AZAINDOLE DERIVATIVES

XLIV.* PECULIARITIES OF THE SYNTHESIS OF 7-AZAINDOLINES DURING THE REACTIONS OF 2,6-DICHLORO-3-(β-CHLOROETHYL-4-METHYLPYRIDINE (TRICHLOROCOLLIDINE) WITH PRIMARY AROMATIC AND STERICALLY HINDERED AMINES
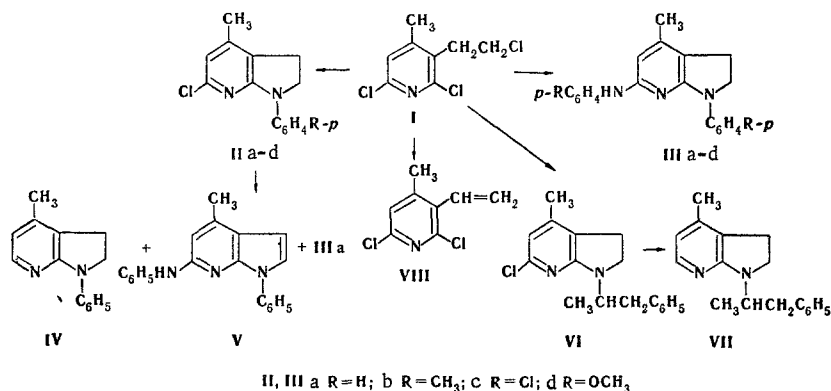
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As in the case of N-substituted anilines, trichlorocollidine forms 6-chloro-7-azaindoline derivatives rather than 6-amino-7-azaindoline derivatives with sterically hindered primary amines of the β-phenylisopropylamine type. On passing to tert-butylamine, nucleophilic attack at the α and α' positions of the pyridine ring proves to be sterically impossible, and dehydrohalogenation of trichlorocollidine to 2,6-dichloro-3-vinyl-4-methylpyridine becomes the principal reaction.

The reaction of 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine (trichlorocollidine) (I) with N-alkyl-anilines at 190°C leads to 1-phenyl-4-methyl-6-chloro-7-azaindoline (IIa), while 1-phenyl-4-methyl-6-anilino-7-azaindoline (III) is obtained with aniline under the same conditions [2-4].

A study of the reactions of I with p-toluidine and p-chloroaniline showed that 6-arylamino-7-azaindo-lines (III) rather than 6-chloro-7-azaindoline derivatives (II) are formed at 190° in these cases. The difference in the products of the reactions of I with N-substituted and N-unsubstituted anilines is associated with the different reactivities of the chlorine atoms in the I molecule. This difference shows up distinctly in reactions with N-alkyl(aralkyl)anilines but levels off in the case of primary aromatic amines at 190°. However, a decrease in the temperature to 140° makes it possible to expose the different labilities of the α and α' chlorine atoms of I in the latter case also: thus, heating it with aniline, p-toluidine, p-chloroaniline, or p-anisidine at 140° for 7 h leads to 1-aryl-4-methyl-6-chloro-7-azaindolines (II), and not even traces of 6-arylamino-7-azaindolines (III) are detected by gas—liquid chromatography (GLC).

II, III a R=H; b R=CH₃; c R=Cl; d R=OCH₃

The yields of azaindolines are directly dependent on the pK$_a$ of the starting amine, and increasing the reaction time from 7 to 14 h, for example, in the case of p-anisidine, makes it possible to only somewhat raise the yield of II (from 48% to 52%) but does not lead to the formation of amine III.

It is evident that it is necessary to overcome a certain energy barrier for replacement of the chlorine atom in the α' position of I. This barrier is apparently lower for primary aromatic amines than for N-alkyl-(aralkyl)anilines. As was demonstrated in [3], 6-arylamino-7-azaindolines are formed only at ~300° on reaction of I with, for example, N-methylaniline. The results of the present study provide evidence that similar reactions are realized even at 190° for N-unsubstituted anilines.

We have previously shown [5] that the reaction of 6-chloro-7-azaindolines with primary and secondary amines at high temperatures proceeds ambiguously: in addition to nucleophilic substitution of the chlorine atom in the 6 position there are redox processes to give products of the dehalogenation of the 7-azaindoline and the corresponding oxidized compounds — 6-amino-7-azaindole derivatives. In particular, a mixture of amine IIIa, 1-phenyl-4-methyl-7-azaindoline (IV), and 1-phenyl-4-methyl-6-anilino-7-azaindole (V) is obtained from 1-phenyl-4-methyl-6-chloro-7-azaindoline (IIa) and aniline (after 10 h at 250°). Carrying out the same reaction at 190° for 7 h with GLC analysis of the products made it possible to show that resinification is reduced under these conditions, and the yields of azaindoline IIIa and azaindole V therefore increase. In addition, 6-chloro-7-azaindoline (II) does not oxidize IIIa under such mild conditions, i.e., oxidation apparently proceeds via a different mechanism, and 6-unsubstituted 1-phenyl-4-methyl-7-azaindoline (IV) is not detected in the reaction mixture by GLC.

Comparing the unambiguous course of the reactions of I with primary aromatic amines at 190°, the high yields of resulting azaindolines III, the absence in the reaction mixtures of 6-arylamino-7-azaindoles, and the ambiguous course, under the same conditions, of the substitution of the chlorine atom in chloroazaindoline II by an arylamine residue, which is accompanied by the formation of significant amounts of 6-arylamino-7-azaindole, one should acknowledge that the conversion of I to azaindoline III on reaction with primary aromatic amines does not proceed through a step involving 6-chloro-7-azaindoline derivative II.

In analyzing the reasons for the different temperature barriers to substitution of the α' chlorine atom in I under the influence of primary aromatic amines and N-alkyl(aralkyl)anilines, one should note that they cannot be reduced to a difference in the basicities of the compounds. In fact, aniline (pK$_a$ 4.58*) and p-chloroaniline (pK$_a$ 3.98) are weaker bases than, for example, N-methyl- (pK$_a$ 4.85) or N-ethylaniline (pK$_a$ 5.11), while p-toluidine (pK$_a$ 5.12) has more basic properties. Nevertheless, the temperature barriers to substitution of the α'-chlorine atom in I under the influence of aniline, p-chloroaniline, and p-toluidine is approximately the same and considerably lower than for N-methyl- or N-ethylanilines. In these cases, steric factors rather than the degree of basicity of the amines evidently play the leading role. The nitrogen atom in primary aromatic amines is shielded to a considerably less extent than in N-substituted anilines, and the energy barrier to nucleophilic attack for nitrogen-unsubstituted anilines should be substantially lower.

The fact that even a base as strong as n-butylamine (pK$_a$ 10.6), which has a more shielded nitrogen atom than aniline, forms at 190° only the 6-chloro derivative of 7-azaindoline [7] with collidine I rather than a 6-butylamino derivative is also in good agreement with this assumption.

A branched primary amine — β-phenylisopropylamine — also behaves similarly on reaction with I; it forms 1-(α-methyl-β-phenylethyl)-4-methyl-6-chloro-7-azaindoline (VI), which is dehalogenated to 1-(α-methyl-β-phenylethyl)-4-methyl-7-azaindoline (VII) on a palladium catalyst. Further branching of the carbon chain in a primary amine — transition to tert-butylamine — leads to such significant steric hindrance that nucleophilic attack in the α and α' positions of the pyridine ring is excluded, and the only reaction path becomes dehydrohalogenation of I to give 2,6-dichloro-3-vinyl-4-methylpyridine (VIII).

EXPERIMENTAL

Analysis by GLC was performed with a Pye–Unicam 104 chromatograph with a flame-ionization detector and a 1.5 m by 4-mm column filled with 2% SE-30 silicone elastomer on Chromosorb W (80–90 mesh). The nitrogen flow rate was 27 ml/min, the program conditions were from 150 to 250°, the initial period was 10 min, and the temperature-rise rate was 32 deg/min. The retention times were: I 2.4, IIa 14.3, IIb 9.4, IIc 9.1, IIIa 20.0, IIIb 14.6, IIIc 16.0, V 18.3, and VI 13.9. The retention times were as follows when the

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*All of the pK$_a$ values given are from [6].

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products were chromatographed under the same conditions but at 250° without programmed operation: IIa 1.2, IIIa 5.0, IV 0.8, and V 3.6 min.

1-Phenyl-4-methyl-6-chloro-7-azaindoline (IIa). A mixture of 2.24 g (10 mmole) of trichlorocollidine (I) and 1.86 g (20 mmole) of aniline was heated at 140° for 7 h. It was then cooled, and 30 ml of chloroform was added. The mixture was filtered to give 0.84 g of aniline hydrochloride. The filtrate was washed with a 25% aqueous potassium carbonate solution, dried with potassium carbonate, evaporated to a small volume, and analyzed by GLC. For preparative separation, it was also applied to a column (height 75 cm, diameter 23 mm) containing 240 g of aluminum oxide and eluted with petroleum ether. The first 200 ml of eluate (containing 0.07 g of substance) was discarded, and evaporation of the next 500 ml of eluate gave 1.11 g (50%) of starting I with mp 69-70°. Evaporation of the next 200 ml of eluate gave 0.23 g (9.5%) of azaindoline IIa with mp 116.5-117°; no melting-point depression was observed for a mixture of this product with the product obtained from I and N-ethylaniline [3]. The results of GLC analysis were in good agreement with the results of preparative separation of the substances.

Reaction of 1-Phenyl-4-methyl-6-chloro-7-azaindoline (IIa) with Aniline. A mixture of 1.22 g (5 mmole) of azaindoline IIa and 1.12 g (12 mmole) of aniline was heated at 190° for 7 h, after which 5 ml of a 25% potassium carbonate solution was added, and the mixture was extracted with benzene. The extract was dried with potassium carbonate and evaporated, and the residue was analyzed by GLC. The yield of azaindoline IIIa was 59%, and the yield of azaindole V was 29%. Compound IV was not detected in the reaction products. Azaindoline IIa was recovered quantitatively when the reaction temperature was lowered to 140° (7 h).

1-(p-Tolyl)-4-methyl-6-chloro-7-azaindoline (IIb). A mixture of 3.36 g (15 mmole) of I and 3.21 g (30 mmole) of p-toluidine was heated at 140° for 7 h, after which it was cooled, and 5 ml of 25% aqueous solution of potassium carbonate was added. The mixture was extracted with benzene, and the extract was dried with potassium carbonate. The extract was evaporated, and the residue was vacuum distilled to give 1.57 g of a fraction with bp 140-210° (3 mm), which, according to GLC, contained 1.44 g (43%) of starting I, 0.13 g of azaindoline IIb, and 1.35 g of a fraction with bp 210-212° (3 mm), which was pure azaindoline IIb. The overall yield of IIb was 38%. The colorless crystals had mp 129-130° (from alcohol) and were quite soluble in ether, benzene, chloroform, acetone, and ethyl acetate, less soluble in alcohol and heptane, and insoluble in water. Found %: Cl 13.6; N 10.7. $C_{15}H_{15}ClN_2$. Calculated %: Cl 13.7; N 10.8. Compound IIIb was not detected in the reaction products by GLC.

1-(p-Tolyl)-4-methyl-6-(p-toluidino)-7-azaindoline (IIIb). A mixture of 2.24 g (10 mmole) of I and 3.21 g (30 mmole) of p-toluidine was heated at 190° for 7 h, after which it was worked up as in the preceding experiment. The benzene extract was evaporated, and the residue was distilled. The fraction with bp 243-245° (1 mm) (2.76 g) was collected and triturated thoroughly with alcohol. The yield of azaindoline IIIb with mp 133-134° was 2.42 g (75%). The product was quite soluble in benzene, acetone, chloroform, and hot ethyl acetate, only slightly soluble in ether and heptane, and insoluble in water. Found %: C 80.6; H 6.7; N 12.6. $C_{22}H_{23}N_3$. Calculated %: C 80.2; H 7.0; N 12.8.

1-(p-Chlorophenyl)-4-methyl-6-chloro-7-azaindoline (IIc). A mixture of 3.36 g (15 mmole) of I and 3.82 g (30 mmole) of p-chloroaniline was heated at 140° for 7 h, after which it was worked up as in the preceding experiment. Distillation gave 0.46 g of a fraction with bp 238-240° (2 mm), which, according to GLC, contained 47% of azaindoline IIc. The yield of IIc was 5.3%. The substance was isolated for analysis by chromatography on Al_2O_3 with elution with $CHCl_3$ to give colorless crystals with mp 145-147° (from isopropyl alcohol). The product was quite soluble in ether, benzene, acetone, chloroform, and ethyl acetate, less soluble in alcohols and heptane, and insoluble in water. Found %: C 60.3; H 4.3; Cl 25.3; N 10.4. $C_{14}H_{12}Cl_2N_2$. Calculated %: C 60.2; H 4.3; Cl 25.4; N 10.1.

1-(p-Chlorophenyl)-4-methyl-6-(p-chloroanilino)-7-azaindoline (IIIc). A mixture of 2.24 g (10 mmole) of I and 3.82 g (30 mmole) of p-chloroaniline was heated at 190° for 7 h. A total of 1.28 g of sublimed p-chloroaniline hydrochloride separated. The residue was made alkaline with 50% aqueous potassium carbonate solution and extracted with benzene. The extract was dried with potassium carbonate and vacuum evaporated. The residue was recrystallized from acetone to give 1.58 g of azaindoline IIIc with mp 150-151°. The acetone mother liquor was evaporated, and the residue was vacuum distilled. The fraction with bp 238-240° (2 mm), which was 1.15 g of azaindoline IIIc, was collected. The overall yield of IIIc with mp 150-151° was 2.73 g (74%). The product was quite soluble in chloroform, hot benzene, and acetone, but insoluble in water. Found %: C 64.6; H 4.7; Cl 19.3; N 11.1. $C_{20}H_{17}Cl_2N_3$. Calculated %: C 64.8; H 4.6; Cl 19.2; N 11.4.

1-(p-Methoxyphenyl)-4-methyl-6-chloro-7-azaindoline (IId). A mixture of 4.48 g (20 mmole) of I and 4.92 g (40 mmole) of p-anisidine was heated at 140° for 7 h. It was then cooled, made alkaline with a 25% solution of potassium carbonate, and extracted with chloroform. The extract was dried with potassium carbonate and evaporated, and the residue was vacuum distilled. The first fraction (5.2 g), with bp 87-218° (1 mm), was dissolved in benzene, and the benzene solution was washed three times with 8% hydrochloric acid to separate the p-anisidine. The benzene layer was dried with potassium carbonate and evaporated to give 1.65 g (37%) of I. The second fraction, with bp 218-220° (1 mm), was azaindoline IId (mp 122-123°). The yield was 2.64 g (48%). The product did not depress the melting point of a sample of IId obtained by reaction of I with N-methyl-p-anisidine [8]. The IR spectra of the two samples were identical.

1-(α-Methyl-β-phenylethyl)-4-methyl-6-chloro-7-azaindoline (VI). A mixture of 4.8 g (21 mmole) of I and 5.8 g (43 mmole) of β-phenylisopropylamine was heated at 190° for 7 h. It was then cooled, made alkaline with a 25% solution of potassium carbonate, and extracted with benzene. The benzene extract was dried with potassium carbonate and evaporated, and the residue was vacuum distilled. Redistillation of the first fraction, with bp 120-130° (2 mm), gave 1.15 g (26%) of I with mp 69-70°. The second fraction, with bp 184-186° (1 mm), was 3.0 g (49%) of azaindoline VI. The colorless crystals had mp 68-69° (from petroleum ether). The product was quite soluble in ether, benzene, acetone, ethyl acetate, and chloroform, less soluble in alcohol and petroleum ether, and insoluble in water. Found %: C 71.0; H 6.4; Cl 12.4; N 9.5. $C_{17}H_{19}ClN_2$. Calculated %: C 71.2; H 6.7; Cl 12.3; N 9.8.

1-(α-Methyl-β-phenylethyl)-4-methyl-7-azaindoline (VII). A solution of 2.36 g (8.2 mmole) of chloroazaindoline VI in 100 ml of alcohol was hydrogenated in the presence of a palladium catalyst, obtained from 2 g of palladous chloride, at 18-20° with an an excess hydrogen pressure of 18-20 cm (water column). After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, the solution was vacuum evaporated, and the residue was dissolved in 10 ml of 18% hydrochloric acid. The acid solution was washed by extraction with ether and made alkaline with a 50% solution of potassium hydroxide. The liberated base was extracted with ether, and the extract was dried with potassium carbonate and evaporated. The residue was vacuum distilled at 185-187° (4 mm) to give 1.78 g (86%) of azaindoline VII as a colorless oily substance that was quite soluble in the common organic solvents but only slightly soluble in water; it had n_D^{20} 1.5775. Found %: C 80.6; H 8.0; N 10.9. $C_{17}H_{20}N_2$. Calculated %: C 80.9; H 8.0; N 11.1.

Reaction of Trichlorocollidine (I) with tert-Butylamine. A mixture of 4.48 g (20 mmole) of I and 10 ml (95 mmole) of tert-butylamine was heated at 140° in a steel autoclave for 7 h. The reaction mixture was treated with 50 ml of 18% hydrochloric acid and 50 ml of ether, and the ether solution was separated and washed additionally with 18% hydrochloric acid. The acid solution was extracted with ether, and the combined ether extracts were dried with potassium carbonate and vacuum distilled to give 1.63 g (41%) of 2,6-dichloro-3-vinyl-4-methylpyridine (VIII), with bp 140-143° (14 mm) and n_D^{20} 1.5712 [2], and 1.83 g (41%) of I, with bp 174-177° (14 mm) and mp 69-70°. The hydrochloric acid solution contained only tert-butylamine hydrochloride.

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