REACTION OF 9-CHLOROACRIDINE WITH HETEROCYCLIC COMPOUNDS CONTAINING AN ACTIVE METHYL GROUP

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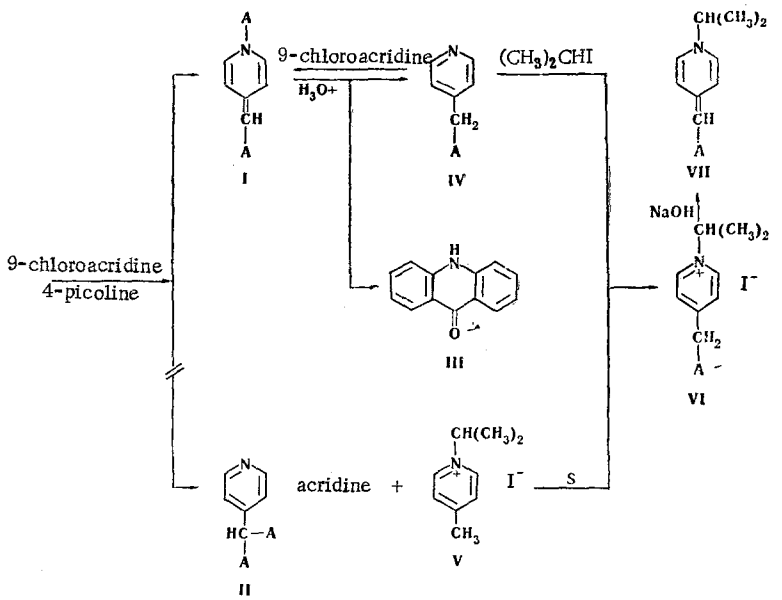
9-Chloroacridine reacts with 4-picoline to form 1-(9-acridinyl)-4-(9-acridinylmethylidene)-1,4-dihydropyridine, whose structure was proved by chemical transformations. A number of such compounds were obtained.

Recently we reported the preparation of 9-acridinylheterylmethanes by the reaction of acridine with some methyl heterocycles in the presence of sulfur [1]. In an attempt to synthesize these compounds by an alternative pathway by the method described for 2,2-diquinolylmethane [2], we found that the reaction takes a different course in the case of 2- and 4-picolines.

Thus heating of a mixture of 9-chloroacridine and 4-picoline at 100 deg C forms a crystalline, chlorine-containing substance, which, after treatment with alkali, gives a base with the composition $C_{32}H_{21}N_3$. This composition indicated that the compound obtained consists of residues of two acridine molecules and one picoline molecule. This assumption was confirmed by the result of the hydrolysis of the base in acid medium, during which acridone (III) and 9-acridinyl-4-pyridylmethane (IV), previously obtained by another route [1], are formed in good yields (Scheme 1).



The presence of two acridine residues in base $C_{32}H_{21}N_3$ also followed from the fact that the reaction of 9-chloroacridine with 9-acridinyl-4-pyridylmethane (IV) gives a substance whose properties are in com-

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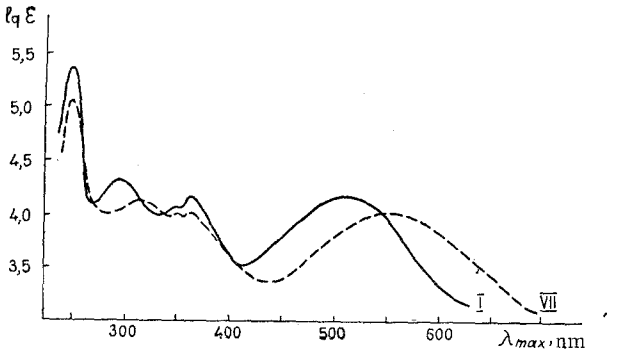


Fig. 1. Electronic spectra of I and VII in chloroform.

plete agreement with those of the base obtained. Compounds XI-XV were synthesized via a similar route starting from 9-acridinyl-4-pyridylmethane and compounds containing a labile halogen (1-nitro-9-chloroacridine, 2,7-dibromo-9-chloroacridine, 4-chloroquinazoline, and 2,4-dinitrochlorobenzene).

These results make it possible to assume structure I or II for base $C_{32}H_{21}N_3$. The results of hydrolysis did not contradict either structure. An examination of Stuart models showed that steric hindrance in the compound that has two acridine residues attached to one nitrogen atom is so great that its formation might be doubtful. In order to confidently choose between I and II, we undertook the synthesis of 1-isopropyl-4-(9-acridinylmethyl)-1,4-dihydropyridine (VII), which is structurally related to base I and is known to have a 1,4-dihydropyridine structure. Compound VII was obtained by the quaternization of 9-acridinyl-4-pyridylmethane (IV) with isopropyl iodide with subsequent treatment with alkali. A method that we developed for the bases of methyl heterocycles and their proton salts [1] was used for the alternative synthesis. It turned out that acridinylation in the presence of sulfur proceeds smoothly also with quaternary salts of methyl heterocycles.

A great similarity in the character of the curves and the presence of new absorption bands at 300-317 and 500-550 nm (Fig. 1) was observed on comparing the electronic spectrum of this compound with the spectrum of base $C_{32}H_{21}N_3$. The IR spectra of I and VII have an intense absorption band at 1650-1660 cm^{-1}, which is not present in the IR spectrum of either acridine or 9-acridinyl-4-pyridylmethane. It can be ascribed to the vibrations of the C=C bond of the 1,4-dihydropyridine ring. According to the data in [3], the band at 1670-1685 cm^{-1} is the characteristic $\gamma_{C=C}$ value of dihydropyridines.

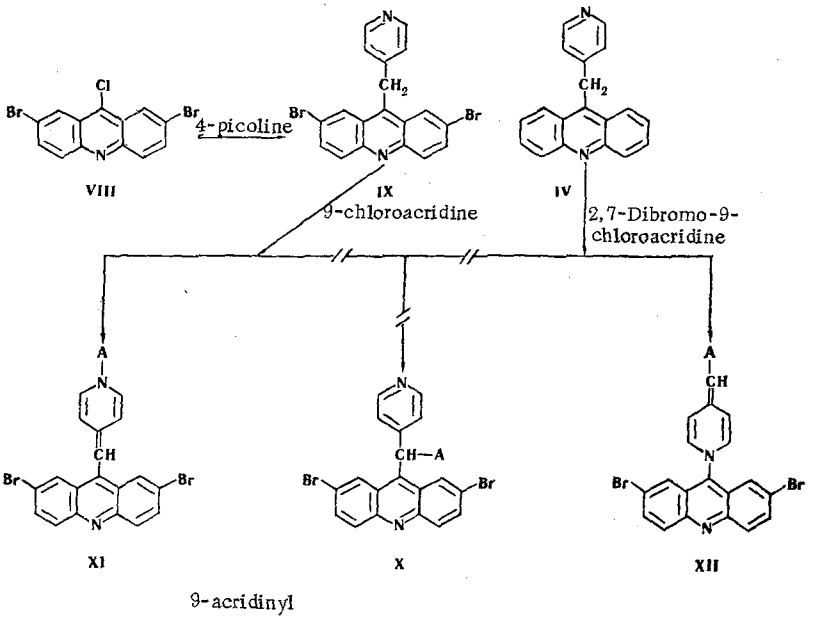
Thus the above data make it possible to draw the conclusion that compound $C_{32}H_{21}N_3$ has the anhydro base structure (I). A similar structure can also be ascribed to the products obtained by the reaction of IV with compounds that contain a labile halogen (Table 1).

As seen from the data in Table 1, an increase in the electron-acceptor properties of the substituent bonded to the nitrogen atom of the 1,4-dihydropyridine ring leads to a hypsochromic shift from 317 nm for VII to 285 nm for XV. The possibility for the free electron pair of the nitrogen atom of the dihydropyridine ring to be included in the overall chromophoric system apparently decreases as the acceptor character of the substituent increases.

Another confirmation of the conclusion regarding the I structure is presented in Scheme 2.

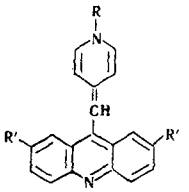
Two products with different UV spectra and thin-layer-chromatographic data (R_f 0.75 for XI and R_f 0.92 for XII) were obtained as a result of crossover reactions between (2,7-dibromo-9-acridinyl)(4-pyridyl) methane (IX) and 9-chloroacridine, on the one hand, and 9-acridinyl-4-pyridylmethane (IV) and 2,7-dibromo-9-chloroacridine, on the other. This is evidence that the condensation proceeded at the nitrogen atom of the pyridine ring. If the condensation had proceeded at the methylene group, only X would have been obtained.

The results obtained in this study make it possible to assume that 4-picoline and, probably, related compounds manifest bifunctional character in the reaction with 9-chloroacridine and can be attacked at both nucleophilic centers –the methyl group and the nitrogen atom.



Scheme 2

TABLE 1. 1-Substituted 4-(9-Acridinylmethylidene)-1,4-dihydropyridines



Compound	R	R′	mp, deg C	UV spectra		Empirical formula	Found, %			Calc., %			Yield, %
				λ_{max}, nm	lg ε		C	H	N	C	H	N	
I	9-Acridinyl	H	292—294[a]	300	4,28	$C_{32}H_{21}N_3$	85,5	4,7	9,7	85,9	4,7	9,4	83
VII	Isopropyl	H	174—176[b]	317	4,11	$C_{22}H_{20}N_2$	84,9	6,5	9,0	84,6	6,4	9,0	73
XI	2,7-Dibromo-9-acridinyl	H	278—280[c]	290[d]	4,28	$C_{32}H_{19}N_3Br_2$	63,8	3,2	7,2	63,5	3,2	6,9	58
XII	9-Acridinyl	Br	272—274[a]	315	4,45	$C_{32}H_{19}N_3Br_2$	63,6	3,5	7,1	63,5	3,2	6,9	71
XIII	1-Nitro-9-acridinyl	H	258—260[e]	294	4,50	$C_{32}H_{20}N_4O_2$	78,3	4,4	11,8	78,0	4,1	11,4	78
XIV	4-Quinoxalinyl	H	168—170[b]	292	4,46	$C_{28}H_{18}N_4$	81,8	4,8	13,6	81,9	4,4	13,7	75
XV	2,4-Dinitrophenyl	H	226—228[b]	285[f]	4,35	$C_{25}H_{16}N_4O_4$	68,9	3,8	13,0	68,8	3,7	12,8	33

[a] From pyridine.
[b] From ethanol.
[c] From chloroform–ethanol.
[d] From aqueous pyridine.
[e] From dimethylformamide.
[f] Displayed as a shoulder.

EXPERIMENTAL

1-(9-Acridinyl)-4-(9-acridinylmethylidene)-1,4-dihydropyridine (I). A mixture of 2.14 g (10 mmole) of 9-chloroacridine and 1.86 g (20 mmole) of 4-picoline was heated for 2 h on a boiling-water bath, 20 ml of water was added, and the mixture was treated with NaOH solution. The precipitate was removed by filtration and crystallized from pyridine to give 1.5 g (70%) of a substance that was identical to the substance obtained from 9-chloroacridine and 9-acridinyl-4-pyridylmethane, according to the IR spectral and thin-layer-chromatographic data.

1-Substituted 4-(9-Acridinylmethylidene)-1,4-dihydropyridines (I, VII, XI-XV) (General Method). Equimolar amounts of 9-acridinyl-4-pyridylmethane (IV) and compounds that contain a labile halogen were refluxed in the minimum amount of anhydrous butyl alcohol (several drops of triethylamine were added to prevent hydrolysis of the chloroacridines) until crystals began to separate out. The mixture was cooled, and the precipitate was filtered and washed with ether. It was then held for 30 min in 5% NaOH solution, filtered, and crystallized. Data on the properties of the compounds obtained are presented in Table 1.

1-Isopropyl-4-(9-acridinylmethylidene)-1,4-dihydropyridine (VII). A mixture of 2.16 g (10 mmole) of acridine hydrochloride, 2.63 g (10 mmole) of 1-isopropyl-4-picolinium iodide, and 0.64 g (20 g-atom) of sulfur was stirred at 130 deg for 3 h. Water (50 ml) was then added to it, and the mixture was refluxed with charcoal, filtered hot, and cooled. The precipitated salt was crystallized from alcohol and dissolved in water. A 10% NaOH solution was added, and the precipitate that crystallized out on brief standing was removed by filtration to give 1.6 g (50%) of product. No melting point depression was observed for mixtures of the substances obtained with those prepared by the general method.

Hydrolysis of 1-(9-Acridinyl)-4-(9-acridinylmethylidene)-1,4-dihydropyridine (I). A 1 g (2.2 mm mmole) sample of I was refluxed for 30 min in 20 ml of 10% H_2SO_4, the mixture was cooled, and 0.35 g (80%) of crystalline acridone III was separated by filtration. The filtrate was made alkaline with 10% NaOH solution, and the mixture was filtered to give 0.6 g (98%) of 9-acridinyl-4-pyridylmethane (IV). This product did not depress the melting point of an authentic sample.

(2,7-Dibromo-9-acridinyl)(4-pyridiyl)methane (IX). A 5 g (13.5 mmole) sample of 2,7-dibromo-9-chloroacridine was refluxed for 2 h in 10 ml of anhydrous 4-picoline. Extraction of this mixture with 1 N hydrochloric acid and treatment of the extract with NH_4OH solution precipitated 2.4 g (42%) of a product with mp 235-237 deg (from butanol). Found: C 53.3; H 2.9; N 6.6%. $C_{19}H_{12}Br_2N_2$. Calculated: C 53.3; H 2.8; N 6.5%.

1-(Acridinyl)-4-[(2,7-dibromo-9-acridinyl)methylidene]-1,4-dihydropyridine (XII). This was obtained from equimolar amounts of IX and 9-chloroacridine by the general method.

The UV spectra of $5 \cdot 10^{-5}$ M solutions in chloroform were recorded with a Perkin-Elmer 402 spectrometer. The IR spectra of mineral oil suspensions were measured with a UR-20 spectrometer. Aluminum oxide was used for the thin-layer chromatography with elution by chloroform.

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3. H. Albrecht and F. Kröhnke, Ann., 717, 96 (1968).