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7-AZAINDOLE DERIVATIVES

X. Synthesis of 2, 4, 6-Trichloro-3-(β-chloroethyl) Pyridine and its Conversion to 5- and 7-Azaindoles*

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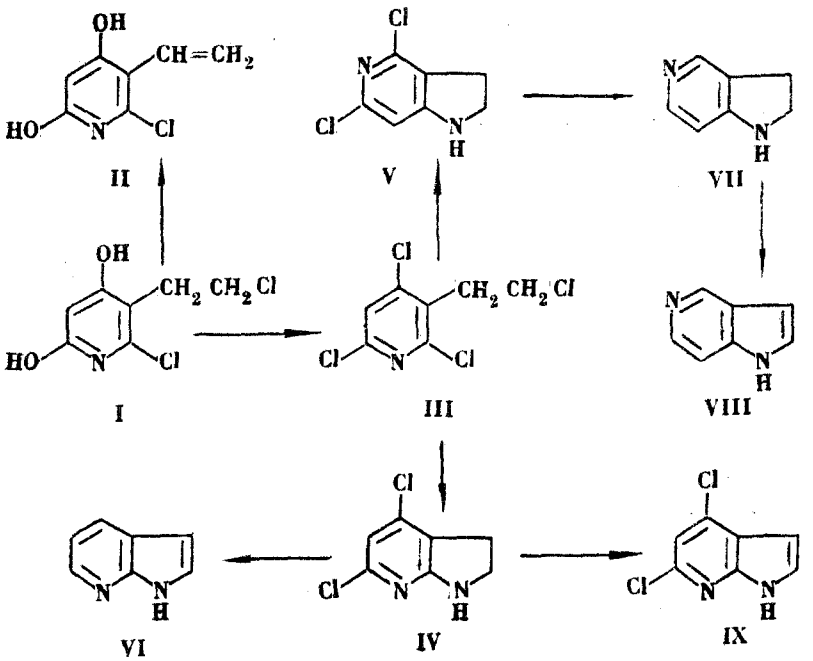
A new method for synthesizing 5- and 7-azaindoles is given. γ-Chlorobutyronitrile and malonyl chloride give 2, 4, 6-trichloro-3-(β-chloroethyl) pyridine, which is cyclized with ammonia to 4, 6-dichloro-7-azaindoline and 4, 6-dichloro-5-azaindoline. 6-Chloro derivatives of 7-azaindolines are not dehydrogenated by chlorainil, but 2, 3-dichloro-5, 6-dicyanobenzoquinone converts them to 6-chloro-7-azaindoles. It is shown that sodium in liquid ammonia is an effective means of dehydrogenating the 5-azaindoline to 5-azaindole. In this case, dehydrogenation of 4, 6-dichloro-7-azaindoline is followed by dehalogenation.

The previously described [2-6] reactions of trichlorocollidine, dichlorocollidine, and chlorohydroxycollidine with various primary and secondary amines, as well as with ammonia, make it possible to synthesize a number of 7-azaindole derivatives with a methyl group at position 4. To prepare 7-azaindole derivatives unsubstituted at position 4 by the same method, it is necessary to start from 2-chloro-(β-chloroethyl) pyridine, unsubstituted at position 4 or with a readily eliminated substituent there. 2-Chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I) was chosen as the starting compound for this kind of synthesis. It is readily prepared by reacting malonyl chloride with γ-chlorobutyronitrile [7].

Investigation of the chemical properties of compound I showed, however that its chlorine atom at position 2 is not very reactive. At the same time I has, even in comparison with trichlorocollidine [8], an enhanced capacity for dehydrogenation on account of its β-chloroethyl group. Reaction of I with 20% ethanolic ammonia at 100°, 60°, or even at room temperature for 7 hr was found to lead to quantitative splitting out of hydrogen chloride, as determined by Volhard's method (titration). The 2-chloro-3-vinyl-4, 5-dihydroxypyridine thus formed was isolated in 75% yield. Raising the reaction temperature cut the yield of II slightly through partial resinification. At 140° (7 hr) the yield was 70%, at 180° (7 hr) it was 65%. However, under the conditions used, Volhard titration did not permit determination of over 1 g eq. Cl'. Hence even under comparatively drastic conditions the chlorine atom at position 2 in com-



*For Part IX see [1].

pound 1 is unreactive towards nucleophilic substitution. The great inertness of this chlorine is evidently due to the effect of electron-donating substituents (hydroxy groups) at positions 4 and 6.

2, 4, 6-Trichloro-3-(β-chloroethyl) pyridine (III), prepared by treating I with phosphorus oxychloride, reacted differently with ammonia. In that case there was no dehydrogenation, but nucleophilic substitution of the chlorine atoms in the pyridine ring by amino groups, with simultaneous closure of the pyrroline ring. The reaction gave 4, 6-dichloro-7-azaindoline (IV) and 4, 6-dichloro-5-azaindoline (V). To separate these two compounds, use was made of their different solubilities in ether and benzene. An initial separation was achieved by extracting V plus a trace of IV from

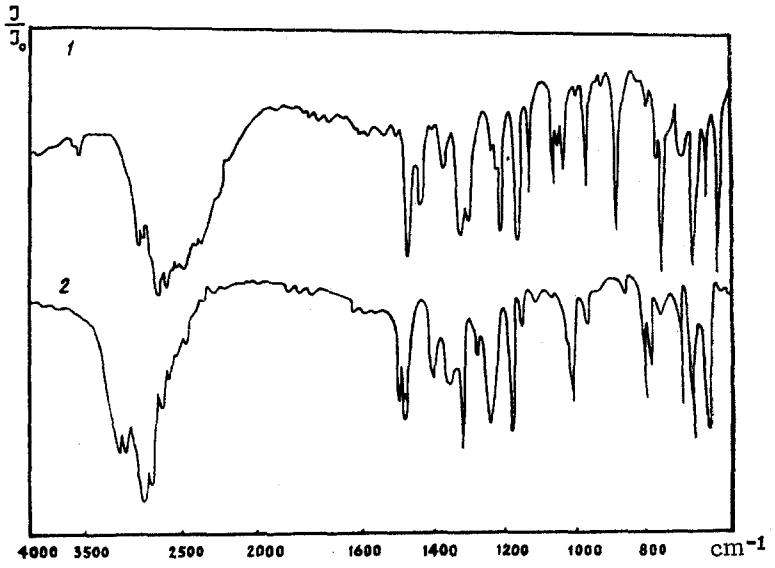


Fig. 1 IR spectra: 1) 5-azaindole (VIII), 2) 7-azaindole (VI).

hydrochloric acid solution with ether, after which pure IV was extracted with benzene. A final separation of mixed IV and V was secured by chromatographing on alumina. Paper chromatography was used to check the course of the separation and the purities of the compounds obtained. Assignment of the individual compounds (IV, V) as 5- or 7-azaindole was based on a conversion, described below, of IV to 7-azaindole (VI), and of V to 5-azaindole (VIII).

The presence, for example in III, of identically sterically shielded chlorine atoms at position 2 and 4 directs the course of the reaction of III with ammonia in two directions. Under the reaction conditions the chlorine atoms of the chloroazaindoline derivatives IV and V cannot be replaced by amino groups. This, and the development of practically quantitative separation of IV and V by chromatography, made it possible to compare, from the product yields, reactivities of α and β chlorine atoms in the pyridine ring. As a result of such comparison it was shown that the reactivity of chlorine in the γ position is somewhat greater than in the α position (yields V 42.2%, IV 34.6%), which falls into line with literature [9] results showing the comparative reactivities at positions 2 and 4 in the pyridine ring towards nucleophilic reagents with other compounds.

For conversion of 4, 6-dichloro-7-azaindoline (IV) to 7-azaindole (VI), use was made of a previously developed [12] and subsequently perfected method of dehydrogenating 7-azaindoline derivatives to 7-azaindole with sodium and liquid ammonia. It is of interest that in the case of IV dehydrogenation was simultaneously accompanied by elimination of two chlorine atoms, at the α and γ positions in the pyridine ring. All the same, the reaction proceeded smoothly enough to give a 44.6% yield of 7-azaindole. Treatment of 4, 6-dichloro-5-azaindoline (V) with sodium in liquid ammonia under the same conditions led to considerable resinification, and 5-azaindole could not be separated from the reaction products. In that case, therefore, it was necessary to first catalytically dehalogenate V in the presence of palladium. The resultant 5-azaindoline (VII) was smoothly converted to an 80% yield of 5-azaindole (VIII) when subsequently dehydrogenated with sodium in liquid ammonia.

The 5-azaindole (VIII) and 7-azaindole (VI) synthesized were identified by their respective IR and UV spectra (Figs. 1, 2), and by mixed melting points with azaindoles prepared by Möller and Süs's method [10], VI from 3-amino-

4-hydroxy-1, 6-naphthyridine-7-carboxylic acid, VIII from 3-amino-4-hydroxy-1, 5-naphthyridine.*

Considerable interest attaches to the conversion of IV and V to the corresponding dichloroazaindoles for synthesizing 5- and 7-azaindole derivatives, with substituents in the pyridine portion of the molecule. Naturally, sodium in liquid ammonia cannot be the dehydrogenating agent here. In the course of previous work [3, 5, 6] it was also shown. that chloranil, while a valuable dehydrogenating agent for 7-azaindole derivatives, cannot dehydrogenate 7-azaindolines with a chlorine atom at position 6. In this connection it was of interest to investigate the dehydrogenation of 6-chloro derivatives of 7-azaindoline to the corresponding 6-chloro-7-azaindoles with a chloranil of higher oxidation reduction potential [11], 2, 3-dichloro-5, 6-dicyanobenzoquinone.**

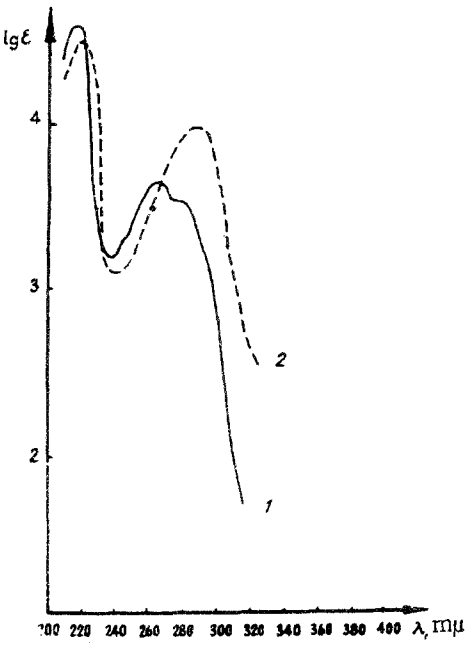
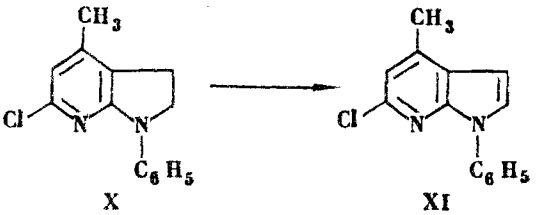


Fig. 2 UV spectra: 1) 5-azaindole (VIII), 2) 7-azaindole (VI).

1-Phenyl-4-methyl-6-chloro-7-azaindoline (X) [2, 5] and 4, 6-dichloro-7-azaindoline (IV) were selected for subjects of the dehydrogenation study. Both were recovered unchanged in practically quantitative yield after boiling with chloranil in xylene for some hours.



However, treatment of IV and X with 2, 3-dichloro-5, 6-dicyanobenzoquinone gave the respective 6-chloro-7-azaindoles. X gave 1-phenyl-4-methyl-6-chloro-7-azaindole (XI) in 50% yield, and IV gave 4, 6-dichloro-7-azaindole (IX) in 71% yield. Comparison of UV spectra (Fig. 3) of azaindolines (IV and X) and azaindoles (IX and XI) again confirmed the previously observed displacement of absorption maxima to the short wave side when 7-azaindoline derivatives are dehydrogenated [5, 6].

Experimental

2, 4, 6-Trichloro-3-(β-chloroethyl) pyridine (III). A mixture of 2.7 g (0.013 mole) 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I) and 20 ml (0.8 mole) $POCl_3$ was heated in a sealed tube at 180° for 5 hr. The contents of the tube were then poured on to ice, and III extracted with benzene. The benzene solution was dried over K_2CO_3, the benzene distilled off, and the residue (3.07 g) vacuum-distilled, to give 2.52 g (79.3%) III bp 118-119° (0.9 mm). The distilled material crystallized. Colorless crystals mp 55° (ex petrol ether). Readily soluble in benzene, acetone, and $CHCl_3$, less soluble in ether, alcohols and petrol ether, insoluble in water. Found: C 34.28; H 2.03; N 5.83; Cl 57.82%. Calculated for $C_7H_5Cl_4N$: C 34.28; H 2.04; N 5.74; Cl 57.95%.

2-Chloro-3-vinyl-4, 6-dihydroxypyridine (II). 5 ml 20% ethanolic ammonia (0.01 mole) was added to 0.5 g (0.0024 mole) 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I), and the mixture left for 7 hr at room temperature. Ethanol and excess ammonia were distilled off under reduced pressure. The residue was washed four times with distilled water (1 ml water each time), and then recrystallized from dry ethanol, to give 0.3 g (75%) II, colorless crystals mp 285° (decomp). It was sparingly soluble in cold water and the usual organic solvents, soluble in hot water and ethanol. Found: C 48.94; H 3.54; N 8.47; Cl 20.86%. Calculated for $C_7H_6ClNO_2$: C 48.98; H 3.50; N 8.16; Cl 20.70%. Volhard titration of the aqueous solution after isolating II gave 0.085 g Cl' (theory 0.085 g).

Reaction of 2, 4, 6-trichloro-3-(β-chloroethyl) pyridine (III) with ammonia. A 170 ml stainless steel autoclave was charged with 12 g (0.5 mole) III and 120 ml 20% ethanolic ammonia (1.5 mole), and heated at 180° for 7 hr. The reaction products were evaporated under reduced pressure. To the residue was added 20 ml 10% hydrochloric acid, and

*We take this opportunity of thanking Prof. O. Süss (Federal German Republic) for kindly providing us with specimens of 7-azaindole and 5-azaindolyl-3-carboxylic acid, which we converted, by his method [10], to 5-azaindole. IR and UV spectra of pairs of indoles were quite identical, and in this connection it should be mentioned that Figs. 1 and 2 give only one spectrum for each azaindole.

**We wish to thank M. N. Preobrazhenskaya for making available samples of 2,3-dichloro-5, 6-dicyanobenzoquinone, and for valuable advice regarding use of this compound.

the resultant solution (solution A) extracted with ether (5 times, each with 50 ml). The ether extracts were dried over calcium chloride, and the ether distilled off, to give 4.6 g residue, which paper chromatography showed to be a mixture of 4, 6-dichloro-7-azaindoline (IV) and 4, 6-dichloro-5-azaindoline (V).* Chromatography on an alumina column was used to separate IV and V. A solution of 4.6 g mixed IV and V in 50 ml ether was run on to a column of 200 g alumina (column diameter 20 mm, height of alumina column introduced as an ether slurry, 580 mm). The eluant was ether. The appearance of a compound in the eluate was checked by sampling on to filter paper and visualizing with iodine vapor followed by illumination with UV light. The eluate was collected in 10 ml cuts, each cut paper chromatographed, and then evaporated under reduced pressure, after which the residue was weighed. The first four cuts did not contain azaindoline derivatives. Cuts 5-17 contained only V, with the largest amount of V in cuts 7-12. Cut 17 still contained traces of V, and IV appeared in it. Evaporation of the first 6 cuts gave traces of material, cut 7 gave 0.7 g, 8) 0.75 g, 9) 0.65 g, 10+11+12) gave up to 0.4 g 13) 0.2 g, 14) 0.15 g, 15+16) total of 0.25 g. In all 3.9 g (42.2%) 4, 6-dichloro-5-azaindoline (V) was isolated. Colorless crystals, mp 158-159° (ex acetone). It was readily soluble in ether, less soluble in ethanol, benzene, and acetone, insoluble in water. Found: C 44.67; H 3.20; N 14.90; Cl 37.86%. Calculated for $C_7H_6Cl_2N_2$: C 44.44; H 3.17; N 14.81; Cl 37.57%.

After separating V, the column was eluted with ethanol, to give 0.7 g practically pure 4, 6-dichloro-7-azaindoline (IV). A further 2.5 g IV was obtained by extracting with benzene the solution A which had previously been extracted with ether, and when paper chromatographed it gave only one spot. Total yield of IV 3.2 g (34.6%). Colorless crystals mp 169-170° (ex benzene). Sparingly soluble in ether, ethanol, benzene, and acetone, more soluble in chloroform, insoluble in water. Found: C 44.32; H 3.40; N 14.67; Cl 37.22%. Calculated for $C_7H_6Cl_2N_2$: C 44.44; H 3.17; N 14.81; Cl 37.57%. UV spectrum,** λ_{max} 212 mμ (lg ε 4.26), 262 mμ (lg ε 3.92), 314 mμ (lg ε 3.42) (Fig. 3).

Fig. 3 UV spectra: 4, 6-dichloro-7-azaindoline (IV), 2) 4, 6-dichloro-7-azaindole (IX), 3) 1-phenyl-4-methyl-6-chloro-7-azaindoline (X), 4) 1-phenyl-4-methyl-6-chloro-7-azaindole (XI).

7-Azaindole (VI). 1.8 g (0.01 mole) 4,6-dichloro-7-azaindoline (IV) was gradually added with stirring to 50 ml liquid ammonia containing 1 g (0.05 mole) sodium metal. Stirring was continued for 2 hr after which the reaction products were left at room temperature until the ammonia had completely evaporated. 50 ml 50% K_2CO_3 solution was added to the residue, and the mixture extracted with benzene. The benzene solution was dried over K_2CO_3, the solvent distilled off under reduced pressure, and the residue of VI recrystallized from water, to give 0.5 g (44.6%) 7-azaindole (VI), mp 106°.*** Found: C 70.79; H 5.20; N 23.64%. Calculated for $C_7H_6N_2$: C 71.19; H 5.08; N 23.73%.

UV spectrum, λ_{max} 219 mμ (lg ε 4.31), 290 mμ (lg ε 3.91). Mixed melting point with an authentic specimen of VI undepressed. The UV and IR spectra of the two specimens were quite identical (Figs. 1 and 2).

5-Azaindoline (VII). 1 g (0.005 mole) palladium chloride in 5 ml 18% hydrochloric acid, was added to a solution of 0.5 g (0.0025 mole) 4, 6-dichloro-5-azaindoline in 10 ml ethanol. The reaction mixture was hydrogenated at room temperature under a hydrogen pressure of 20-30 cm water. Hydrogenation was completed in 2 hr. 244 ml H_2 was absorbed. The catalyst was filtered off, and washed with ethanol. The filtrate was evaporated under reduced pressure, to give 0.4 g (96.5%) 5-azaindole hydrochloride, colorless crystals mp 129-130° (from ethanol-ethyl acetate). The

*Here, and henceforth, ascending paper chromatography was used for chromatographic analysis of IV and V, the mobile phase being ether. To visualize the chromatogram it was put for 1-2 min in a chamber containing iodine vapor, then examined by UV light. V appeared as a spot which absorbed UV light, R_f 0.97, while IV appeared as an UV light absorbing spot which stayed at the starting line. The method makes it possible to detect down to 10 γ of each isomer (IV and V).

**All UV spectra were determined with a SF-4 instrument, solvent ethanol; the IR spectra were measured on an IKS-14 instrument, in vaseline.

***The literature gives for 7-azaindole, bp 107° [14], 106-107° [10, 15], 105-106° [16], 105° [17]; γ_{max} 290 mμ (lg ε 3.91) [17].

compound is soluble in ethanol and water, sparingly soluble in acetone and ethyl acetate, insoluble in ether. Found: N 17.72; Cl 22.51%. Calculated for $C_7H_8N_2 \cdot HCl$: N 17.89; Cl 22.68%.

5-Azaindole (VIII). 0.07 g (0.003 mole) sodium metal was dissolved in 20 ml liquid ammonia. 0.2 g (0.0015 mole) 5-azaindoline was added to this solution. The reaction mixture was stirred for 2 hr, then left at room temperature until all the ammonia had evaporated. 10 ml 50% K_2CO_3 solution was added to the residue, and the mixture extracted with ether. The ether extract was dried over K_2CO_3, and the ether evaporated under reduced pressure, to give 0.12 g (80%) 5-azaindole (VIII), colorless crystals MP 111-112° (ex water).* Found: C 70.80; H 5.18; N 23.67%. Calculated for $C_7H_6N_2$: C 71.19; H 5.08; N 23.73%.

UV spectrum, λ_{max} 216 mμ (lg ε 4.59), 265 mμ (lg ε 3.60). Mixed melting point with an authentic specimen of VIII prepared from 5-azaindolyl-3-carboxylic acid. UV and IR spectra of the two specimens were quite identical (Figs. 1, 2).

Dehydrogenation of 1-phenyl-4-methyl-6-chloro-7-azaindoline (X). 0.16 g (0.007 mole) X and 0.15 g (0.007 mole) 2, 3-dichloro-5, 6-dicyanobenzoquinone in 5 ml xylene was boiled for 10 min. The initially red solution became colorless, and a precipitate of 2, 3-dichloro-5, 6-dicyanohydroquinone separated. The reaction products were cooled to room temperature, the precipitate filtered off, and washed with xylene. The xylene solutions were bulked and twice extracted with 10 ml 50% KOH each time, then dried over K_2CO_3. The xylene was distilled off under reduced pressure. The residue (0.15 g) was recrystallized from petrol ether, to give 0.05 g crystals mp 91-93°, which UV spectrum data showed to be a mixture of X and XI. After separating off the crystals, the xylene was evaporated off under reduced pressure, to give 0.08 g (50%) pure 1-phenyl-4-methyl-6-chloro-7-azaindole (XI), colorless crystals, mp 71-72°. Readily soluble in the usual organic solvents, insoluble in water. Found: C 69.23; 68.94; H 4.63, 4.69; N 11.64, 11.69; Cl 14.95%. Calculated for $C_{14}H_{11}ClN_2$: C 69.28; H 4.54; N 11.55; Cl 14.63%. UV spectrum, λ_{max} 234 mμ (lg ε 4.29), 287 mμ (lg ε 4.00) (Fig. 3).

1-Phenyl-4-methyl-6-chloro-7-azaindoline (X) [2, 5] gave a UV spectrum with λ_{max} 286 mμ (lg ε 4.26), 329 mμ (lg ε 4.16) (Fig. 3).

4, 6-Dichloro-7-azaindole (IX). 0.5 g (0.002 mole) 2, 3-dichloro-5, 6-dicyanobenzoquinone was added to a solution of 0.4 g (0.002 mole) 4, 6-dichloro-7-azaindoline (IV) in 5 ml dry xylene, and the whole refluxed for 8 hr. The precipitate of 2, 3-dichloro-5, 6-dicyanohydroquinone was filtered off, and washed five times with 3 ml xylene each time. The bulked xylene solutions were washed three times with 40% NaOH solution, using 2 ml each time, then dried over K_2CO_3. The xylene was distilled off under reduced pressure, to give 0.28 g (71%) IX. For analysis the compound was recrystallized from benzene. Colorless crystals mp 207-208°, readily soluble in alcohols and $CHCl_3$, sparingly soluble in benzene, acetone, and ether, insoluble in water. Found: C 45.21; H 2.46; N 15.34; Cl 37.62%. Calculated for $C_7H_4Cl_2N_2$: C 44.92; H 2.14; N 14.97; Cl 37.97%. UV spectrum, λ_{max} 294 mμ (lg ε 3.74), 270 mμ (lg ε 3.66), 225 mμ (lg ε 4.40).

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*The literature gives, mp 111° [10], 111.5-112.5° [18], 112° [17]; λ_{max} 265 mμ (lg ε 3.62) [18].

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