the hydrochloride had mp 189° [4]); 0.45 g (8%) of 2-nitropropiophenone (IV) with n_D^{20} 1.5420. Found: C 60.2; H 5.0%. $C_9H_9NO_3$. Calculated: C 60.3; H 5.0%; and 0.1 g (2%) of 2,2'-dipropionylazoxybenzene (V) with mp 73-74° (from alcohol). PMR spectrum, δ, ppm: 1.07 t (6H); two quartets (5H) from ethyl groups centered at 2.77; 7.06-7.73 m (7H); and an ArH multiplet (1H) at 7.80-8.12. Found: C 69.5; H 5.7%. $C_{18}H_{18}N_2O_3$. Calculated: C 69.7; H 5.8%.

Reaction of 2-Nitrosopropiophenone (I) with Hydrogen Chloride in Methanol. Methanol (200 ml) was saturated with hydrogen chloride gas for 15 min, after which 5 g (0.031 mole) of nitroso ketone I was added to the resulting solution, and the mixture was stirred until the solid had dissolved completely (~ 3 h). The solution was poured into 200 ml of water, and the organic products were extracted with ether. The ether extracts were washed to neutrality with water, dried with magnesium sulfate, and evaporated. The residue was chromatographed as described above to give, successively 0.8 g (14%) of 5- (XI) and 7-chloro-3-ethylanthranils (XII) (identified by physiochemical methods with authentic samples [3]); 2.1 g (39%) of 5-methoxy-3-ethylanthranil (X),† with n_D^{20} 1.5633. Found: C 67.6; H 6.2%. $C_{10}H_{11}NO_2$. Calculated: C 67.8; H 6.2%; 0.13 g (~3%) of 2-aminopropiophenone (VI); 0.21 g (4%) of 2-nitropropiophenone (IV); and 0.4 g (8%) of 2,2'-dipropionylazoxybenzene (V).

Transformations of 2-Nitrosopropiophenone (I) in Methanol with a Lower Concentration of Hydrogen Chloride. A stream of hydrogen was bubbled into a suspension of 5 g (0.031 mole) of nitroso ketone I in 200 ml of methanol for 1 min, after which the mixture was stirred for 48 h. The methanol was then removed by distillation,

*We were unable to establish the characteristic boiling point because this compound underwent resinification during distillation.

†We were unable to establish the characteristic boiling point because this compound underwent resinification on distillation.

and the residue was treated with 50 ml of water and extracted three times with 40-ml portions of ether. The ether extracts were washed with water, dried with magnesium sulfate, and evaporated, and the residue was chromatographed as described above to give, successively, 0.22 g (4%) of a mixture of 5- and 7-chloro-3-ethylanthranils (XI, XII), 0.3 g (9%) of 3-ethylanthranil (III), 0.6 g (11%) of 5-methoxy-3-ethylanthranil (X), 1.4 g (26%) of 2-nitropropiophenone (IV), 0.4 g (8%) of 2,2'-dipropionylazoxybenzene (V), and traces of 2-aminopropiophenone (VI).

Conversion of 2-Nitrosopropiophenone (I) in Benzene at 60° in the Dark. A 2-g (0.012 mole) sample of nitroso compound I and 50 ml of absolute benzene were placed in a light-protected flask, after which the air was evacuated from the mixture several times (three to four times) under a vacuum of 1-2 mm, and the flask was filled with argon. The contents of the flask were heated to 60° and maintained at this temperature for 1 h, after which the solvent was evaporated, and the residue was chromatographed on plates in a thin layer of activity II aluminum oxide in an ether-petroleum ether (40-70°) system (1 : 3) to give 0.1 g (5.5%) of 3-ethylanthranil (III), 0.1 g (4.5%) of 2-nitropropiophenone (IV), 0.2 g (11%) of 2-aminopropiophenone (VI), and 0.27 g (14%) of 2,2'-dipropionylazoxybenzene (V).

Reaction of 3-Ethylanthranil (III) with Hydrogen Bromide. A stream of hydrogen bromide was bubbled into a solution of 0.5 g (0.0034 mole) of 3-ethylanthranil (III) in 30 ml of absolute benzene for 2 h, after which the mixture was poured into 100 ml of water. The aqueous mixture was neutralized with 2 N sodium carbonate solution and extracted with three 30-ml portions of ether. The extract was washed twice with water, dried with magnesium sulfate, and evaporated, and the residue was chromatographed in a thin layer of activity II aluminum oxide in the system indicated above to give 0.24 g (31%) of 5-bromo-2-aminopropiophenone (VII), with mp 76-77°. Found: C 47.1; H 4.2%. $C_9H_{10}BrNO$. Calculated: C 47.4; H 4.4%; and 0.18 g (18%) of 1-(5-bromo-2-aminophenyl)-1-bromopropene (IX) with mp 106-107°. Found: C 36.9; H 3.2%. $C_9H_9Br_2N$. Calculated: C 37.1; H 3.1%.

Reduction of 5-Bromo-3-ethylanthranil (II). A solution of 1 g (0.0045 mole) of 5-bromo-3-ethylanthranil (II) in 4.5 ml of ethanol was added to 1.8 g (0.032 mole) of reduced iron in 11.8 ml of glacial acetic acid, and the mixture was stirred at 40-50° for 1 h. It was then poured into 50 ml of water, and the aqueous mixture was neutralized with a saturated sodium carbonate solution and extracted with three 20-ml portions of ether. The ether extracts were combined, washed with water, dried with magnesium sulfate, and evaporated, and the residue was chromatographed in a thin layer of activity II aluminum oxide in an ether-petroleum ether (40-70°) system (1 : 3) to give 0.82 g (81%) of 5-bromo-2-aminopropiophenone (VII) with mp 76-77°.

Reduction of 5-Methoxy-3-ethylanthranil (X). Reduction of 0.8 g (0.0045 mole) of X by the method in the preceding experiment gave 0.64 g (79%) of 5-methoxy-2-aminopropiophenone (XIII) with mp 66°. Found: C 66.9; H 7.1%. $C_{10}H_{13}NO_2$. Calculated: C 67.0; H 7.3%.

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