REACTION OF BENZO[*a*]PHENOXAZIN-9-ONE WITH ETHYLENIMINE

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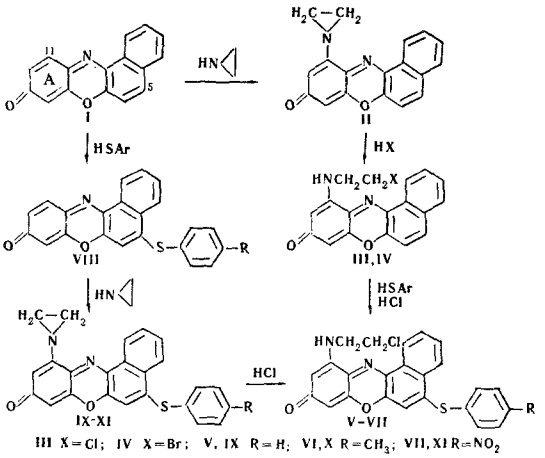
The reaction of benzo[*a*]phenoxazin-9-one and its 5-sulfides with ethylenimine has given 11-ethyleneamino derivatives. It has been shown that in contrast to the arylamines, which enter position 5 of benzo[*a*]-phenoxazin-9-one, ethylenimine reacts at the quinoid nucleus of the phenoxazine system. Absorption spectra in the visible region for phenoxazinones substituted in the quinoid nucleus have been recorded.

Some time ago, Fischer [1] established that benzo[*a*]phenoxazin-9-one adds arylamines in position 5. We have recently [2] shown that the addition of HS containing aromatic compounds to benzo[*a*]phenoxazin-9-one (I) also takes place with transfer of the reaction center and leads to the formation of the 5-aryl-thio derivatives VIII.

The presence of the p-quinoid nucleus A in I leads one to expect that, in addition to nucleophilic addition reactions at position 5, a nucleophilic agent will also enter the quinoid nucleus, by analogy with the reactions of quinones [3]. Since the addition of ethylenimine to p-benzoquinones leads to compounds with an appreciable antitumoral effect [4, 5], it appeared of interest to check whether the addition of ethylenimine to the quinoid nucleus would also take place in I. This interest was also justified by the fact that the phenoxazine ring is present in antitumoral antibiotics, e.g., actinomycin [6] and aurantin [7].

In this work we found that in benzene solution ethylenimine reacts with I giving ethyleneaminobenzo[*a*]phenoxazin-9-one (II). Compound II smoothly adds hydrogen chloride and bromide, forming the corresponding halogeno-ethylaminobenzo[*a*]phenoxazin-9-ones (III, IV), which confirms the entry of an ethyleneimino group into the molecule of I. Compounds III and IV are less reactive with respect to HS-containing aromatic compounds than I. Only under conditions of acid catalysis does compound III add thiophenol and its p-methyl and p-nitro derivatives with the formation of 5-arylthio(chloroethylamino)benzo[*a*]phenoxazin-9-ones (V-VII). Since it has been shown previously [2, 8] that under the conditions described, thiopenols enter position 5 of benzo[*a*]phenoxazin-9-one (I), the reaction of III with thiopenols is proof of the addition of ethylenimine to the quinoid nucleus of I. To confirm this we have studied the reaction of 5-arylthiobenzo[*a*]phenoxazin-9-ones (VIII) [2] with ethylenimine and have shown that VIII reacts with ethylenimine in a manner similar to I, forming 5-arylthioethylenaminobenzo[*a*]phenoxazin-9-ones (IX–XI). The opening of the ethylenimine ring in compounds IX–XI by gaseous hydrogen chloride leads to 5-arylthio(chloroethylamino)benzo[*a*]phenoxazin-9-ones identical to compounds V–VII obtained by the addition of thiophenols to III (the absorption spectra of these compounds in the visible region coincide completely).

Since 11-methylbenzo[*a*]phenoxazin-9-one does not react with ethylenimine (the initial phenoxazinone was isolated from the reaction mixture) we may assume that the ethyleneamino group is likewise present in position 11 of the phenoxazine system.



The facts reported above unamibiguously show that in benzene solution ethyleneimine enters the quinoid nucleus of benzo[*a*]phenoxazin-9-ones.

Comparison of the absorption spectra in the visible region (table) shows that the introduction of an ethyleneamino group into both I and VIII (λ_{max} for VIII when R = H is 508 nm; R = NO_2, 492 nm; R = CH_3, 512 nm; in dioxane [2]), leads to a hypsochromic shift of the absorption maximum. In contrast, the opening of the ring leads to a bathchromic shift of the absorption maximum, while a substituent (Br, Cl) in the side chain has no appreciable effect on the absorption of these compounds in the visible region. The extent of solvatochromism on passing from dioxane to 70% aqueous dioxane (increase in the polarity of the solvent) for phenoxazinones having a substituent in the quinoid nucleus is considerably less than for the corresponding benzo[*a*]phenoxazin-9-ones unsubstituted in the quinoid nucleus: for example, for III $\Delta\lambda_{max}$ is 4 nm and for I it is 18 nm [2]; for V it is 8 nm, and for VIII, R = H, 18 nm [2]. This shows the smaller tendency of the former to give rise to a bipolar ionic structure [2]. In the light of this, the lower reactivity at position 5 of the benzo[*a*]phenoxazines substituted in the quinoid nucleus (see the mechanism proposed earlier for addition reactions to I [8]) becomes understandable: the addition of thiophenols takes place only under conditions of acid catalysis, and arylamines do not react with III even in the presence of their hydrochlorides.

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EXPERIMENTAL

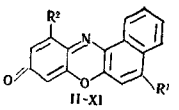
11-Ethyleneaminobenzo[*a*]phenoxazin-9-one (II). Ethylenimine, 10 ml, was added to 5 g (0.02 mole) of I in 20 ml of anhydrous benzene and the mixture was kept at 50–60° C for 1 hr, and then at room temperature for 2–3 hr, after which it was cooled to 0–5° C. The precipitate that had separated out was filtered off and washed with a small amount of benzene and ether.

Compounds IX–XI were obtained similarly; the time of the reaction for IX and XI was 2 hr at 60–65° C, and for X 6 hr at 70–80° C (table).

11-(2-Chloroethylamino)benzo[*a*]phenoxazin-9-one (III). A suspension of 0.005 mole of II in 10 ml of absolute ether and 3 ml of methanol was saturated with anhydrous hydrogen chloride. The reaction mixture became warm and acquired a crimson coloration. It was left to stand at room temperature for 2 hr, after which the precipitate was filtered off, washed with methanol and then with water until the acid reaction had disappeared.

Compounds III–VI were obtained similarly (table).

11-(2-Chloroethylamino)-5-phenylthiobenzo[*a*]phenoxazin-9-one (V). A mixture of 0.005 mole of III, 10 ml of ethanol, 0.03 mole of thiophenol, and 0.05 mole of conc HCl was boiled until it had become decolorized (~30 min). Then 3–5 ml of a 10% aqueous solution of $FeCl_3$ was added to the reaction mixture. The violet precipitate was filtered off and was washed with hot water.



II-XI

Compound	R^1	R^2	Mp, °C (decomp)*	Dioxane		70% Aqueous dioxane		Empirical formula	Found, %					Calculated, %					Yield, %
				λ_{max}, nm	lg ε	λ_{max}, nm	lg ε		N	S	Cl (Br)	C	H	N	S	Cl (Br)	C	H	
II	H		240—242	460	4.412	—	—	$C_{18}H_{12}N_2O_2$	10.0	—	—	75.0	4.3	9.7	—	—	75.0	4.2	30—35
III	H	$NHCH_2CH_2Cl$	218—220	490	4.588	494	4.574	$C_{18}H_{13}N_2O_2Cl$	8.9	—	11.1	66.2	4.3	8.6	—	10.9	66.6	4.0	80—90
IV	H	$NHCH_2CH_2Br$	206—208	490	4.546	494	4.529	$C_{18}H_{13}N_2O_2Br$	7.4	—	21.1	—	—	7.6	—	21.6	—	—	65
V	C_6H_5S	$NHCH_2CH_2Cl$	236—237	508	4.608	516	4.596	$C_{24}H_{17}N_2O_2SCl$	6.4	7.3	8.0	—	—	6.5	7.7	8.2	—	—	85
VI	p-$CH_3 \cdot C_6H_4S$	$NHCH_2CH_2Cl$	259—260	514	4.629	521	4.615	$C_{25}H_{19}N_2O_2SCl$	—	7.4	8.0	—	—	6.3	7.2	7.9	—	—	87
VII	p-$NO_2 \cdot C_6H_4S$	$NHCH_2CH_2Cl$	229—230	503	4.636	506	4.610	$C_{24}H_{16}N_3O_4SCl$	—	7.0	7.7	—	—	—	6.7	7.4	—	—	90
IX	C_6H_5S		238—240	498	4.528	—	—	$C_{24}H_{16}N_2O_2S$	7.4	8.4	—	73.1	4.1	7.1	8.1	—	72.7	4.1	45
X	p-$CH_3 \cdot C_6H_4S$		212—214	502	4.518	—	—	$C_{25}H_{18}N_2O_2S$	7.2	7.4	—	73.4	4.4	6.8	7.8	—	73.2	4.4	40
XI	p-$NO_2 \cdot C_6H_4S$		217—218	474	4.492	—	—	$C_{24}H_{15}N_3O_4S$	9.2	7.3	—	—	—	9.5	7.3	—	—	—	45

*Solvent for recrystallization: VII used pyridine and water; the others, dimethylformamide (IV with water, V and VI with ethanol).

Compounds VI and VII were obtained similarly (table). In the preparation of V–VII from IX–XI, the yields amounted to 90%.

The absorption spectra in the visible region were taken on an SF-10 spectrophotometer in dioxane, and in 70% aqueous dioxane; c 10^{-4} M; layer thickness 0.5 cm.

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