Nucleophilic Addition Reactions of Benzo-\([\alpha]\)-phenoxazinone-9 and 9-Dimethylamino-benzo-\([\alpha]\)-phenoxazonium Chloride

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Abstract

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Nucleophilic Addition Reactions of Benzo-[α]-phenoxazinone-9 and 9-Dimethylamino-benzo-[α]-phenoxazonium Chloride

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It is known that benzo-[α]-phenoxazinone-9 (I) ([1]) and 9-dialkylamino-benzo-[α]-phenoxazonium chlorides (II) ([2]) are capable of adding arylamines in position 5, giving the corresponding 5-arylamino derivatives (scheme 1 (XVII) and scheme 2 (III)). Among dyes of type (III), physiologically active substances (antitubercular and antitumor) were later discovered ([3]). The addition reactions of arylamines to compounds (I) and (II)

Scheme 1*

Scheme 1: reaction scheme of benzo-[α]-phenoxazinone-9 derivatives

are similar to the nucleophilic addition reactions of arylamines to *p*-benzoquinone ([4]). In this connection it seemed of interest to test the possibility of carrying out such nucleophilic addition reactions in the benzo-[α]-phenoxazine series (I) and (II), which had previously been described for benzoquinone. Such reactions include reactions with thiourea ([5]), mercaptans ([6]), and sulfinic acids ([7]). In this case one could expect the formation of S-analogs of benzophenoxazine dyes.

We have established for the first time that these reactions are feasible in the benzo-[α]-phenoxazine series and proceed smoothly, in most cases already in the cold; in this process beautifully crystallizing isothiuronium salts, sulfides, and sulfones are formed.

* In fact, in all compounds with ionic structure there is delocalization of the positive charge over the nitrogen and oxygen atoms. In the article, quinoid structures with a fixed positive charge are given conventionally.

Benzo-[α]-phenoxazines

Table 1

Compound No.	X	R	Y	External appearance, crystallization solvent: leuco compound	External appearance, crystallization solvent: dye*	Yield of dye, %	Mp of dye*, °C	λ_{max}, mμ: chloride	λ_{max}, mμ: base	Formula of dye*	Found, %	Calculated, %
V	O	$-S-C(=NH_2^+)NH_2$	Cl^-	yellow prisms (alcohol + HCl in a stream of CO_2)	brown-red prisms with a golden sheen (methanol + H_2O)	65	decomposes above 210			$C_{17}H_{17}N_3OS_3 \cdot HCl \cdot H_2O$	8.54N 10.89Cl 54.19H 3.79	8.53N 11.18Cl 54.33H 3.75
VI**	$(CH_3)_2N$	$-S-C(=NH_2^+)NH_2$	Cl^-	yellow needles (alcohol + HCl)	violet needles (alcohol + HCl)	82		607	437	$C_{19}H_{17}ClN_4OS \cdot HCl \cdot H_2O$	6.87N 12.15Cl 50.12H 4.47	7.01N 12.24Cl 49.89H 4.58
VII	O	$-S-CO-CH_3$		yellow needles (alcohol in a stream of CO_2)	brown-red needles (acetone)	95	with decomp. 200–201			$C_{18}H_{17}NO_3S$	9.91N 4.31	10.00N 4.36

Compound No.	X	R	Y	External appearance, crystallization solvent: leuco compound	External appearance, crystallization solvent: dye*	Yield of dye, %	Mp of dye*, °C	λ_{max}, mμ: chloride	λ_{max}, mμ: base	Formula of dye*	Found, %	Calculated, %
VIII	$(CH_3)_2N^{\pm}$	$-CO-CH_3$	Cl^-	yellow prisms (alcohol + HCl)	violet needles (alcohol + HCl)	89		608	433	$C_{20}H_{17}ClN_2O_2S$	8.16N 7.62	8.33N 7.28
IX	O	$-S-C_6H_4COOH$-o	–	–	brown-red fern-like crystals (butanol)	80	with decomp. 230–231			$C_{23}H_{13}NO_4S$	8.11N 3.53	8.02N 3.51
X	$(CH_3)_2N^{\pm}$	$-C_6H_4COOH$-o	Cl^-	greenish-yellow needles (alcohol + HCl)	blue needles with a green sheen (dimethylformamide or alcohol + HCl)	67		616	432	$C_{25}H_{19}ClN_2O_3S$	6.55N 5.91	6.92N 6.05

Compound No.	X	R	Y	External appearance, crystallization solvent: leuco compound	External appearance, crystallization solvent: dye*	Yield of dye, %	Mp of dye*, °C	λ_{max}, mμ: chloride	λ_{max}, mμ: base	Formula of dye*	Found, %	Calculated, %
XI	O	$-S-C_6H_5$	—	—	brown-red needles (dimethylformamide)	86	with decomp. 248-249			$C_{22}H_{13}SNO_2S$	8.84N 3.97	9.02N 3.94
XII	$(CH_3)_2N^{\pm}$	$-C_6H_5$	Cl^-	greenish-yellow needles (alcohol + HCl)	blue needles with a green sheen (dimethylformamide, heated to 100°)	66		614	437	$C_{24}H_{19}ClN_2OS$	7.54N 6.35	7.56N 6.69
XIII	O	$-SO_2-C_6H_5$	—	yellow plates (acetone + H_2O)	red plates (dimethylformamide + methanol)	88	with decomp. 240-241			$C_{22}H_{13}NO_4S$	8.56N 3.81	8.27N 3.62

Compound No.	X	R	Y	External appearance, crystallization solvent: leuco compound	External appearance, crystallization solvent: dye*	Yield of dye, %	Mp of dye*, °C	λ_{max}, mμ: chloride	λ_{max}, mμ: base	Formula of dye*	Found, %	Calculated, %
XIV	$(CH_3)_2N$	SO_2	Cl^- C_6H_5	yellow needles (alcohol + HCl)	violet needles (alcohol + HCl)	66		566	456	$C_{24}H_{19}ClN_2O_3S$	7.36N 5.94	7.11N 6.22
XV	O	SO_2	— $C_6H_4CH_3$-n	yellow plates (acetone + H_2O)	red plates (dimethylformamide — methanol)	87	with decomp. 233–234			$C_{23}H_{18}N_4O_4S$	8.00N 3.31	7.99N 3.48
XVI	$(CH_3)_2N$	SO_2	Cl^- $C_6H_4CH_3$-n	yellow needles (alcohol + HCl)	violet needles (alcohol + HCl)	65		565	455	$C_{25}H_{21}ClN_2O_3S$	6.86N 5.76	6.90N 6.03

* "Dye" is the conventional designation for a product of quinoid structure.
** Dyes (VI, VIII, X, XII, XIV, XVI) do not show characteristic melting or decomposition temperatures (cf. [5]); for them the table gives λ_{max}.

Thiourea adds in the presence of hydrochloric acid, giving hydrochlorides of leuco compounds, which in air gradually (more readily upon oxidation with a ferric chloride solution) pass into water-soluble hydrochlorides of isothiuronium compounds (V and VI). In the absence of acid this reaction does not proceed.

Evidently, addition of the acid proton to benzo-[α]-phenoxazines (I) and (II) promotes the induction of a positive charge on the carbon in position 5 (Ia).

Mercapto compounds, such as thioglycolic and thiosalicylic acids and thiophenol, also add readily to benzo-[α]-phenoxazines (I) and (II). The proton necessary for initiating the reaction is probably supplied by these thiols themselves. As a result of the reactions, leuco products are first obtained, which are then oxidized to sulfides of quinonoid structure (VII, VIII, IX, X, XI, XII in Table 1).

Reactions with arylsulfinic acids proceed in the cold; in this case more stable leuco compounds are formed, which can readily be recrystallized from aqueous acetone for derivatives of compound (I), or from alcohol for derivatives of compound (II). Oxidation of them with a $FeCl_3$ solution gives sulfones (XIII–XVI).

Scheme 2

Scheme 2: reaction scheme showing 9-dimethylamino-benzo-[α]-phenoxazonium chloride (II), addition of $ArSO_2H$ to give a yellow hydrochloride, conversion with aniline in the cold to a red base, oxidation with $FeCl_3$ + HCl to violet dyes (XIV, XVI), and conversion with aniline upon heating to the blue dye (III).

In the scheme: HSO_2Ar; $C_6H_5NH_2$ in the cold; yellow hydrochloride; red base; $FeCl_3$ + HCl; violet dye (XIV, XVI); $C_6H_5NH_2$ on heating; blue dye (III).

Confirmation that the reactions proceed at position 5 of benzo-[α]-phenoxazines is provided by the results of the following experiments.

Upon heating the thioacetyl derivative (VIII) with aniline in the presence of aniline hydrochloride in an alcoholic medium, the aniline dye already described in the literature ([1]) is obtained (Scheme 1 (XVIII)). In exactly the same way, 9-dimethylamino-benzo-[α]-phenoxazine-5-phenyl sulfone (Scheme 2 (XIV)), upon heating with aniline, is converted into the dye (III) previously obtained by Nietzki ([2]). The process of formation of this dye can be followed stepwise, and all the products indicated in Scheme 2 can be isolated as well-crystallizing compounds.

Some properties of the compounds obtained are presented in the summary Table 1.

Experimental Part

Hydrochlorides of 5-isothiuronium-benzo-[α]-phenoxazines (IV) and (VIa). A mixture of 0.005 g-mol of benzo-[α]-phenoxazine (I) or (II), 0.01 g-mol of thiourea in alcohol, is thoroughly stirred, with

on cooling, 0.005 g-mol (for (II), 0.01 g-mol) of concentrated hydrochloric acid is added, and the mixture is left to stand at room temperature for 1 h. The precipitated hydrochloride of the leuco compound is filtered off and washed with a small amount of alcohol.

5-Arylsulfonylbenzo-[α]-phenoxazines (XIII–XVI). 0.005 g-mol of benzo-[α]-phenoxazine (I) or (II) and 0.008 g-mol of a sulfinic acid are kept for 30 min at room temperature in 10 ml of methyl alcohol. The precipitate is filtered off and washed with methanol. In all cases, oxidation of the leuco compounds is carried out with an excess of a 10% aqueous solution of ferric chloride.

5-Thioacetyl-9-dimethylaminobenzo-[α]-phenoxazonium chloride (VIII). 0.005 g-mol of benzo-[α]-phenoxazine (II) is gradually added to a solution of 0.015 g-mol of thioacetic acid in 10 ml of alcohol, and the mixture is left to stand until a light-yellow solution forms. The leuco compound that forms is precipitated with anhydrous ether, filtered off, and recrystallized from alcohol saturated with dry HCl. It is oxidized with an aqueous solution of $FeCl_3$.

Example of displacement of an S-containing residue by aniline. 0.003 g-mol of the thioacetyl derivative (VII) is boiled with 0.015 g-mol of aniline hydrochloride and 0.03 g-mol of aniline in 20 ml of alcohol; the precipitate is filtered off and washed with alcohol. In the visible spectrum, $\lambda_{\max} = 455$ mμ (conc. 10^{-4}, in pyridine). The same $\lambda_{\max}$ was shown by the product (XVII) obtained according to O. Fischer [1].

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Note: Figure translations are in progress. See original paper for figures.