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NUCLEOPHILIC SUBSTITUTION OF HYDROGEN (9-H) IN ACRIDINIUM SALTS BY PHENOLS

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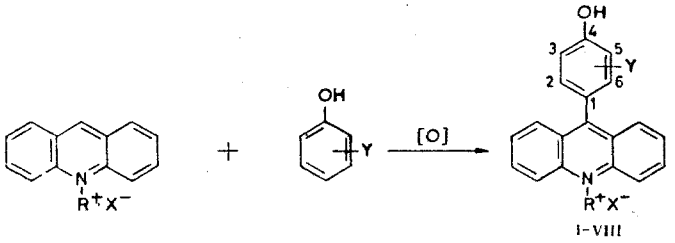
Under oxidative conditions, quaternary and protic acridinium salts undergo substitution of the hydrogen atom in the 9 position by a phenol residue to give 9-hydroxyarylacridines. The latter may be formed under the same conditions from complexes of acridine hydrochloride with phenols obtained by an independent method.

Nucleophilic substitution of hydrogen in charge-activated aza-aromatic compounds is presently realized with various nucleophilic agents [1-3]. The introduction of phenol residues into azinium cations has been described only in the case of quinoline in a little-known Japanese study [4] that has not been included in Chemical Abstracts. The structures of the reaction products were not studied, and the results of elementary analysis are presented for only one compound.

In the present paper we have investigated the reaction of phenols with acridinium salts. Experiments showed that quaternary and protic acridinium salts react with mono- and polyhydric phenols in an oxidative medium to give 9-(4-hydroxyaryl)acridines.



I-VIII

The oxidative dehydrocondensation with phenols was carried out under the conditions previously used* for the replacement of hydrogen in azines by residues of arylamines and their derivatives [3], CH-active compounds [5], and other nucleophiles. We were able to obtain condensation products I-VIII (Table 1) of acridine hydrochloride (AHC) with aminophenols, resorcinol monomethyl ether, 8-hydroxyquinoline, and polyphenols in good yields. The reaction of AHC with pyrogallol in dimethyl sulfoxide (DMSO) is realized at room temperature.

The reaction begins only at 160-170° in a melt with a threefold excess of sulfur. The yields of final products under these conditions are reduced to 20% because of a competitive reaction — thionation of acridine. The scope of this reaction can be expanded if the reagents are simply fused at a high temperature (200-210°) in air. This method was used to obtain condensation products with phenol, cresols, and naphthols that cannot be synthesized by the methods in [3, 5].

*By fusion with sulfur or by bubbling air through a solution in dimethylformamide.

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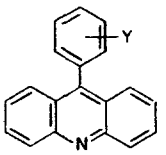
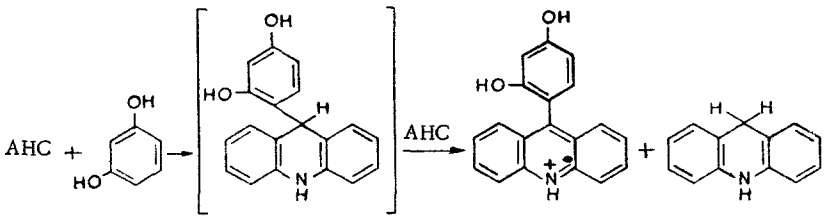
TABLE 1. 9-Hydroxyarylacridines and Their Derivatives



Compound*	Y	mp, °C (from ethanol)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
Ia	2,4 $(OH)_2$	316—318	$C_{19}H_{13}NO_2$	79,1	4,7	4,8	79,4	4,6	4,9	77
Ib	2,4 $(OH)_2$	315—319	$C_{19}H_{13}NO_2 \cdot 0{,}5H_2O$	76,9	4,7	5,0	77,0	4,7	4,7	77
Ic	2,4 $(OH)_2$	251—252	$C_{20}H_{16}INO_2$ †	56,1	3,8	3,2	56,0	3,8	3,3	74
II	2,4 $(OCH_3)_2$	212	$C_{21}H_{17}NO_2$	79,7	5,4	4,8	80,0	5,4	4,5	73
IIIa	2,4,6 $(OH)_3$	268—271	$C_{19}H_{13}NO_3 \cdot 0{,}5H_2O$	73,3	4,8	4,5	73,1	4,5	4,5	62
IIIc	2,4,6 $(OH)_3$	249—252 (dec.)	$C_{20}H_{16}INO_3$	54,1	3,7	3,1	54,0	3,6	3,1	60
IV	2,4,6 $(OCOCH_3)_3$	181	$C_{25}H_{19}NO_6$	69,8	4,6	3,3	69,9	4,5	3,3	72
Va	2,3,4 $(OH)_3$	327—329	$C_{19}H_{13}NO_3$	75,5	4,4	4,7	75,2	4,3	4,6	63
Vc	2,3,4 $(OH)_3$	251—254 (dec.)	$C_{20}H_{16}INO_3$	54,0	3,7	3,1	54,0	3,6	3,1	60
Vd	2,3,4 $(OH)_3$	329—332	$C_{19}H_{14}ClNO_3 \cdot 0{,}5H_2O$ ‡	65,6	4,2	4,1	65,4	4,3	4,0	65
VI	2,3,4 $(OCOCH_3)_3$	202	$C_{25}H_{19}NO_6$	70,2	4,7	3,4	69,9	4,5	3,3	71
VIIa	2,4,5 $(OH)_3$	320—323	$C_{19}H_{13}NO_3$	74,7	4,5	4,5	75,2	4,3	4,6	60
VIII	2,4,5 $(OCOCH_3)_3$	194	$C_{25}H_{19}NO_6$	70,2	4,4	3,5	69,9	4,5	3,3	70

*Symbols: a and b are the bases, c indicates the N-methiodides, d is the hydrochloride, e represents the dihydrochlorides, and f is the diquaternary salt with CH_3I.
†Found: I 29.5%. Calculated: I 29.6%.
‡Found: Cl 10.2%. Calculated: Cl 10.2%.

In the absence of air — in an inert-gas medium — AHC also reacts with pyrogallol, phloroglucinol, and resorcinol. The acridinium cation, which is converted to 9,10-dihydroacridine (see the Experimental section), in this case acts as the hydride-ion acceptor.



Phenols with aromatic rings containing groupings that have a +M effect (NH_2, CH_3, and OCH_3) undergo oxidative condensation with the acridinium cation. The introduction into the phenol of groupings that have —I and —M effects (NO_2, NO, and COOH) completely deactivates the nucleophile, and substitution products are not detected even by chromatography.

Of the dihydric phenols, only resorcinol undergoes the reaction. Hydroquinone and pyrocatechol are unreactive, possibly because of differences in the structure or stability of the complexes formed from AHC and various phenols.

Primary reaction of acridinium salts with polyphenols (including pyrocatechol and hydroquinone) at room temperature leads to the formation of stable complexes having a 2:1 AHC—phenol composition.

It was experimentally established that pyrogallol replaces the hydrogen in AHC both when the reagents are mixed in the usual manner and when the previously obtained complex with AHC is heated, whereas hydroquinone does not give substitution products in either case.

Thermogravimetric studies of the complexes of AHC with pyrogallol and hydroquinone were made. It is seen from Fig. 1 that a considerable endothermic effect, associated with melting and, apparently, dissociation of the complex (inasmuch as heat is evolved when the complex is formed), is observed on the differential thermal curve (DTA) of complex XIII at 180-

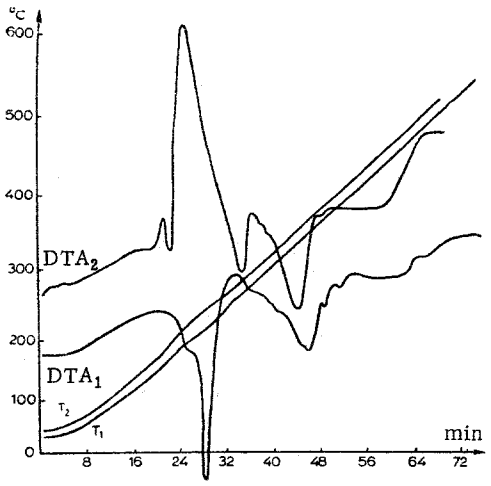
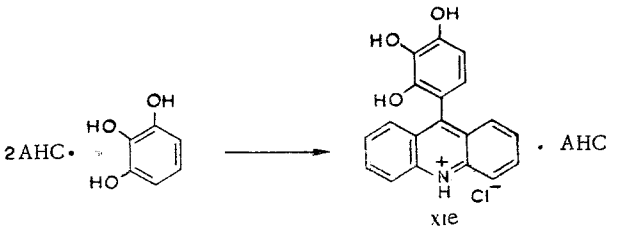


Fig. 1. Derivatogram of AHC—hydroquinone (XIII) and AHC—pyrogallol (XIV) complexes: DTA_1 and DTA_2 are the differential thermal curves of complexes XIII and XIV, and T_1 and T_2 are the thermal curves of complexes XIII and XIV.

200°, obtained from unreactive hydroquinone. Pyrogallol complex XIV at 180-200° displays a powerful exothermic effect associated with a condensation reaction. This provides a basis to assume that the complexes formed lie on the reaction coordinate.

In the thermal oxidative transformation of the AHC—pyrogallol complex (2:1), one acridine molecule forms a covalent bond with phenol, whereas the second molecule forms a complex of the XIe type with the reaction product. The complex is not decomposed on treatment with sodium carbonate and is isolated in the form of base XIa. Complexes of this sort (IX-XIa, Table 2) were obtained for resorcinol, phloroglucinol, and pyrogallol derivatives. Complexes identical to those isolated from the reaction mixture are formed by mixing polyhydroxyphenylacridines Ia, IIIa, and Va with acridine in alcohol (see the Experimental section).

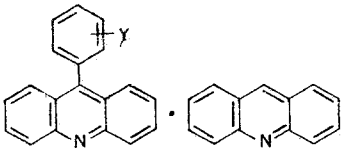


XIe

The ratios of the integral intensities in the PMR spectrum for the lone 2-H and 9-H protons confirm the results of elementary analysis, which attest to the formation of an 1:1 9-hydroxyarylacridine—acridine complex.

Complexes IXa, Xa, and XIa are decomposed on treatment with alkali or when alcohol solutions of them are passed through a column filled with aluminum oxide. In this case "normal" substitution products Ia, IIIa, and Va are formed. Crystallization from high-boiling sol-

TABLE 2. 9-Hydroxyarylacridine Complexes



Compound	Y	mp, °C (from ethanol)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IXa	2,4 $(OH)_2$	272—273	$C_{32}H_{22}N_2O_2 \cdot 0{,}5H_2O$	81,0	4,8	6,0	80,8	4,9	5,9	77
IXe	2,4 $(OH)_2$	258—262	$C_{32}H_{24}Cl_2N_2O_2 \cdot 0{,}5H_2O$	70,0	4,6	4,9	70,0	4,6	5,1	78
Xa	2,4,6 $(OH)_3$	224—225	$C_{32}H_{22}N_2O_3 \cdot 0{,}5H_2O$	77,6	5,0	6,0	78,2	4,7	5,7	62
XIa	2,3,4 $(OH)_3$	319—322	$C_{32}H_{22}N_2O_3 \cdot 0{,}5H_2O$	78,0	4,7	5,8	78,2	4,7	5,7	63
XIe	2,3,4 $(OH)_3$	287—289	$C_{32}H_{24}Cl_2N_2O_3 \cdot 0{,}5H_2O$	68,7	4,7	5,1	68,4	4,4	5,0	65
XIIf	2,4,5 $(OH)_3$	244—248 (dec.)	$C_{34}H_{23}I_2N_2O_3$	53,2	3,7	3,7	53,2	3,7	3,7	40

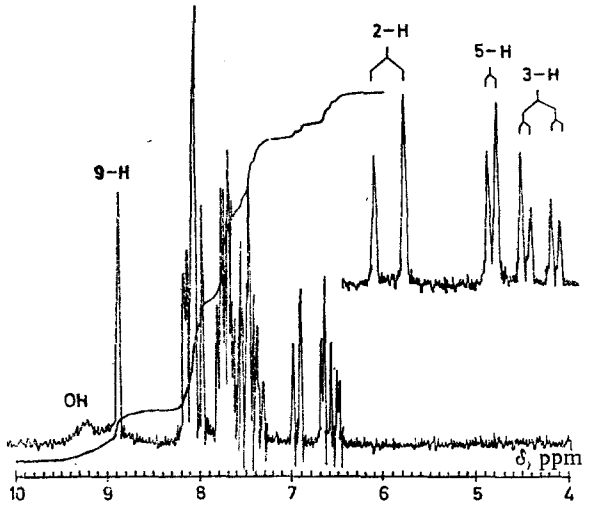


Fig. 2. PMR spectrum of IXa in dimethyl sulfoxide.

vents (for example, DMF) also leads to decomposition of the XIa complex, whereas the complex is preserved on crystallization from ethanol. Complexes IXa and Xa are also preserved when they are crystallized from DMF.

Compounds Ib, IIIa, Vd, IXa,e, Xa, and XIa,e are obtained as crystal hydrates with 0.5 mole of H_2O. The water is split out when the compounds are dried *in vacuo* over P_2O_5 at 200°. Compound Ia was obtained in this way from crystal hydrate Ib.

The UV spectra of all of the investigated compounds contain absorption maxima at 250-255 and 350-355 nm, and this constitutes evidence for the formation of substituted acridines rather than addition products, which are characterized by an absorption band at 280-290 nm [6].

The PMR spectra of all of the 9-hydroxylarylacridines and their acetyl derivatives contain a multiplet at 7.3-8.5 ppm corresponding to resonance of the protons of the acridine ring. The aromatic phenol residue appears at weaker field at 6.2-7.0 ppm, and this makes it possible to assign the signals and establish the character of the substitution in the phenolic fragment (see the Experimental section). A hydroxyl group is observed at 8.6-8.8 ppm in the form of a broad signal that characterizes an exchange process, either intramolecular or intermolecular. The broad weak bands at 3200-3300 cm^{-1} (OH stretching vibrations) in the IR spectra also attest to the participation of the hydroxyl group in the exchange interaction.

The IR spectra of the products of substitution of AHC with aminophenols, naphthols, cresols, resorcinol monomethyl ether, and 8-hydroxyquinoline show that they are identical to the substances obtained by reaction of the acridine base with the appropriate phenoxide ions [7]. The structures of the quaternary salts of hydroxyphenylacridines Ic, IIIc, Vc, and XIIf were additionally confirmed by quaternization with methyl iodide of the corresponding bases Ia, IIIa, Va, and VIIa.

The synthesized 9-hydroxyarylacridine hydrochlorides are deeply colored high-melting crystalline substances that are moderately soluble in water and most polar organic solvents.

Bases Ib, IIIa, Va, and VIIa were obtained by treatment of alcohol solutions of the corresponding salts with alkali, whereas IXa, Xa, and XIa were obtained by treatment of alcohol solutions of the salts with sodium carbonate. These bases are high-melting crystalline substances that are soluble in alkalis and acids, slightly soluble in organic solvents, and difficult to crystallize. The purification of Ia, IIIa, and Va is difficult because of their tendency to undergo complexing. These compounds can be identified in the form of the satisfactorily crystallized O-alkyl or acetyl derivatives. Products VIIa, IIIa, and Va can be obtained in the individual state after hydrolysis of acetyl derivatives VIII, IV, and VI.

EXPERIMENTAL

The electronic spectra of 10^{-5}-10^{-6} M alcohol solutions of the compounds were recorded with a Perkin–Elmer 402 spectrometer. The IR spectra of perfluorohydrocarbon suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of 5% solutions of the compounds in DMSO and methylene chloride were recorded with Chart-60T and XL-100 spectrom-

eters at room temperature for acetyl derivatives IV, VI, and VIII and at 80° for Ia, IIIa, Va, and VIIa (in DMSO in the case of complexes IXa, Xa, and XIa). The internal standard was hexamethyldisiloxane. The derivatogram of a 381-mg sample was recorded with a Paulik–Paulik–Erdey derivatograph; the time of one revolution of the drum was 75 min, the DTA sensitivity was $^1/_2$, the heating rate was 8 deg/min, and the standard was Al_2O_3. Thin-layer chromatography (TLC) was carried out on activity–II aluminum oxide with elution by chloroform.

9-Hydroxyarylacridine Dihydrochlorides (IXe, XIe). A mixture of 20 mmole of AHC, 10 mmole of resorcinol or pyrogallol, 30 mg-atom of sulfur, and 10 ml of DMF was heated at 120-140° for about 2 h, after which the solid product was washed with ether, pulverized, extracted with benzene, and crystallized.

9-Hydroxyarylacridine Complexes (IXa, XIa). A 10-mmole sample of the appropriate 9-hydroxyarylacridine dihydrochloride (IXe, XIe) was dissolved in alcohol, and the solution was diluted with water and neutralized with sodium carbonate. The resulting precipitate was removed by filtration, washed on the filter with water, dried, and crystallized.

9-Hydroxyarylacridines (Ia, Va). A 10-mmole sample of the appropriate 9-hydroxyarylacridine dihydrochloride (Xe, XIe) was treated with excess 2 N NaOH, and the resulting solution was filtered. The filtrate was neutralized to pH 7 with acetic acid, and the yellow precipitate was removed by filtration, washed on the filter with water, dried, and crystallized.

Alkylation of IXa. A 4.66-g (10 mmole) sample of complex IXa was dissolved in 20 ml of methanol containing 3 g of KOH, after which 1.26 g (10 mmole) of dimethyl sulfate was added carefully, and the mixture was refluxed for 45 min. The resulting precipitate was removed by filtration, dried, and crystallized to give 2.3 g (73%) of II.

Acetylation of Bases Xa, XIa, and VIIa. A 10-mmole sample of Xa, XIa, or VIIa was mixed with 10 ml of acetic anhydride and 0.082 g (1 mmole) of anhydrous sodium acetate, and the mixture was refluxed for 20-25 min. The hot solution was poured into 70 ml of cold water, and the aqueous mixture was allowed to stand for 10-12 h. The resulting oil began to crystallize to give a solid, which was removed by filtration, washed thoroughly with water, dried, and crystallized to give the product in 70-72% yield.

Hydrolysis of Acetyl Derivatives IV, VI, and VIII. A 10-mmole sample of IV, VI, or VIII was mixed with 30 ml of 12% HCl and 7 ml of glacial CH_3COOH, and the mixture was refluxed for 15-20 min. The resulting precipitates were removed by filtration, dried, and crystallized.

Preparation of 9-hydroxyarylacridines Ia, IIIa, and Va in an Inert-Gas Medium. A 20-mmole sample of resorcinol, pyrogallol, or phloroglucinol was mixed with 2.16 g (10 mmole) of AHC and 10 ml of DMF, and argon was bubbled through the resulting solution at 140° for 1-2 h. The mixture was then washed with ether and dissolved in excess 2 N NaOH. The resulting solution was filtered, the filtrate was neutralized to pH 7 with acetic acid, and the precipitate was removed by filtration, washed on the filter with water, dried, and crystallized.

Preparation of Complexes IXa, Xa, and XIa from 9-Hydroxyarylacridines Ia, IIIa, and Va. Alcohol solutions of 10 mmole of Ia, IIIa, or Va were mixed with 1.79 g (10 mmole) of acridine, after which the alcohol was removed by distillation, and the residue was washed with benzene and crystallized from ethanol. IR spectrum, cm^{-1}: IIIa, ν_{OH} 3200 w; Va, ν_{OH} 3278 w and 3150 w. PMR spectra, δ, ppm: IV in DMSO 7.39 s (3- and 5-H); VI in CH_2Cl_2 8.24 d (J_{6-5} = 5 Hz, 6-H), 8.12 (J_{5-6} = 5 Hz, 5-H), 2.27 s (3-$OCOCH_3$), 2.21 s (4-$OCOCH_3$), 1.49 (2-$OCOCH_3$); VIII in DMSO 7.39 s (J_{3-6} = 0.5 Hz, 3-H), 7.48 s (J_{6-3} = 0.5 Hz, 6-H); Xa in DMSO 9.45 s (4-OH), 9.15 s (2- and 6-OH), 9.05 s (acridine 9-H), 6.17 s (3- and 5-H); XIa in DMSO 9.10 s (acridine 9-H), 6.65 d (J_{6-5} = 9 Hz, 6-H), and 6.50 d (J_{5-6} = 9 Hz, 5-H).

Compounds Ic, IIIc, Vc, and XIIf. A mixture of 3.21 g (10 mmole) of acridine methiodide, 10 mmole of resorcinol or a trihydric phenol, 0.96 g (30 mg-atom) of sulfur, and 10 ml of DMF was stirred at 130-140° for 2 h, after which the resinous mass was washed with ether, and the solid was pulverized, extracted with benzene, and crystallized.

Quaternization of Ia, IIIa, Va, and VIIa. A 10-mmole sample of 9-hydroxyacridine Ia, IIIa, Va, or VIIa was mixed with 1 ml of methyl iodide and 10 ml of DMF, and the mixture was heated for 4-5 h, after which it was washed with ether, and the solid material was pulverized and crystallized.

AHC–Hydroquinone Complex (2:1) (XIII). Alcohol solutions of 4.32 g (20 mmole) of AHC and 10 mmole of hydroquinone were mixed, after which the solvent was removed by vacuum distillation at room temperature, and the dry residue was pulverized, washed with ether, dried, and crystallized to give a product with mp 201-206°. Found, %: C 70.5; H 4.8; N 5.1. $C_{32}H_{26}Cl_2N_2O_2$. Calculated, %: C 71.0; H 4.8; N 5.2.

AHC–Pyrogallol Complex (2:1) (XIV). Complex XIV was similarly obtained and had mp 190-194°. Found, %: C 69.1; H 4.9; N 5.1. $C_{32}H_{26}Cl_2N_2O_2$. Calculated, %: C 68.9; H 4.7; N 5.0.

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1,4-DIAZABICYCLO[2.2.2]OCTANES.

I. METHOD FOR THE SYNTHESIS OF 1,4-DIAZABICYCLO[2.2.2]OCTANES WITH FUNCTIONAL SUBSTITUENTS OR CONDENSED WITH BENZENE RINGS

L. B. Mrachkovskaya, K. F. Turchin, and L. N. Yakhontov

UDC 547.895.07

The reaction of substituted 1,4-dimethylpiperazines and tetrahydroquinoxaline with dibromoethane gives the corresponding 1,4-diazabicyclo[2.2.2]octanes.

In contrast to quinuclidine compounds which have been investigated in detail [1], insufficient study has been devoted to 4-azaquinuclidines (1,4-diazabicyclo[2.2.2]octanes). Only the unsubstituted 1,4-diazabicycle [2] and its C-alkyl [3] and quaternary [4] derivatives have been described. Compounds with functional substituents are unknown. The available information regarding the strange properties of benzo(b)-1,4-diazabicyclo[2.2.2]octane [5] raises doubts that a compound with precisely this structure was obtained.

The difficulties involved in the synthesis of 1,4-diazabicyclo[2.2.2]octanes are determined by the fact that the methods for the construction of the quinuclidine ring are usually unsuitable for the corresponding 4-azaquinuclidines. It has been shown [6] that N-(β-carboxy-β-methyleneethyl)piperazine derivatives are formed in the reaction of piperazines with formaldehyde and malonic acid (or its esters) instead of the products of the Mannich reaction — 4-(β,β-dicarbonylethyl)piperazines — due to intramolecular fragmentation. Reductive fragmentation also occurs in the reaction of piperazinylmethylenemalonic esters with sodium borohydride or hydrogen [7]. 1,1,4,4-Tetramethylpiperazinium dibromide is formed in all cases in the reaction of 1,4-dimethylpiperazine with substituted 1,2-dibromoalkanes [8].

In the present paper we describe a method for the synthesis of 1,4-diazabicyclo[2.2.2]-octanes with functional substituents attached to the carbon atoms of the bicycle or condensed with aromatic rings; the method is based on the reaction of the corresponding sub-

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