STUDIES IN THE ANTHRAPYRIDONE FIELD

VI. Catalytic Arylamination of Anthrapyridine Halogeno-Derivatives and Transamination of 2, 6-Diarylaminoanthrapyridines*

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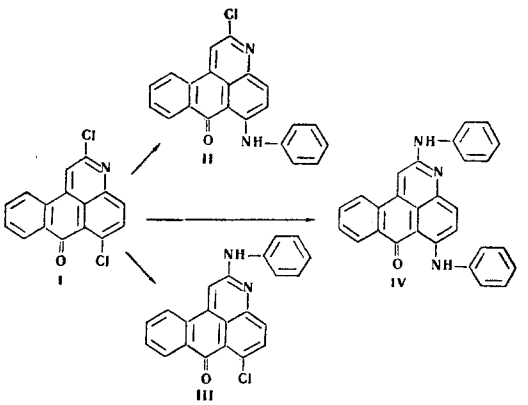
It is shown that hydrogen chloride catalyzes the replacement of halogen in the reaction of halogenoanthrapyridines with aromatic amines. Cupric acetate, in the presence of potassium acetate at 80–120° C, does not catalyze the replacement of halogen in these substances. The replacement of the arylamino residues in position 6 of a number of 2, 6-diarylaminoanthrapyridines by alkylamine residues under the action of aliphatic amines, was noted.

We have previously shown [1], that 2, 6-dichloroanthrapyridine forms 2-chloro-6-amino derivatives with amines under mild conditions and 2, 6-diaminoanthrapyridines when the temperature is raised to 180° in the presence of copper compounds and potassium acetate. The use of the catalytic properties of copper compounds and the addition of acetate as an acid-binding agent in the arylamination of 2-chloroanthrapyridine has been described previously [2, 3]. Later [4] it was shown, that in aqueous media the rate of the exchange of halogen for an aromatic amine residue in heterocyclic compounds rises with increasing H^+ concentration. It was also shown that the presence of strong bases hinders the replacement of halogen [5].

We studied the influence of acidic or basic agents and copper salts in the reaction medium on the reactivity of the chlorine atoms in 2, 6-dichloroanthrapyridine (I), 2-chloro-6-anilinoanthrapyridine (II), and 2-anilino-6-chloroanthrapyridine (III).



All experiments were conducted in an excess of aniline at 76–77° C over 3 hr 20 min. In the absence of additives, three substances were formed from compound I under these conditions: 2-chloro-6-anilinoanthrapyridine (II), 2-anilino-6-chloroanthrapyridine (III) and 2, 6-dianilinoanthrapyridine (IV) in 92.2, 5.6, and 2.0% yields, respectively. Under the conditions given, the rate of transformation of isomers II and III into the disubstituted compound IV was small, although significantly greater for isomer III. It is interesting to note that, with n-hexylamine the reaction proceeds more selectively and the amounts of the products are 98.6, 0.55 and 0.2%, respectively. Possible causes of this selectivity will be discussed below. When hydrogen chloride is introduced into the reaction in the form of aniline hydrochloride, a sharp change is noted in the ratio of the rates of exchange of halogen atoms (in the reaction products, the amounts of II, III and IV are 65.0, 16.0 and 18.2% respectively). The increased quantity of the monosubstituted compound III is explained by the activity of the 2-chloro atom in the given conditions. The ratio of the isomers II and III changed in the presence of acid from 16.5 : 1 to 4 : 1. The vigorous formation of IV is also a consequence of the activation of halogen in the monosubstituted compounds II and III. Arylamination of the isomers in the presence of acids showed that in this case the degree of transformation of isomer III is significantly higher than that of II. However, the relative increase in velocity of the reaction of isomer II is greater than for isomer III; with acid catalysis II forms 10 times more of the disubstituted compound IV and isomer III only 3 times more. It could be assumed that with a rise in the reaction temperature together with the use of acid it is possible to achieve a more complete transformation of II into IV. In actual fact up to 92% IV was obtained at 120° C in the presence of hydrogen chloride in the same time.

A general explanation was given [4] of a similar phenomenon with heterocyclic compounds. The protonation of heterocyclic nitrogen gives a positive charge to the entire molecule. Hence the activation energy in the nucleophilic reaction with the amine is lowered. Naturally, the greatest effect is to be expected for the nearest carbon atom and for the halogen atom attached to it. Actually, as shown above, the 2-chloro atom in 2, 6-dichloroanthrapyridine is the more highly activated and the relative mobility of the halogen in isomer II increases to a greater extent than in isomer III. However, protonic catalysis apparently occurs in these cases where the equilibrium

$$\text{Heterocycle} \cdot H^+ \rightleftharpoons \text{amine} \cdot H^+$$

does not shift fully in the direction of the amine, i.e. where the basicities of the reactants are comparable. It was shown [4], that acid catalysis extends only to aromatic amines and morpholine. Later, an increase

*For part V, see [8].

Reaction of Halogen Derivatives of Anthrapyridine with Aniline

Expt. no.	Starting compound	Reaction temp., °C	Reaction time, hr	HCl, mole*	CH_3COOK, mole*	$(CH_3COO)_2Cu$, mole*	Reaction products, %		
							II	III	IV
1	2,6-Dichloroanthra-	77	3.33	—	—	—	92.2	5.6	2.0
2	pyridine (I)	77	3.33	4			65.0	16.0	18.2
3	2-Chloro-6-anilinoan-	77	3.33	—	—	—	99.4	—	<0.3
4	thrapyridine	77	3.33	—	2	—	94.0	5.1	1.0
5	(II)	77	3.33	4	—	—	97.5	—	2.9
6		77	3.33	4	—	0.05	93.7	—	2.9
7			3.33	—	2	0.05	99.0	—	Traces
8		120	3.5	4	—	—	6.5	—	91.5
9		120	3.5	—	2	0.05	98.8	—	<0.3
10	2-Anilino-6-chloran-	77	3.33	—	—	—	—	87.7	12.3
11	thrapyridine	77	3.33	6	—	—	—	65.0	34.0
12	(III)	77	3.33	—	2	0.05	—	88.0	12.0

*Per 1 mole of halogen derivative.

in rate constant for the reaction of 2-chloropyridine with morpholine (pK 5.6) during the reaction was found (liberation of HCl) while in the use of piperidine (pK 2.8) it remained constant [6].

We have noted the absence of acid catalysis in the reaction with n-hexylamine: even at 120° C only traces of 2,6-dihexylaminoanthrapyridine are formed.

On the basis of these ideas it is also easy to understand the high directional selectivity of the reaction of 2,6-dichloroanthrapyridine with hexylamine, forming 10 times less of the type III isomer than in the reaction with aniline.

If the reaction of the dichloride I with aniline is performed in the presence of potassium acetate, an acid-binding agent, a certain lowering of the yields of III and IV is observed.

It has also been shown that at 80–120°, where acid catalysis is particularly energetic, cupric acetate does not have a significant catalytic influence on the formation of the disubstituted compound (see table, exp. 6, 7, 9, 12).

The results obtained enable the replacement of halogen by an amine residue to be directed toward the formation of one of the derivatives. 2-Chloro-6-arylaminoanthrapyridines are prepared by reacting 2,6-dichloroanthrapyridine with an amine in the presence of an acid-binding agent. In the arylamination of 2-chloro-6-aryl (alkyl)-aminoanthrapyridines the use of hydrogen chloride permits the reaction to be performed smoothly at temperatures $\leq 130°$. The replacement of the chlorine atom in position 2 by an alkylamino group is not catalyzed by hydrogen chloride and proceeds at temperatures > 200° C without additives.

A study of the reaction of 2-chloro-6-arylaminoanthrapyridines with aliphatic amines showed that both chlorine and arylamino groups are replaced by residues of aliphatic amines forming 2,6-dialkylaminoanthrapyridines. More detailed study of this reaction showed that transamination of 2,6-diarylaminoanthrapyridines is observed in those cases where the basicity of the amine being introduced (in the particular example, aliphatic) is greater than that of the displaced (aromatic) amine, while the substituent in position 6 undergoes transamination exclusively and the arylamine residue in position 2 is completely unaffected. It is interesting to note that an analogous transamination effect is found in derivatives of 6-aminobenzoanthrone, which has a similar structure to anthrapyridine [7].

EXPERIMENTAL

Description of a typical experiment. A mixture of 0.01 mole of chloroanthrapyridine and 0.22 mole of aniline with or without the appropriate additives was thermostatted at 80° C in a glycerol bath and stirred for the determined period. The reaction mixture was poured into a sufficient quantity of hot water to dissolve the aniline. The residue was filtered off, washed several times with hot water, and dried. The dry residue was dissolved in toluene and chromatographed on aluminium oxide. The mobile orange zone (2-chloro-6-anilinoanthrapyridine) was eluted with toluene and the crimson zone (the disubstituted derivative IV and the orange 2-anilino-6-chloroanthrapyridine were eluted with dichloroethane or chloroform. The addition of ethanol to the chloroform improved the elution of the latter. The eluates were concentrated in vacuo to 3–5 ml, diluted with petroleum ether, and left to crystallize. All these substances were practically insoluble in petroleum ether. They were filtered, dried and weighed (accuracy 0.01 g).

2-Anilino-6-n-hexylaminoanthrapyridine. 2.07 g (0.005 mole) of 2,6-dianilinoanthrapyridine and 20 ml of n-hexylamine were heated in a sealed tube at 225° C for 8 hr. The reaction mixture was cooled and diluted with an excess of 5% hydrochloric acid. The precipitate was extracted with chloroform, and the extract was washed with several portions of water, followed by sodium carbonate solution and more water. The extract was evaporated on a steam-bath and the residue recrystallized from ethanol. Yield 1.65 g (78.7%) of 2-anilino-6-n-hexylaminoanthrapyridine, mp 129–130° C. The mixed melting point with an authentic specimen, (mp 129–130° C) was undepressed. Their UV spectra in the 275–600 nm region were identical.

2-p-Toluidino-6-cyclohexylaminoanthrapyridine. a) 2 g of (I) and 15 ml of cyclohexylamine were stirred at 70° C for 4 hr and then poured into dilute hydrochloric acid. The precipitate was filtered off. Yield 2.38 g (99%) of 2-chloro-6-cyclohexylaminoanthrapyridine, mp 213.4–214.6° C (from propanol). Found, %: Cl 9.84, 9.76; N 7.80, 7.89. Calculated for $C_{22}H_{19}ClN_2O$, %: Cl 9.77; N 7.72. 1.0 g of the latter, 10 g of p-toluidine and 5 g of p-toluidine hydrochloride were stirred at 125–130° C over 4 hr, dilute HCl was added, the mixture was filtered, and the residue was washed with water, 2% ammonia solution and more water. The precipitate was chromatographed on aluminum oxide in chloroform. Yield 1.12 g (94%) of 2-p-toluidino-6-cyclohexylaminoanthrapyridine, mp 225.4–226.2° C (from propanol).

b) 0.5 g of 2,6-di-p-toluidinoanthrapyridine and 10 ml of cyclohexylamine were heated in a sealed tube at 275° C for 8 hr. After the addition of dilute HCl, the precipitate was filtered off and washed with water and dilute ammonia solution. Yield 0.48 g (98%) of a product which was free from starting material (on a chromatogram). It was purified by chromatography on aluminum oxide in toluene and recrystallized from propanol to give 2-p-toluidino-6-cyclohexyl-

aminoanthrapyridine, mp 223.6–224.8°C. Mixed melting point of samples produced by the two methods 225.0–226.0°C.

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