SYNTHESIS OF ANTHRADIPYRIDONE DERIVATIVES

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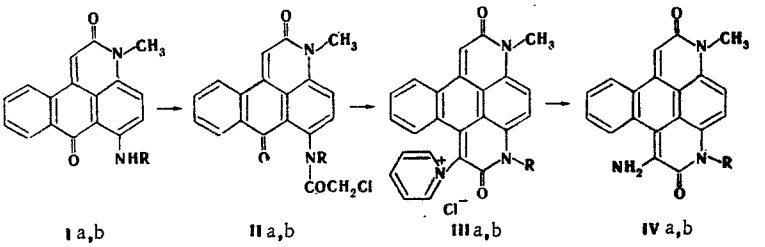
Anthradipyridones containing pyridinium groups in one or two pyridone rings were obtained by the action of pyridine on 6-chloroacetamido derivatives of anthrapyridone and on 1,4- and 1,5-di(chloroacetamido)anthraquinones. Heating of the anthradipyridonyl-pyridinium salts in aniline gives the corresponding mono- and diamino derivatives of anthradipyridones, while reduction gives unsubstituted anthradipyridones.

As we have previously shown, anthrapyridonyl-1-pyridinium salts readily form 1-aminoanthrapyridones (1-amino-3H-dibenzo[f,i,j]isoquinoline-2,7-diones) on heating in high-boiling amines [1]. The present paper is devoted to extension of this method to the synthesis of amino derivatives of anthradipyridones (3,6-dihydrodibenzo[f,*l*mn]-2,9-phenanthroline-2,7-dione and 3,9-dihydrobenzo[1,2,3-de:4,5,6-d'e']diquinoline-2,8-dione).

We have obtained anthradipyridonylmono- and bispyridinium salts, which were converted to the corresponding amino derivatives. The monopyridinium salts were obtained from 6-amino-3-methylanthrapyridones (Ia, b), the chloroacetyl derivatives (IIa, b) of which are readily cyclized in pyridine to give IIIa, b, and heating of the latter in aniline gives 1-aminoanthra[1,9:4,10]dipyridones (IVa, b).



I a,b II a,b III a,b IV a,b

I–IV a R=H; b R=CH_3

The formation of a second heteroring is confirmed by the resistance of IIIa, b to prolonged heating in concentrated sulfuric acid; in the case of uncyclized ω-pyridinium salts, these conditions should have led to hydrolysis to Ia, b.

1,4- and 1,5-Di(chloroacetamido)anthraquinones (Va, b; a is the 1,4 isomer, b is the 1,5 isomer) also readily undergo reaction with pyridine to give, however, 6- and 8-chloroacetamidoanthrapyridonyl-1-pyridinium chlorides (VIIIa, b) rather than bispyridinium derivatives. Since replacement of the chlorine atoms by pyridinium groups, which precedes cyclization [2], is equally probable in both chloroacetyl groups, compounds with two pyridinium groups (in the heteroring and in the open chain) should have been formed in the second cyclization in the case of hindrance. The structures of VIIIa, b were proved by reaction with aniline, as a result of which 6- and 8-ω-anilinoacetamido-1-aminoanthrapyridones (VIIIa, b) were obtained, and also by their hydrolysis with sulfuric acid to 6- and 8-aminoanthrapyridonyl-1-pyridinium salts (IXa, b). In turn, acid hydrolysis of VIIIa, b and heating in aniline of IXa, b lead to identical compounds, respectively – 1,6- and 1,8-diaminoanthrapyridones (Xa, b). The transformations of the 1,4 isomers (a) are presented in the scheme that follows.

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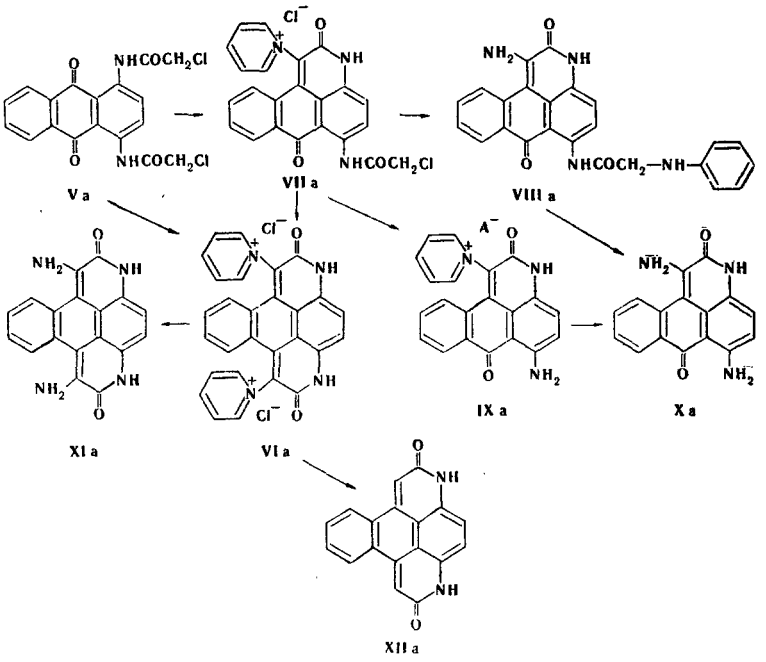
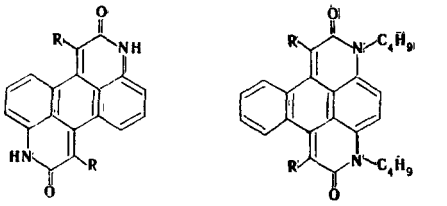


We were able to establish that the reason for the cessation of the reaction at the step involving the formation of VIIa, b is the low solubility of the latter in pyridine, as a result of which they precipitate and exit from the reaction sphere. The addition of water to the pyridine leads to an increase in the solubility of VIIa, b and subsequent reaction to form bispyridinium derivatives of anthradipyridones (VIa, b), which in turn precipitate from the aqueous pyridine as crystalline substances. Final compounds VIa, b, which do not contain intermediate reaction products, are formed directly in the reaction of the starting 1,4- and 1,5-bis(chloroacetamido)anthraquinones (Va, b) with aqueous pyridine. Their structure is confirmed by their resistance to hydrolysis in concentrated sulfuric acid, in which they remain unchanged even on heating at 250° for 4 h.



VIb, XIb, XIIb VIc, XIc, XIIc

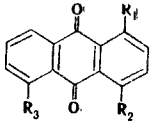
VIb, c R= ; XIb, c R=NH_2; XIIb, c R=H

If there are substituents that promote greater solubility in pyridine (for example, aliphatic chains) in the starting diaminoanthraquinones, the formation of monopyridinium salts of the VII type is not observed, and closing of both pyridone rings occurs in the absence of water. Thus bispyridinium derivative VIc was obtained by heating 1,4-bis(chloroacetylbutylamino)anthraquinone (Vc) in pyridine.

1,8-Diaminoanthra[1,9 : 4,10]dipyridone (XIa), its 3,6-dibutyl derivative (XIc), and 1,7-diaminoanthra-[1,9 : 5,10]dipyridone (XIb), respectively, are formed on heating bispyridinium salts VIa, c in aniline. The complete cleavage of two pyridine rings occurs with greater difficulty than in the case of one — in monopyridinium derivatives of anthrapyridone and anthradipyridone. While it is sufficient to heat the latter in aniline to the boiling point, the bispyridinium salts (VI) require refluxing for 3 h.

It is known that facile reductive elimination of the pyridinium group [3] is peculiar to anthrapyridonyl-1-pyridinium salts. Pyridinium derivatives of anthradipyridones also have a similar property. Thus, even in the cold, bispyridinium salts (VIa-c) are rapidly converted to unsubstituted anthradipyridones (XIIa-c) by mixing aqueous solutions of them with sodium carbonate solution of sodium hydrosulfite. Compounds XII can also be obtained from VI by reduction with zinc in aqueous acetic acid; this reduction requires prolonged heating.

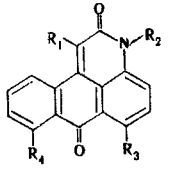
TABLE 1. Bis(chloroacetamido)anthraquinones



Compound	R_1	R_2	R_3	Mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	Cl	N	C	H	Cl	N	
Va	$NHCOCH_2Cl$	$NHCOCH_2Cl$	H	281—282	$C_{18}H_{12}Cl_2N_2O_4$	55,4	3,2	18,3	7,2	55,3	3,1	18,2	7,2	82
Vb	$NHCOCH_2Cl$	H	$NHCOCH_2Cl$	301—302	$C_{18}H_{12}Cl_2N_2O_4$	55,1	3,0	18,0	7,4	55,3	3,1	18,2	7,2	90
Vc	$N(C_4H_9)COCH_2Cl$	$N(C_4H_9)COCH_2Cl$	H	95—96	$C_{26}H_{28}Cl_2N_2O_4$	62,2	5,6	13,8	5,7	62,0	5,6	14,1	5,6	89

*Compounds Va, b were crystallized from aqueous dimethylformamide, while Vc was crystallized from benzene–ether.

TABLE 2. 3H-Dibenzo[f,i,j]isoquinoline-2,7-diones

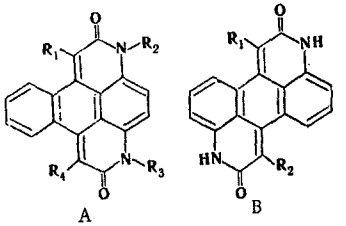


Compound	R_1	R_2	R_3	R_4	Mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	Cl	N	C	H	Cl	N	
Ia	H	CH_3	NH_2	H	304—306	$C_{17}H_{12}N_2O_2$	—	—	—	10,2	—	—	—	10,2	85
Ib	H	CH_3	$NHCH_3$	H	195—196	$C_{18}H_{14}N_2O_2$	74,5	4,8	—	9,6	74,5	4,9	—	9,7	74
IIa	H	CH_3	$NHCOCH_2Cl$	H	321—322	$C_{19}H_{15}ClN_2O_3$	64,4	3,8	10,5	7,9	64,5	3,7	10,3	7,9	78
IIb	H	CH_3	$N(CH_3)COCH_2Cl$	H	264—265	$C_{20}H_{15}ClN_2O_3$	65,4	3,9	9,6	7,6	65,5	4,0	9,6	7,6	82
VIIa	$C_5H_5\overset{+}{N}Cl^-$	H	$NHCOCH_2Cl$	H	—†	$C_{23}H_{15}Cl_2N_3O_3$	60,5	3,5	15,4	9,4	61,0	3,3	15,6	9,3	82
VIIb	$C_5H_5\overset{+}{N}Cl^-$	H	H	$NHCOCH_2Cl$	284—285	$C_{23}H_{15}Cl_2N_3O_3$	61,2	3,1	15,5	9,1	61,0	3,3	15,6	9,3	84
VIIIa	HH_2	H	$NHCOCH_2NHC_6H_5$	H	283—284	$C_{24}H_{18}N_4O_3$	70,1	4,8	—	13,4	70,2	4,9	—	13,6	94
VIIIb	HH_2	H	H	$NHCOCH_2NHC_6H_5$	254—255	$C_{24}H_{18}N_4O_3$	70,2	4,6	—	13,5	70,2	4,9	—	13,6	91
IXa	$C_5H_5\overset{+}{N}ClO_4^-$	H	NH_2	H	—*	$C_{21}H_{14}ClN_3O_6$	57,2	3,0	8,1	9,4	57,4	3,2	8,1	9,6	80
IXb	$C_5H_5\overset{+}{N}ClO_4^-$	H	H	NH_2	—†	$C_{21}H_{14}ClN_3O_6$	57,1	3,1	8,1	9,5	57,4	3,2	8,1	9,6	82
Xa	NH_2	H	NH_2	H	—†	$C_{16}H_{11}N_3O_2$	69,3	3,8	—	15,1	69,3	4,0	—	15,2	81
Xb	NH_2	H	H	NH_2	—†	$C_{16}H_{11}N_3O_2$	69,2	3,7	—	15,1	69,3	4,0	—	15,2	78

*Compound Ia was crystallized from nitrobenzene, VIIa, b were crystallized from aqueous alcohol, IXa, b were crystallized from water, and the remaining compounds were crystallized from dimethylformamide.

†Melts above 350°.

TABLE 3. 3,6-Dihydrodibenzo[f,*l*mn]-2,9-phenantholine-2,7-diones (A) and 3,9-dihydrobenzo[1,2,3-de : 4,5,6-d'e']diquinoline-2,8- -diones (B)



A B

Formula	Compound	R_1	R_2	R_3	R_4	Mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
								C	H	Cl	N	C	H	Cl	N	
A	IIIa	H	CH_3	H	$C_5H_5\overset{+}{N}Cl^-$	296—297	$C_{24}H_{16}ClN_3O_2$	69,5	3,8	8,5	9,9	69,6	3,9	8,6	10,1	91
	IIIb	H	CH_3	CH_3	$C_5H_5\overset{+}{N}Cl^-$	256—257	$C_{25}H_{18}ClN_3O_2$	70,3	4,1	8,2	9,7	70,2	4,2	8,3	9,8	92
	IVa	H	CH_3	H	NH_2	—†	$C_{19}H_{13}N_3O_2$	72,1	4,2	—	13,4	72,3	4,2	—	13,3	96
	IVb	H	CH_3	CH_3	NH_2	—†	$C_{20}H_{15}N_3O_2$	72,9	4,4	—	12,4	72,9	4,6	—	12,7	98
	VIa	$C_5H_5\overset{+}{N}ClO_4^-$	H	H	$C_5H_5\overset{+}{N}ClO_4^-$	—†	$C_{28}H_{18}Cl_2N_4O_{10}$	52,4	2,8	11,0	8,6	52,4	2,8	11,1	8,7	80
	VIc	$C_5H_5\overset{+}{N}ClO_4^-$	C_4H_9-*n*	C_4H_9-*n*	$C_5H_5\overset{+}{N}ClO_4^-$	255—256	$C_{36}H_{34}Cl_2N_4O_{10}$	57,4	4,4	9,3	7,5	57,4	4,5	9,4	7,4	80
	XIa	NH_2	H	H	NH_2	—†	$C_{18}H_{12}N_4O_2$	68,3	3,7	—	17,3	68,4	3,8	—	17,7	89
	XIc	NH_2	C_4H_9-*n*	C_4H_9-*n*	NH_2	219—220	$C_{26}H_{28}N_4O_2$	72,7	6,4	—	13,2	72,9	6,6	—	13,1	88
	XIIa	H	H	H	H	—†	$C_{18}H_{10}N_2O_2$	—	—	—	9,8	—	—	—	9,8	80
	XIIc	H	C_4H_9-*n*	C_4H_9-*n*	H	264—265	$C_{26}H_{26}N_2O_2$	78,3	6,3	—	7,3	78,4	6,6	—	7,0	87
B	VIb	$C_5H_5\overset{+}{N}ClO_4^-$	$C_5H_5\overset{+}{N}ClO_4^-$	—	—	—†	$C_{28}H_{18}Cl_2N_4O_{10}$	52,1	3,0	11,1	8,4	52,4	2,8	11,1	8,7	76
	XIb	NH_2	NH_2	—	—	—†	$C_{18}H_{12}N_4O_2$	68,3	3,8	—	17,6	68,4	3,8	—	17,7	89
	XIIb	H	H	—	—	—†	$C_{18}H_{12}N_2O_2$	—	—	—	9,6	—	—	—	9,8	82

*Compound VIa was crystallized from water, IVa, b were crystallized from aqueous dimethylformamide, and XIc and XIIc were crystallized from chlorobenzene.

†Melts above 350°.

Thus the transformations presented previously are a method for the preparation not only of amino derivatives of anthradipyridones but also of unsubstituted anthradipyridones.

EXPERIMENTAL

The physical constants and yields of the compounds obtained are presented in Tables 1-3.

Chloroacetyl Derivatives. A mixture of 1 g (3 mmole) of Ia,b, 1 ml (13 mmole) of chloroacetyl chloride, and 30 ml of chlorobenzene was heated for 2-4 h until the starting substance was absent on the chromatogram from thin-layer chromatography (TLC) on Al_2O_3 (chloroform). The mixture was then cooled and filtered, and the solid was washed with ether to give IIa, b (Table 2). The amount of chloroacetyl chloride was doubled in the preparation of Va-c (Table 1); in the case of Vc, 10 ml of benzene was used in place of chlorobenzene, and the compound was isolated by dilution with 10 ml of ether.

Pyridinium Salts. A 1.5-g sample of IIa, b or Va-c was refluxed in 30 ml of pyridine, after which the mixture was cooled, and the needles were removed by filtration and washed with ether to give, respectively, IIIa, b (Table 3), VIIa, b (Table 2), and VIc (Table 3).

Compounds VIa, b (Table 3) were obtained by refluxing a solution of 1 g of Va, b or VIIa, b in 47 ml of pyridine and 10 ml of water for 3 h. The mixture was cooled and filtered after the formation of crystalline precipitate, and the solid was dried. For analysis, a sample was dissolved in water, perchloric acid was added to the solution until the perchlorate precipitated, and the mixture was filtered. The precipitate was then crystallized from water (needles).

Amino Derivatives. A mixture of 1 g of IIIa, b or VIIa, b and 10 ml of aniline was heated to the boiling point, after which it was cooled to 70° and treated with 10 ml of methanol. The mixture was filtered, and the solid was washed with methanol to give, respectively, IVa, b (Table 3) and VIIIa, b (Table 2).

In the preparation of XIa-c (Table 3), VIa-c were refluxed in aniline for 3 h, and the products were isolated as indicated above.

6- and 8-Amino-3H-dibenzo[f,i,j]isoquinoline-2,7-dione-1-pyridinium Perchlorates (IXa, b). A mixture of 1 g of VIIa, b and 10 ml of 95% sulfuric acid was heated at 90° for 2 h, after which it was poured into ice water. The solid was washed with water and methanol and converted to the perchlorate as in the case of VIa, b (Table 2).

1,6- and 1,8-Diamino-3H-dibenzo[f,i,j]isoquinoline-2,7-diones (Xa, b). A. These compounds were obtained from IXa,b by heating in aniline via the method presented above (Table 2).

B. These compounds were also obtained in 80% yield from VIIIa, b by the method used to prepare IX.

3,6-Dihydrodibenzo[f,*l*mn]-2,9-phenanthroline-2,7-diones (XIIa, c) and 3,9-Dihydro[1,2,3-de:4,5,6-d'e']diquinoline-2,8-dione (XIIb). A 0.5-g (1 mmole) sample of VIa-c was dissolved in 100 ml of water, and a solution of 2 g (23 mmole) of sodium bicarbonate and 2 g (11 mmole) of sodium hydrosulfite in 50 ml of water was then added with stirring. The resulting precipitate was removed by filtration, washed with water, and dried. Compounds XIIa, b were purified by reprecipitation through the sulfate: 0.1 g was dissolved in 10 ml of 95% sulfuric acid, a few drops of water were added until the sulfate (needles) began to precipitate, and the mixture was filtered. The solid was washed with acetic anhydride and then decomposed by boiling in water. The mixture was filtered, and the solid was washed with water and alcohol to give 0.09 g of product. 3,6-di-n-butylbenzo[f,*l*mn]-2,9-phenanthroline-2,7-dione (XIIc) was crystallized from chlorobenzene (Table 3).

6-Amino-3-methyldibenzo[f,i,j]isoquinoline-2,7-dione (Ia). A mixture of 4 g (14.4 mmole) of 6-bromo-3-methyldibenzo[f,i,j]isoquinoline-2,7-dione, 5 g (35 mmole) of p-toluenesulfonamide, 1 g (12 mmole) of anhydrous sodium acetate, 0.1 g (0.5 mmole) of copper acetate, 0.1 g (0.9 mmole) of copper powder, and 12 ml of nitrobenzene was heated at 180° for 6 h, after which it was cooled to 70°, diluted with 30 ml of methanol, and filtered. The solid was washed with methanol, dried, and dissolved in 30 ml of 95% sulfuric acid. The solution was heated at 90° for 4 h, cooled, and poured into ice water. The mixture was filtered, and the solid was washed (Table 2).

6-Methylamino-3-methyldibenzo[f,i,j]isoquinoline-2,7-dione (Ib). A mixture of 5 g of 6-bromo-3-methyldibenzo[f,i,j]isoquinoline-2,7-dione, 50 ml of dimethylformamide, and 10 ml of 20% methylamine solution was heated in a sealed ampul at 140° for 6 h, after which the contents were poured into water. The mixture was filtered, and the solid was washed with water, dried, and purified by chromatography on Al_2O_3 (chloroform) (Table 2).

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