AZAINDOLE DERIVATIVES

XXVII. Formation of a Pyrroline Ring from 2,4-Dichloro-5-(β-chloroethyl)pyridine Synthesis of 2,3-Dihydro-5-azaindoles*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 3, pp. 550–554, 1969

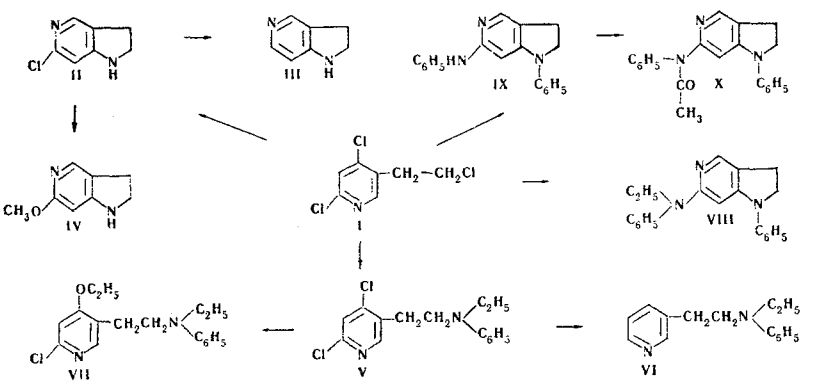
UDC 547.752'822.7:541.67:543.422.4.6

The reaction of 2,4-dichloro-5-(β-chloroethyl)pyridine with ammonia and N-ethylaniline, leading to the formation of 5-azaindoline derivatives, has been studied. The processes of the formation of 6-phenylamino and 6-(N-alkyl-N-phenylamino) derivatives of 7-azaindoline, 5-azaindoline, and 5,7-diazaindoline taking place with N-dealkylation and without it have been compared.

Derivatives of 5-azaindoline are difficult of access. The Madelung reaction, which is used for the synthesis of the isomeric 4-, 6-, and 7-azaindoles is unsuitable for the conversion of 4-formylamino-3-methylpyridine into 5-azaindole. The homologous 2-methyl-5-azaindole is obtained by this method with a yield of only about 1% [1]. The formation of 5-azaindole by the Madelung reaction with a yield of 21% by the use of sodium anilide as condensing agent described by Okuda and Robison [2] could not subsequently be reproduced [3]. Attempts to obtain 5-azaindole by the Reissert reaction, by the Harly-Mason method [4], from 4-aminonicotinic acid via 4-aminopyrid-3-ylacetic acid with subsequent closure of the five-membered lactam ring [3], and also by the cyclization of 4-acetylamino-3-bromopyridine [2] have likewise been unsuccessful. Of the various pyrid-4-ylhydrazones, only the cyclohexanone and 2,3-dioxopiperidine derivatives (in the latter case the N-oxide of the pyridine hydrazone was used) have been successfully subjected to Fischer cyclization with the formation of condensed 5-azaindole systems [5,6]. 4-Methyl- and 4-phenyl-5-azaindoles have been synthesized from acylated 2-(β-aminoethyl) pyrroles by the Bischler-Napieralski method with yields of 10 and 24%, respectively. It was impossible to cyclize the corresponding N-formyl- and N-homoveratroyl derivatives [7].

Unsubstituted 5-azaindole was first obtained by Möller and Süs [8] by a multistage scheme based on the photochemical contraction of the naphthyridine ring. With M. Ya. Uritskaya, we [9] have shown that the reaction of 2,4,6-trichloro-3-(β-chloroethyl)pyridine with ammonia takes place in two competing directions with the formation of 4,6-dichloro-7-azaindoline and 4,6-dichloro-5-azaindoline, which can be separated chromatographically and converted into 7- and 5-azaindoles, respectively.

In order to ensure that the reaction takes place unambiguously in the direction of the 5-azaindoline compounds and to exclude the possibility of the simultaneous formation of the isomeric 7-azaindolines, as the starting material we used 2,4-dichloro-5-(β-chloroethyl)pyridine (I) [10]. The reaction of I with ethanolic ammonia at 180° C led to 6-chloro-5-azaindoline (II) with a yield of 60.2%. Raising the temperature to 200° C enabled the yield of II to be increased to 71.5%. It is an interesting fact that as in the case of 2,4,6-trichloro-3-(β-chloroethyl)pyridine [9] the chlorine atom in position 6 of the pyridine nucleus of I did not react with ammonia. The dehydrohalogenation of II gave 5-azaindoline (III), which we had obtained previously [9] by the catalytic reduction of 4,6-dichloro-5-azaindoline.



As in the 7-azaindoline system [11,12], nucleophilic substitution reactions in position 6 of the molecule of 5-azaindoline take place with greater difficulty than in the α position of the pyridine nucleus. Thus, for example, after compound II had been boiled with potassium methoxide in methanol for 10 hr the initial chlorine derivative was recovered quantitatively, while raising the temperature to 190° C enabled the chlorine in II to be replaced by a methoxy group with a 44% yield of IV.

*For part XXVI, see [16].

Interesting results were obtained in the reaction of 2,4-dichloro-5-(β-chloroethyl)pyridine (I) with N-ethylaniline. Heating the mixture of these products in a molar ratio of 1 : 2 at 140° C for 7 hr led to the formation of 2,4-dichloro-5-[β-(N-ethyl-N-phenylamino) ethyl]pyridine (V), the structure of which was shown by its dehalogenation to 3-[β-(N-ethyl-N-phenylamino) ethyl]pyridine (VI), with a yield of 20.9%. The reaction of V with caustic soda in boiling ethanol led to the replacement of the chlorine in position 4 by an ethoxy group and to the formation of 2-chloro-4-ethoxy-5-[β-(N-ethyl-N-phenylamino)ethyl]pyridine (VII).

The reaction of 2,4-dichloro-5-(β-chloroethyl)pyridine (I) with N-ethylaniline at 190° C took place in a qualitatively different manner and, after chromatographic separation of the products formed, 1-phenyl-6-(N-ethyl-N-phenylamino)-5-azaindoline (VIII) was obtained with a yield of 41% and 1-phenyl-6-phenylamino-5-azaindoline (IX) with a yield of 6.6%. Thus, as in the case of the various 2-chloro-3-(β-chloroethyl)pyridines [10, 11, 13–15], the reaction under these conditions of a substituted 4-chloro-3-(β-chloroethyl) pyridine with N-ethylaniline took place with the formation of a pyridine ring accompanied by N-dealkylation. We have shown previously [11] that the reaction of 2, 6-dichloro-3-(β-chloroethyl)-4-methylpyridine with N-alkylanilines at 300° C forms 4-methyl-1-phenyl-6-phenylamino-7-azaindoline, i. e., the replacement of chlorine in position 6, like the formation of a pyrroline ring, is accompanied by N-dealkylation. In addition to this, it was shown that the product of the reaction of 6-chloro-4-methyl-1-phenyl-7-azaindoline with N-alkylanilines at 300° C is not the 6-phenylamino derivative but a 4-methyl-1-phenyl-6-(N-alkyl-N-phenylamino)-7-azaindoline, i. e., in this case substitution in position 6 is not accompanied by N-dealkylation. All this has permitted the assumption that in the reaction of 2, 6-dichloro-3-(β-chloroethyl)-4-methylpyridine with N-alkylanilines at 300° C the replacement of chlorine in position 6 by an amine residue takes place before or during, but not after, the formation of the pyrroline ring.

A subsequent study of the reaction of 2,4-dichloro-5-(β-chloroethyl)pyrimidine with N-ethylaniline showed [16] that in this case, too, the formation of a pyrroline ring accompanied by N-dealkylation takes place. However, in view of the high mobility of the halogen atoms in the pyrimidine nucleus, the temperature barrier of the reaction is considerably lower (the process takes place at 140° C). In this case, the replacement of a chlorine atom in the α' position of the pyrimidine system by a secondary amine residue is not accompanied by N-dealkylation and the only reaction product is 6-(N-ethyl-N-phenylamino)-1-phenyl-5, 7-diazaindoline.

The reaction of 2,4-dichloro-5-(β-chloroethyl)pyridine (I) with N-ethylaniline occupies an intermediate position between the above two different types of reaction. In this case the process takes place at 190° C and products of both types are formed: both the 6-(N-ethyl-N-phenylamino) derivative (VIII) and the 6-phenylamino compound (IX). The structure of the latter was confirmed by its conversion into 6-(N-acetyl-N-phenylamino)-1-phenyl-5-azaindoline (X).

It is an interesting fact that 2,4-dichloro-5-[β-(N-ethyl-N-phenylamino)-ethyl]pyridine (V), which is formed from I and N-ethylaniline at 140° C, is not an intermediate in the synthesis of the 5-azaindolines. When compound V was heated under the conditions for the synthesis of the 5-azaindolines (190° C, 7 hr), only the initial compound was recovered, with a yield of 83%, and while raising the temperature to 250° C (7 hr) led to the destruction of the molecule it was impossible in this case, as well, to detect the formation of 5-azaindoline derivatives. Thus, it may be assumed that in the reaction of I with N-ethylaniline under milder conditions (140° C) the slow replacement of the halogen in the side chain by a N-ethylaniline residue takes place. When the temperature is raised (to 190° C), the more rapid replacement of the halogen in position 4 of the pyridine nucleus comes to the fore, which leads to the subsequent formation of the pyrroline ring to give a 5-azaindoline system, accompanied by N-dealkylation. The replacement of the chlorine in position 2, the reactivity of which is not much less than that of the chlorine atom in position 4, takes place in parallel. The N-dealkylation of the entering substituent does or does not take place according to the stage of the formation of the pyrroline ring at which the attack at position 6 of the molecule occurs.

EXPERIMENTAL

6-Chloro-5-azaindoline (II). A mixture of 5 g (24 mM) of I [10] and 50 ml of 25% ethanolic ammonia (740 mM) was heated in an autoclave at 200° C for 4 hr and was then evaporated in vacuum. The residue was treated with 50% potassium carbonate solution and extracted with benzene. After the solvent had been driven off, the residue was distilled in vacuum. Bp 152–154° C (1.5 mm). Yield 2.39 g (71.5%). Colorless crystals, mp 106–107° C (from ethyl acetate). Readily soluble in alcohols, acetone, benzene, and chloroform, sparingly soluble in ether, and insoluble in petroleum ether and water. UV spectrum: λ_{max} 260 nm (log ε 3.96)*. IR spectrum: 3200 cm^{-1} (NH), 1618 cm^{-1} (C=N); PMR spectrum (in $CDCl_3$): two triplets with J ~ ~ 8 Hz at 3.05 and 3.77 ppm each of 2 p.u (CH_2—CH_2 of a pyrroline ring), two singlets each of 1 p.e. at 6.40 ppm (proton at C_7) and 7.77 ppm (proton at C_4—in the α-position to the nitrogen of the pyridine nucleus), and a broad signal at 5.15–5.50 ppm (NH). Found, %: C 54.05; H 4.71; Cl 23.10, 23.24; N 17.87, 18.24. Calculated for $C_7H_7ClN_2$, %: C 54.37; H 4.53; Cl 22.98; N 18.12.

5-Azaindoline (III). In the presence of a palladium catalyst prepared from 1.5 g of palladium chloride, 1.7 g (11 mM) of II in 170 ml of ethanol was hydrogenated at a pressure of 20–30 cm of water. The catalyst was filtered off and the solvent was evaporated off in vacuum. This gave 1.7 g of the hydrochloride of III (quantitative yield). Colorless crystals, mp 188–189° C (from a mixture of ethanol and ethyl acetate)**. The hydrochloride is readily soluble in water,

*The UV spectra were taken on an SF-4 spectrophotometer with ethanol as the solvent, the IR spectra on a UR-10 recording spectrometer with samples in the form of pastes in paraffin oil, and the PMR spectra on a JNM-100 (100 MHz) spectrometer with TMS as internal standard (the solvents are given in brackets). We consider it our pleasant duty to express our thanks to Yu. N. Sheinker, E. M. Peresleni, and Yu. I. Pomerantsev for assistance in the spectral determinations.

**Previously [9] through an uncorrected printing error the melting point of the hydrochloride of III was erroneously given as 129–130° C.

alcohols, and chloroform, sparingly soluble in acetone, ethyl acetate, and benzene, and insoluble in ether. UV spectrum: λ_{max} 282 nm (log ε 4.04). Found, %: C 53.76; H 5.76; Cl 22.33; N 17.96. Calculated for $C_7H_8N_2 \cdot HCl$, %: C 53.67; H 5.75; Cl 22.68; N 17.89.

The base III—colorless crystals, mp 102–103° C (from cyclohexane). Readily soluble in ether, benzene, chloroform, ethyl acetate, alcohols, and water, insoluble in petroleum ether. UV spectrum: λ_{max} 260 nm (log ε 3.96). IR spectrum: 3165 cm^{-1} (NH), 1611 cm^{-1} (C=N). PMR spectrum (in CD_3OD): two triplets with J ~ 8 Hz at 2.89 and 3.50 ppm, each of 2 p.u. (CH_2CH_2 group of a pyrroline ring), doublet with J ~ 7 Hz at 6.47 ppm of 1 p.u. (proton at C_7) coinciding in its chemical shift with a singlet from the proton at C_4, and a doublet (J ~ 7 Hz) from the proton at C_6 with δ 7.7 ppm (2 p.u.). Found, %: C 69.94; H 6.70; N 23.34. Calculated for $C_7H_8N_2$, %: C 70.00; H 6.67; N 23.33.

1-Acetyl-5-azaindoline. A mixture of 0.5 g (4.2 mM) of III and 5 ml of acetic anhydride was boiled for 1 hr and was evaporated in vacuum. Yield 0.66 g (98.5%). Colorless crystals, mp 161–162° C (after recrystallization from benzene the mp did not change). Readily soluble in alcohols, acetone, chloroform, and water, less readily in benzene, insoluble in ether and petroleum ether. UV spectrum: λ_{max} 257 nm (log ε 4.08). IR spectrum: 1678 cm^{-1} ($CH_3CON<$). Found, %: C 66.39; H 6.08; N 17.28. Calculated for $C_9H_{10}N_2O$, %: C 66.67; H 6.17; N 17.28.

6-Methoxy-5-azaindoline (IV). The potassium methoxide from 0.37 g (9.5 mM) of potassium and 13 ml of methanol and 1 g (6.5 mM) of II were heated in a sealed glass tube at 190° C for 15 hr. Then the mixture was evaporated in vacuum and the residue was treated with 20 ml of 50% potassium carbonate solution and extracted with ether. The ethereal extract was dried with potassium carbonate and evaporated in vacuum. Yield 0.43 g (44.3%). Colorless crystals, mp 99–100° C (from cyclohexane). Readily soluble in the usual organic solvents, less readily in water and cyclohexane, insoluble in petroleum ether. Found, %: C 63.62; H 6.84; N 18.44. Calculated for $C_8H_{10}N_2O$, %: C 64.00; H 6.66; N 18.70.

2,4-Dichloro-5-[β-(N-ethyl-N-phenylamino)ethyl]pyridine (V). A mixture of 5 g (24 mM) of I and 5.8 g (48 mM) of N-ethylaniline was heated at 140° C for 7 hr. The excess of N-ethylaniline was distilled off in vacuum. The residue was treated with 30 ml of 10% HCl, and the 2.4 g (48%) of compound I that had not reacted was extracted with benzene. The hydrochloric acid solution was made alkaline with potassium carbonate and extracted with benzene. The benzene extract was dried with potassium carbonate and evaporated in vacuum, and the residue was distilled at 191–193° C (1.5 mm). Yield 1.46 g (20.9%). Colorless oily substance readily soluble in the usual organic solvents, n_D^{20} 1.6012. Found, %: N 9.60. Calculated for $C_{15}H_{16}Cl_2N_2$, %: N 9.49. **Hydrochloride**—colorless crystals, mp 175–176° C (from ethanol). Found, %: C 54.64; H 5.42; N 8.26; Cl 32.02. Calculated for $C_{15}H_{17}N_2Cl_3$, %: C 54.30; H 5.13; N 8.44; Cl 32.13. **Picrate**—yellow crystals, mp 143–144° C (from ethanol). Found, %: C 48.38; H 3.56; Cl 13.23; N 13.48; 13.56. Calculated for $C_{15}H_{16}Cl_2N_2 \cdot C_6H_3N_3O$, %: C 48.09; H 3.63; Cl 13.55; N 13.36.

3-[β-(N-Ethyl-N-phenylamino)ethyl]pyridine (VI). One gram (3.4 mM) of V was reduced in the presence of a palladium catalyst (from 0.5 g of palladium chloride) in 50 ml of methanol at an overpressure of hydrogen of 20–30 cm water. The catalyst was filtered off and the solution was evaporated in vacuum. The base was liberated with 50% potassium carbonate solution and extracted with ether. Distillation of the ether yielded 0.7 g (91%) of a colorless oily substance with bp 158–160° C (1 mm). Soluble in the usual organic solvents, insoluble in water. Found, %: C 79.36; H 8.00; N 12.52. Calculated for $C_{15}H_{18}N_2$, %: C 79.64; H 7.96; N 12.40.

2-Chloro-4-ethoxy-5-[β-(N-ethyl-N-phenylamino)ethyl]pyridine (VII). A solution of 0.6 g (2 mM) of V and 0.12 g (3 mM) of caustic soda in 10 ml of ethanol was boiled for 7 hr. The ethanol was distilled off in vacuum. The residue was treated with 10 ml of water and extracted with ether. The residue after the distillation of the ether (0.58 g) was crystallized from anhydrous ethanol. This gave 0.17 g (32.7%) of colorless crystals with mp 85–86° C (from ethanol). Readily soluble in ether, acetone, chloroform, and water, less readily in ethyl acetate, and poorly soluble in alcohols. Found, %: C 66.80; H 6.65; Cl 11. Cl 11.89; N 9.24. Calculated for $C_{17}H_{21}ClN_2O$, %: C 66.99; H 6.89; Cl 11.68; N 9.19.

Reaction of 2,4-dichloro-5-(β-chloroethyl)pyridine with N-ethylaniline at 190° C. A mixture of 5 (24 mM) of I and 5.8 g (48 mM) of N-ethylaniline was heated at 190° C for 7 hr. After cooling, 25 ml of 10% HCl was added to the reaction mixture and the nonbasic substances (0.75 g) were extracted with benzene. The resulting mixture did not contain the initial I and boiled at 209–210° C (1 mm); it was not studied further. The hydrochloric acid solution after extraction with benzene was made alkaline with 50% potassium carbonate solution. The base that separated out was extracted with chloroform and, after vacuum distillation of the solvent and the unchanged N-ethylaniline, was chromatographed on a column of alumina (240 g of Al_2O_3, column height 85 cm, diameter 2.5 cm) and was eluted with petroleum ether. After evaporation, 7.8 *l* of petroleum ether yielded 3.07 g (41%) of 6-(N-ethyl-N-phenylamino)-1-phenyl-5-azaindoline (VIII). Colorless crystals, mp 99–99.5° C (from isopropanol), bp 209–210° C (1 mm). Compound VIII is readily soluble in ether, acetone, ethyl acetate, chloroform, benzene, and methanol, less readily in ethanol, isopropanol, and petroleum ether, and insoluble in water. IR spectrum: 1620 cm^{-1} (C=N); absence of absorption in the 3000–3800 cm^{-1} region. PMR spectrum (in CCl_4): triplet (3 p.u.) ~ 1.15 ppm (CH_3 of an ethyl group); triplet (2 p.u.) 3.00 ppm (CH_2 of a pyrroline ring) with J ~ 8 Hz; superposed triplet of the CH_2 group of the pyrroline ring and quadruplet from the CH_2 of the ethyl group (4 p.u.) at 3.92 ppm; two 1-p.u. singlets at 6.02 ppm (proton at C_7) and at 7.70 ppm (proton at C_4); multiplet signal of the protons of the phenyl nuclei in the 6.0–7.37 ppm region (10 p.u.). Found, %: C 79.60; H 6.66; N 13.42. Calculated for $C_{21}H_{21}N_3$, %: C 80.00; H 6.67; N 13.33. **Picrate**—yellow crystals, mp 164.5–165° C (from ethanol). Readily soluble in acetone, sparingly soluble in ethanol and ether. Found, %: C 59.46; H 4.33; N 15.51. Calculated for $C_{21}H_{21}N_3 \cdot C_6H_3N_3O_7$, %: C 59.56; H 4.41; N 15.44.

After the elution of compound VIII with petroleum ether, the column was washed with 1 *l* of diethyl ether. The ethereal eluate was evaporated in vacuum, the residue was treated with 10 ml of ether, and the mixture was filtered. This gave 0.39 g (6.63%) of 1-phenyl-6-phenylamino-5-azaindoline (IX). Colorless crystals, mp 166–167° C (from ethanol). Readily soluble in chloroform, less readily in alcohols, acetone, ethyl acetate, and benzene, and sparingly soluble in ether, petroleum ether, and water. IR spectrum: 3260 cm^{-1} (NH), 1627 cm^{-1} (C=N). PMR spectrum (in CF_3COOH): two triplets with J ~ ~ 8 Hz at 3.13 and 4.18 ppm (each of 2 p.u.—CH_2CH_2 group of a pyrroline ring), singlet of the proton at C_7 (1 p.u.) at 6.05 ppm, and a multiplet of phenyl protons in the 6.75–7.15 ppm region (10 p.u.). Found, %: C 79.22; H 5.92; N 14.52. Calculated for $C_{19}H_{17}N_3$, %: C 79.44; H 5.92; N 14.63.

6-(N-Acetyl-N-phenylamino)-1-phenyl-5-azaindoline (X). A mixture of 0.2 g (0.7 mM) of IX and 1 ml (10 mM) of acetic anhydride was boiled for 30 min. The reaction mixture was evaporated in vacuum and the residue was crystallized from ether to give 0.19 g (82.7%) of colorless crystals with mp 128–129° C. Readily soluble in benzene, acetone, chloroform, ethyl acetate, and alcohols, less readily in ether, and insoluble in petroleum ether and water. IR spectrum: 1679 cm^{-1} ($CH_3CON<$). Found, %: C 76.30; H 5.78; N 12.42. Calculated for $C_{21}H_{19}N_3O$, %: C 76.60; H 5.78; N 12.75.

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3 January 1967

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