OXIDATIVE CONDENSATION OF ACRIDINE WITH PHENOXIDES

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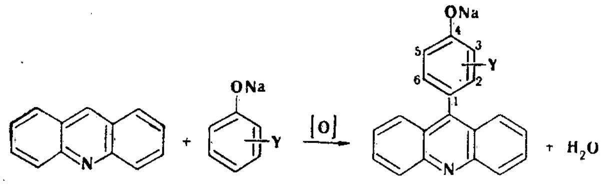
Acridine condenses under oxidative conditions with phenoxides to give 9-hydroxyarylacridines.

In a continuation of our research on nucleophilic substitution of hydrogen in azines [1, 2], in the present research we studied the replacement of hydrogen in acridine by phenol residues. Up until now it has not been possible to condense π-deficient heteroaromatic compounds with phenols. O-acylation of phenols occurs when active acyl salts of azines are used [3].

Our experiments showed that phenols do not react with acridines, whereas phenoxides, which have high nucleophilicities, smoothly undergo reaction to give 9-hydroxyarylacridines. The reaction is carried out in dimethylformamide (DMF) as air is bubbled through the reaction mixture via the scheme



Both phenol itself and its homologs containing electron-donor groupings (CH_3, NH_2, OH, and OCH_3) in the ring react (in the form of the sodium salts) with acridine. In the case of m-substituted phenols the reaction gives higher yields of the final products, and this can be explained by the coordinated orienting effect of the substituents. Thus in the reaction of isomeric cresolates with acridine the highest yield is achieved in the case of m-cresol (Table 1). In the reaction with aminophenoxides we were able to obtain the final hydroxyarylacridine only with m-aminophenol. Electron-acceptor substituents in the ring (nitrophenols, hydroxybenzoic acids, and nitrosophenols) deactivate the phenols and naphthols, and the hydroxyarylation reaction does not occur.

Absorption maxima at 250-255 and 355-360 nm are observed in the electronic spectra of all of the synthesized compounds, and this constitutes evidence for the formation of substituted acridines rather than addition products — 9,10-dihydroacridines, which are characterized by a broad absorption band at 290 nm [4]. The structure of I, which has mp ~360°, was established by conversion to the lower-melting acetyl derivative (XII), which proved to be identical to 9-(4-acetoxyphenyl)acridine obtained from diphenylamine and p-acetoxybenzoic acid [5] by closing of the acridine ring.

The PMR spectra of VII and VIII are complex and do not lend themselves to interpretation as first-order spectra. The elementary compositions of these compounds attest to incorporation of naphthol residues in the acridine ring. One can form a tentative judgment regarding the structure of VII on the basis of alternative synthesis (see the scheme below). With respect to its R_f value, VII proved to be identical to the substance obtained from 2-(9-acridinyl)-1-naphthylamine. The structure of the latter was proved [1] by deamination and

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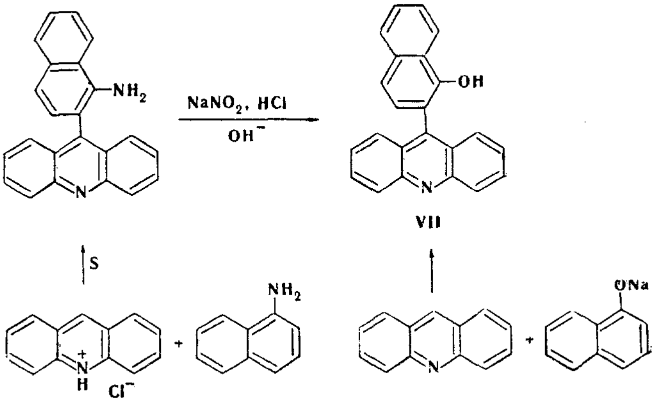
comparison of the resulting naphthylacridine with a sample synthesized from diphenylamine and naphthoic acid. It is well known that 2-naphthol couples with weak electrophiles, for example, with the diazonium cation, only in the 1 position [7], and this makes it possible to propose the 1-(9-acridinyl)-2-naphthol structure for VIII.

Salts of polyphenols also undergo reaction with acridines. The reaction products in this case have the ability to form stable complexes with acridine. This sort of 1:1 complex was isolated in pure form for the resorcinol derivative (see the experimental section). The acridine can be separated by dissolving the complex in alkali. 9-(2,4-Dihydroxyphenyl)-acridine, which was isolated from the filtrate, could be identified in the form of the satisfactorily crystallizable diacetyl derivative (IV).



The acridine derivative of resorcinol obtained after acid hydrolysis again forms a complex identical to that isolated from the reaction mass when it is mixed with acridine in alcohol. Evidence for the formation of the complex is presented not only by the results of elementary analysis but also by the PMR spectrum in dimethyl sulfoxide (DMSO), in which a singlet at 9.97 ppm, which is characteristic for 9-H in unsubstituted acridine, is observed.

The acridine residue gives a complex multiplet at 8.5-8.8 ppm in the PMR spectra of all of the synthesized compounds in CF_3COOH. The character of the multiplet of this portion of the spectrum of the aromatic protons is typical for a four-spin system and has a common form for the protonated form of 9-substituted aryl derivatives of acridine.

The proton of the phenolic hydroxyl group can be detected in DMSO solutions as a singlet at weak field: 9.48 ppm (I), 9.80 ppm (X) or 9.04 ppm (III). An analysis of the PMR spectra for the remaining compounds (see the experimental section) shows that the phenoxide group dominates in the orientation of the entering acridenyl residue, directing it to the para position. An exception to this is aminophenol derivative VI, in which the acridinyl residue is oriented in the para position relative to the amino group, as attested to by the identical character of the spectra of VI and the substance of known structure [1]. When the para position relative to the phenoxide group is occupied, the substituent is oriented in the ortho position (II). The appearance in the spectrum of IX of a multiplet at weak field at 9.4-9.6 ppm, which is absent in the spectra of naphthalene derivatives VII and VIII, constitutes evidence for the presence of a quinoline fragment; the two doublets with J = 9 Hz correspond to the signals of the less shielded 6-H (8.42 ppm) and 7-H (8.15 ppm) protons, which are in the ortho position relative to the OH group in the quinoline ring.

All of the synthesized 9-hydroxyarylacridines are high-melting yellow crystalline substances. They are only slightly soluble in most organic solvents, crystallize poorly, and are soluble in acids and alkali. Some data on their properties are presented in Table 1.

The above-described reaction is a rather rare instance [2, 6] of hetarylation by means of an unactivated π-deficient heteroatomatic compound. The experiments show that the closest analogs of acridine — quinoline and isoquinoline — do not react with phenoxides. This is probably explained by the high electrophilicity of acridine and also by the greatest possibilities of stabilization of the intermediate σ complex through bilateral annelation of benzene rings.

TABLE 1. 9-Hydroxyarylacridines

Compound	Starting phenol	X, Y	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
I	Phenol	4-OH	358—360 a	$C_{19}H_{13}NO$	84.1	5,0	5,2	84,1	4,8	5,1	33
II	o-Cresol	3-CH_3-4-OH	314—316 b	$C_{20}H_{15}NO$	84,2	5,2	5,2	84,2	5,3	4,9	35
III	m-Cresol	2-CH_3-4-OH	326—328 a	$C_{20}H_{15}NO$	84.4	5,4	5,1	84,2	5,3	4,9	51
IV	p-Cresol	2-OH-5-CH_3	320—322 a	$C_{20}H_{15}NO$	84.5	5,3	5,3	84,2	5,3	4,9	27
V	o-Bromophenol	3-Br-4-OH	288—290 c	$C_{19}H_{12}BrNO$	65.3	3,6	4,0	65,2	3,5	4,0	91
VI	m-Aminophenol	2-OH-4-NH_2	346—348 c	$C_{19}H_{14}N_2O$	79,9	5,0	10,1	79,7	4,9	9,8	82
VII	1-Naphthol	2-OH-3,4-benzo	355—357 a	$C_{23}H_{15}NO$	85,7	4,9	4,4	86,0	4,7	4,4	74
VIII	2-Naphthol	2-OH-5,6-benzo	330—332 a	$C_{23}H_{15}NO$	86,1	4,8	4,5	86,0	4,7	4,4	72
IX	8-Hydroxyquinoline	4-OH-5,6-[*b*]-pyrido	274—276 a	$C_{22}H_{14}N_2O$	82,3	4,4	9,0	82,0	4,4	8,8	81
X	o-Methoxyphenol	3-OCH_3-4-OH	302—304 c	$C_{20}H_{15}NO_2$	79,9	5,2	4,6	79,7	5,0	4,6	15
XI	m-Methoxyphenol	2-OCH_3-4-OH	306—308 c	$C_{20}H_{15}NO_2$	79.5	5,0	4,8	79,7	5,0	4,6	43
XII	d	4-$OCOCH_3$	218 b	$C_{21}H_{15}NO_2$	80,2	4,8	4,7	80,5	4,8	4,5	70
XIII	d	4-$OCOCH_3$-5,6-benzo	218—219 b	$C_{25}H_{17}NO_2$	82.6	4,7	3,7	82,6	4,7	3,9	83
XIV	d	2,4-$OCOCH_3$	182 b	$C_{23}H_{17}NO_4$	74.1	4,7	3,9	74,4	4,6	3,8	83

a) From DMF; b) from ethanol; c) from xylene; d) obtained by acetylation of the corresponding 9-hydroxyarylacridines.

EXPERIMENTAL METHOD

The PMR spectra of DMSO and CF_3COOH solutions of the compounds were recorded with Varian XL-100 and CHART-60 spectrometers. The IR spectra of perfluorohydrocarbon suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of $5 \cdot 10^{-4}$ mole/liter solutions in alcohol were recorded with an SF-4 spectrophotometer. Thin-layer chromatograms were obtained on activity II aluminum oxide.

Preparation of the Phenoxides. The phenols were dissolved in absolute ether or benzene, and the equivalent amount of sodium metal was added. The solvent was then removed by distillation after hydrogen evolution ceased.

9-Hydroxyarylacridines. Air was bubbled at 130-140° through a solution of 0.02 mole of acridine and 0.03 mole of phenoxide in DMF for 1.5-2 h, and the resulting resinous mass was washed repeatedly with ether and drenched with dilute HCl (1:1). The solid product was pulverized, washed with water, dried, and crystallized from a suitable solvent (Table 1). IR spectrum, cm^{-1}: XII 1770 (C=O) and XIII 1750 (C=O). PMR spectra, δ, pp,: IIIc CF_3COOH 8.3 d* (J = 9 Hz, 6-H), 7.38 d (J = 9 Hz, 5-H), 2.74 s (2-CH_3); XI in DMSO 7.16 d (J = 10 Hz, 5-H), 7.49 d (J = 10 Hz, 6-H), and 4.23 s (2-OCH_3).

Acetylation of 9-Hydroxyarylacridines. A 0.01-mole sample of 9-hydroxyarylacridine and 1 mole of anhydrous sodium acetate were refluxed in 12 ml of acetic anhydride for 20 min, after which the resulting solution was poured into water, and the crystallized precipitate was removed by filtration, washed with water, dried, and crystallized from ethanol.

Complex of 9-(2,4-Dihydroxyphenyl)acridine with Acridine. A 0.92-g (0.04 g-atom) sample of sodium was added to a solution of 2.2 g (0.02 mole) of resorcinol in anhydrous ether, the ether was removed by distillation after hydrogen evolution had ceased, and 3.58 g (0.02 mole) acridine and 10 ml of DMF were added to the resinous mass. The mixture was then heated to 140°, and air was bubbled through the resulting solution for 1 h. The reaction mixture was then diluted with an equal volume of water, and the aqueous mixture was neutralized with acetic acid. The resulting precipitate was removed by filtration, dried, and crystallized from DMF to give 4.6 g (48%) of a product with mp 276-278° and R_f 0.4 [chloroform—ethanol (40:1)]. Found: C 82.3; H 5.0; N 6.7%. $C_{19}H_{13}N_2O_2$. Calculated: C 82.4; H 4.8; N 6.0%. An identical compound was formed by refluxing equimolar amounts of acridine and 9-(2,4-dihydroxyphenyl)acridine, obtained by hydrolysis of its diacetyl derivative (XIV), in alcohol; the complex had mp 274-278° and R_f 0.4 [chloroform—ethanol (40:1)]. Compound XIV was hydrolized by refluxing in dilute acetic acid containing a few drops of concentrated HCl for 20 min. The resulting precipitate was dissolved in alcohol, and the alcohol

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*Here and subsequently: s — singlet, d — doublet.

solution was neutralized with sodium carbonate solution. The resulting amorphous precipitate was used for the synthesis of the complex.

Preparation of 9-Hydroxynaphthylacridine (VII) from 2-(9-Acridinyl)-1-naphthylamine. 2-(9-Acridinyl)-1-naphthylamine was diazotized in the usual way [8], the excess nitrous acid was removed by the addition of urea, and the diazonium salt solution was heated to 100° until nitrogen evolution ceased. The resulting precipitate was removed by filtration, washed with water, dried, and chromatographed to give a product with R_f 0.18 (chloroform), which was in agreement with the value obtained for VII.

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