THE REACTION OF ARYL(β-HALOGENOALLYL)AMINES WITH ORTHOPHOSPHORIC AND POLYPHOSPHORIC ACIDS

Yu. A. Degutis and V. P. Barkauskas

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 6, pp. 1003–1006, 1969

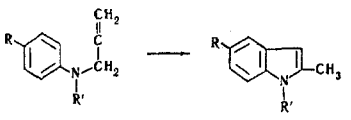
UDC 547.753+547.551+547.552

The cyclization of secondary and tertiary aryl(β-halogenoallyl)amines into 2-methylindoles on heating in orthophosphoric or polyphosphoric acid has been studied. Cyclization of N,N-di(β-bromoallyl)-p-toluidines in polyphosphoric acid forms 1-(β-bromoallyl)-2,5-dimethylindole and 2,5-dimethylindole. The probable mechanism of the rearrangement in the formation of the indole ring is put forward.

A method for obtaining 2-methylindoles by heating aryl(β-chloroallyl)amines with anhydrous hydrofluoric acid under pressure has been described in the patent literature [1]. Experiments that we have performed have shown that 2-alkylindoles can be obtained by heating aryl(β-halogenoallyl)amines with orthophosphoric or polyphosphoric acid at atmospheric pressure.

Heating N-(β-chloroallyl)aniline (Ia) with 85% orthophosphoric acid at 175–180° C for 1.5 hr led to 2-methylindole (IIIa) with a yield of 65–75%. Even better results were obtained by using anhydrous orthophosphoric acid and also by using polyphosphoric acid (the yields of IIIa were 73 and 82%, respectively).

In the cyclization of the N-(β-halogenoallyl) derivatives of p-toluidine (Ib, IIb), p-anisidine (Ic), and β-naphthylamine (Id), again the main products were 2-methylindoles (IIIb), their yields depending on the substituent in the nucleus and being almost independent of the nature of the halogen in the initial compound.

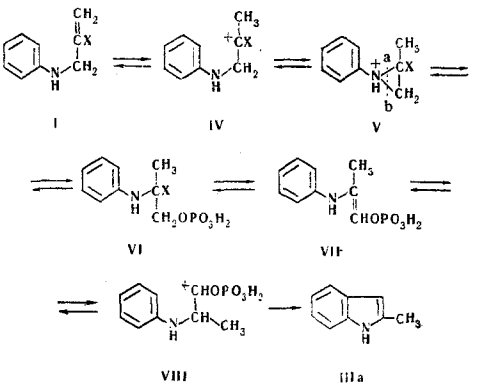


I X=Cl; II X=Br III

a R=H, R′=H; b R=CH_3, R′=H; c R=OCH_3, R′=H;
d R = β-naphthylamine R′=H; e R=H, R′=CH_3

There is no information in the literature on the cyclization of alkyl-(β-halogenoallyl)amines and therefore we have studied the possibility of extending this method to the cyclization of tertiary arylamines. When the N-methyl-N-(β-halogenoallyl)anilines Ie and IIe were heated with polyphosphoric acid under conditions identical with those for the cyclization of secondary amines, 1,2-dimethylindole (IIIe) was obtained with a yield of 72–74%.

Thus, both secondary and tertiary aryl(halogenoallyl) amines, on being heated with orthophosphoric or polyphosphoric acid, form not the 3-methylindole derivatives that might have been expected, but 2-methylindole derivatives. Such a closure of the ring is possible only after an appropriate rearrangement of the carbon atoms in the side chain. We assume that the formation of indoles from aryl(halogenoallyl)amines may take place by the following mechanism:



I IV V VI VII VIII IIIa

The conversion of I into III takes place only in the presence of acids. When a compound I was heated in ethylene glycol or diethyleneglycol, no formation of indoles took place, as was shown chromatographically. It is possible that the catalytic action of acids is due to the protonation of the double bond of the halogenoallyl group. As a result, the positive charge appears on the β-atom (IV). The nitrogen atom, being more basic, can be protonated more readily than the double bond. However, the salt of a weak base so formed readily dissociates with the formation of the initial compounds at a higher temperature.

It has been established experimentally that the copious evolution of hydrogen halide begins at a temperature as low as 150° C, while the maximum yield of 2-methylindoles is obtained at 175–180° C. It is not excluded that with a large excess of phosphoric acid and a high temperature the replacement of halogen by a phosphoric acid residue takes place (IV–VI; X = = OPO_3H_2). This does not essentially change the mechanism of the reaction.

The formation of an ethyleneimmonium ring is also possible (V). The cleavage of compound V at a C—N bond gives compound VI.

In the scheme shown, all the stages apart from the last are reversible. In this case, the formation of 2-methylindole can be explained by the fact that the cation VIII is more active in electrophilic attack than the cation IV. In the case of the cation IV, the cyclization process may also be hindered by steric factors.

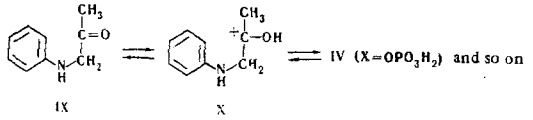
Similar intermediates can be formed in the reaction of β-arylaminoketones with phosphoric acids. Consequently, we studied the transformation of acetonyl-p-toluidine (IX) when it was heated with polyphosphoric acid. The reaction of IX with polyphosphoric acid took place with greater difficulty than those of Ib and IIb. Only after IX had been heated with a large excess of polyphosphoric acid at 190–195° C for 1 hr was IIIb

isolated from the reaction mixture with a yield of 45%.

Since under similar conditions (at 175° C), Ib and IIb are converted into alkylindoles while IX is not so converted, it could be assumed that the hydrogen halide formed during the reaction plays an important part in the cyclization of the aryl(β-halogenoallyl)-amines in polyphosphoric acid. In order to check this, we carried out the reaction of acetonyl-p-toluidine with polyphosphoric acid in the presence of sodium chloride. The vigorous evolution of hydrogen chloride began at a temperature as low as 118° C. In spite of this, the results obtained were the same as in the experiment without sodium chloride. It follows from this that the main role in the formation of the alkylindoles in this reaction is played by the polyphosphoric acid itself.

Thus, it has been shown that, in contrast to the mechanism proposed previously [3–10], the cyclization of acetonylarylamines can also take place in the absence of salts on foreign arylamines.

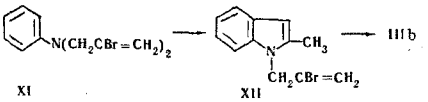
The mechanism of the reaction can be explained in a similar manner to that given above:



IX X

This rearrangement mechanism is possible only when the nitrogen atom is sufficiently basic. Otherwise the formation of the ethyleneimmonium ring would be inhibited and so, consequently, would be the rearrangement. An investigation of the reaction of benzenesulfonamide derivatives of aryl(β-halogenoallyl)-amines with polyphosphoric acid showed that the presence of the strongly electron-attracting benzenesulfonyl group in these compounds completely eliminates the possibility of cyclization to 2-methylindoles. For example, when N-(β-bromoallyl)-p-toluenebenzenesulfonamide was heated with polyphosphoric acid at 185° C, no reaction took place, while at higher temperatures (200–205° C) decomposition occurred.

We were interested in studying the possibility of the cyclization of aryldi(β-halogenoallyl)amines. The presence of a second halogenoallyl group considerably lowers the basicity of an aromatic amine and it could therefore be expected a priori that the cyclization reaction of the aryldi(β-halogenoallyl)amines would take place with greater difficulty than that of arylmono(β-halogenoallyl)amines. The reaction of N,N-di(β-bromoallyl)-p-toluidine (XI) with polyphosphoric acid began at 175° C. Two compounds were obtained: 1-(β-bromoallyl)-2,5-dimethylindole (XII) and 2,5-dimethylindole (IIIb). At 180° C, the main product was compound XII. At a higher temperature (190–198° C) the splitting off of one β-bromoallyl group took place with the formation of the indole IIIb.



XI XII

As is well known, at high temperatures alkylindoles spontaneously undergo the migration of alkyl groups in the five-membered ring. Consequently, to determine the structure of the β-bromoallyl derivative obtained by the cyclization of XI we studied the IR spectra of synthesized indoles and related compounds. The absence of the band of a stretching vibration in the 3300–3500 cm^{-1} region showed that after cyclization one β-bromoallyl grouping remained attached to the nitrogen atom.

It was established chromatographically that the splitting out of the β-bromoallyl group takes place after the formation of the indole ring.

EXPERIMENTAL

Thin-layer chromatography in alumina of activity grade II was used to monitor the reaction and to determine the purity of the products. The following solvent systems were used: A) benzene–n-hexane (1:1); B) benzene; iodine was used as the revealing agent.

Cyclization of aryl(β-halogenoallyl)amines. A mixture of one part by weight of the amine [11] and two parts by weight of polyphosphoric acid obtained from 11.3 g of 85% orthophosphoric acid and 5.7 g of P_2O_5 was heated at 175–185° C under the conditions given in the table. The cooled mass was neutralized with 10% sodium carbonate solution and extracted with dichloroethane or chloroform. The extract was dried with magnesium sulfate, the solvent was driven off, and the 2-methylindole was distilled in vacuum.

Cyclization of N-acetonyl-p-toluidine. A mixture of 0.4 g of N-acetonyl-p-toluidine [10] and 1.4 g of polyphosphoric acid was heated

Cyclization Conditions, Yield, and Constants of the Indoles Synthesized

Initial compounds	Time of heating, hr	Compound obtained	Mp, °C	Yield, %
N-(β-Chloroallyl)aniline	1.5a	IIIa	59–61c	69
N-(β-Chloroallyl)aniline	1b	IIIa	59–61c	73
N-(β-Chloroallyl)aniline	1	IIIa	59–61c	82
N-(β-Chloroallyl)-p-toluidine	0.75	IIIb	113.5–115d	86
N-(β-Chloroallyl)-p-anisidine	1.2	IIIc	88.5–89.5e	27
N-(β-Chloroallyl)-β-naphthylamine	1.2	IIId	f	65
N-(β-Bromoallyl)aniline	0.75	IIIa	59–61c	79
N-(β-Bromoallyl)-p-toluidine	1	IIIb	113.5–115d	84
N-(β-Chloroallyl)-N-methylaniline	1.5	I	55–56.3g	70
N-(β-Bromoallyl)-N-methylaniline	1.5	I	55–56.3g	72

[a]Heating with 85% phosphoric acid. [b]Heating with anhydrous orthophosphoric acid. [c]Mp 61° C [12]. [d]Mp 114-115° C [13]. [e]Mp 89-90° C [90]. [f]Bp 196-200° C (8.5 mm); according to the literature [1], bp 205-210° C (10 mm); [g]Mp 56° C [15].

at 190-195° C for 1 hr. After cooling, the reaction mixture was neutralized with 10% sodium carbonate solution and extracted with benzene. The extract was dried with magnesium sulfate, treated with activated carbon, and passed through a column of alumina. The eluant was benzene. This gave 0.162 g (45%) of 2,5-dimethylindole with mp 113.5-115° C, R_f 0.51 (system A).

Reaction of N,N-di(β-bromoallyl)-p-toluidine with polyphosphoric acid. a) A mixture of 6 g of N,N-di(β-bromoallyl)-p-toluidine [16] and polyphosphoric acid was heated at 175-180° C for 2 hr. The absence of the starting material was checked by chromatography. After cooling and treatment with 10% sodium carbonate solution, the mass was extracted with benzene. The extract was dried with magnesium sulfate and after the bulk of the solvent had been distilled off it was passed through a column of alumina with benzene as eluant. This gave 1.7 g (37%) of 1-(β-bromoallyl)-2,5-dimethylindole with mp 61-63° C, R_f 0.8 (system A), R_f 0.92 (system B). Found, %: Br 31.1, 31.0; N 5.37, 5.30. Calculated for $C_{13}H_{14}BrN$, %: Br 30.7; N 5.37. The substance dissolves readily in acetone, ethanol, ether, and chloroform, and crystallizes from methanol and petroleum ether.

b) A mixture of 6 g of N,N-di(β-bromoallyl)-p-toluidine and 20 g of polyphosphoric acid was heated at 175-180° C for 2 hr and then at 195-198° C for 2 hr. The mixture was cooled, treated with 10% sodium carbonate solution, and extracted with n-hexane. The extract was dried with magnesium sulfate and the solvent was distilled off. This gave IIIb (28%) with mp 113.5-115° C (from ligroin), R_f 0.84 (system A). A mixture with authentic 2,5-dimethylindole gave no depression of the melting point.

REFERENCES

1. E. B. Towne and H. M. Hill, US patent no. 2607779, 1952; C. A. 47, 5452, 1953.

2. Yu. A. Degutis and V. P. Barkauskas, USSR patent no. 186486, 1965; Byull. izobr., no. 19, 34, 1966.

3. A. Bischler and H. Brion. Ber., 25, 2860, 1893.

4. A. Bischler and P. Fireman, Ber., 26, 1336, 1893.

5. R. M. Cowper and T. S. Stevens, J. Chem. Soc., Soc., 1041, 1947.

6. F. Brown and F. G. Mann, J. Chem. Soc., 847, 1948.

7. E. F. Fanetzky, P. E. Verkade, J. Lieste, and H. Meerburg, Rec. trav. chim., 65, 897, 1946.

8. E. F. Janetzky, P. E. Verkade, and H. Meerburg, Rec. trav. chim., 66, 317, 1947.

9. M. Julia and J. Lenzi, Bull. soc. chim. France, 226, 1962.

10. V. Wolf, Ann., 578, 6, 1952.

11. Yu. A. Degutis and V. P. Barkauskas, Trudy AN Litovsk. SSR, ser. B, 2 (45), 69, 1966.

12. E. Fischer, Ann., 236, 126, 1886.

13. J. Raschen, Ann., 239, 227, 1887.

14. A. I. Grinev, V. N. Shvedov, and A. P. Terent'ev, ZhOKh, 26, 1449, 1956.

15. J. Degen, Ann., 236, 153, 1886.

16. Yu. A. Degutis and V. P. Barkauskas, Trudy AN Litovsk. SSR, ser. B, 2 (45), 77, 1966.

19 July 1967 Kaunas Polytechnic Institute