AZAINDOLE DERIVATIVES

XXVI. The Formation of 5,7-Diazaindoline Derivatives by the Reaction of 4-Chloro-5-(β-chloroethyl)pyrimidines with Secondary Amines*

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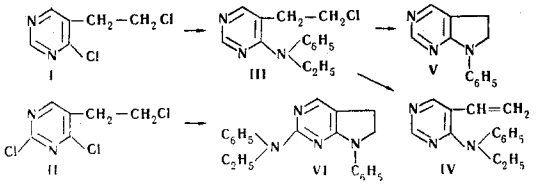
It has been shown that the closure of the pyrroline ring with simultaneous N-dealkylation observed previously for the reactions of 2- and 4-chloro-3-(β-chloroethyl)pyrimidines with secondary amines has a general nature and is suitable for the synthesis of 5,7-diazaindoline derivatives from 4-chloro-5-(β-chloroethyl)pyrimidines. Features of the structure of 5,7-diazaindoline systems connected with the electron-accepting properties of the nitrogen atom of the pyrimidine nucleus are discussed.

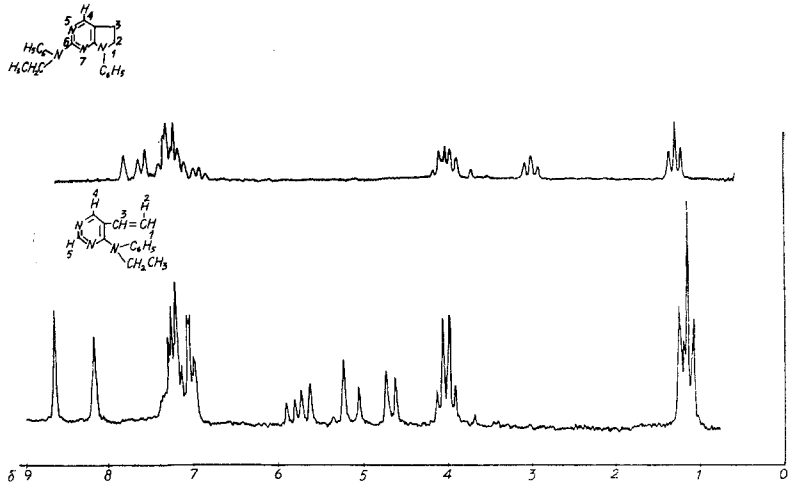
In preceding communications of this series it has been shown that the reaction of 3-(β-chloroethyl)pyrimidines containing halogen atoms in position 2 or 4 with ammonia and primary and secondary amines takes place with the formation of azaindoline derivatives. In the case of the reaction with secondary amines, a new type of closure of the pyrroline ring takes place which is accompanied by N-dealkylation. In order to extend the reaction discovered to other heterocyclic systems, we have studied the reaction with secondary amines (with N-ethylaniline as example) of 5-(β-chloroethyl)-pyrimidines containing a chlorine atom in position 4 of the pyrimidine nucleus.



As the pyrimidine components of the synthesis we used 4-chloro-5-(β-chloroethyl)pyrimidine (I) [2] and 2,4-dichloro-5-(β-chloroethyl)pyrimidine (II) [2]. As was to be expected, the transition from the pyridine derivatives to the analogous compounds of the pyrimidine series with an additional heterocyclic nitrogen atom causes a decrease in the electron density in positions 2, 4, and 6 and an appreciable increase in the capacity of the corresponding halogen atoms for nucleophilic substitution reactions. While 2-chloro-3-(β-chloroethyl)-4-methylpyridine reacts with N-alkylanilines only at 190° C [3], I reacts with N-ethylaniline even on heating in boiling ethanol. In the case of the pyrimidine derivative I, the lowering of the reaction temperature permits the observation of two successive stages of the formation of the pyrroline ring: the replacement of the chlorine atom in position 4 of the pyrimidine nucleus by a N-ethylaniline residue, and cyclization, which is accompanied by N-dealkylation and leads to 1-phenyl-5,7-diazaindoline (V).

For the 2-chloro-3-(β-chloroethyl)pyridines a similar separation of the process into stages can be observed only in reactions with cyclic secondary amines (piperidine and pyrrolidine) [4]. The structure of 5-(β-chloroethyl)-4-(ethylphenylamino)pyrimidine (III) was confirmed by its conversion by dehydrohalogenation into 4-(ethylphenyl)-5-vinylpyrimidine (IV). In this case the dehydrohalogenation process competed with the cyclization of III into V, as was detected by means of paper chromatography. (The chromatography was in all cases carried out in the butanol—acetic—water (5 : 1 : 4) system by the descending method. Under UV irradiation, III possessed greenish, IV yellow, and V blue fluorescence; the color of the complex with Dragendorff's reagent is given in brackets.) Two spots with R_f 0.90 (orange-pink) and 0.75 (pink), characteristic for IV and V, respectively, appeared clearly on the chromatogram. In order to isolate pure IV, we used its capacity, distinguishing it from V, of readily undergoing distillation in vacuum. The presence of a vinyl group in IV was confirmed by means of the PMR spectrum in which there are two doublets at δ 4.75 and 5.15 ppm with spin-spin coupling constants of, respectively, 11 and 17.5 Hz, which are characteristic for the H_1 and H_2 protons of a vinyl group (figure) present in the trans and cis positions with respect to the methine proton H_3. (All the PMR spectra were taken on a JNM-100 spectrometer in $CdCl_3$ with TMS as internal standard. We consider it our pleasant duty to express our gratitude to Yu. N. Sheinker, L. M. Pankratova, and G. P. Syrova for determining the PMR spectra and for assistance in their interpretation.) The additional splitting of the signals with J 1.25 Hz is due to the geminal interaction of the H_1 and H_2 protons. Moreover, at 5.75 ppm there is a quartet with an intensity of one proton unit from the H_3 proton interacting with the cis and trans proton H_1 and H_2. The other signals are: triplet at 1.15 ppm and quartet at 4.00 ppm from the protons of the N-ethyl group, singlet signals of H_4 and H_5 (8.17 and 8.65 ppm), and a multiplet of the phenyl protons in the 6.90–7.45 ppm region, also well agreeing with the structure IV. The exceptional ease of conversion of III into V is observed even in the preparation and isolation of III. Cyclization with the splitting out of ethyl chloride takes place even when pure III is subjected to prolonged storage. The separation of the mixture of III and V can be effected by chroma-

*For part XXV, see [1].



NMR spectra.

tography on alumina with a check by paper chromatography (for III, R_f 0.93, orange spot). The cyclization of III can be carried out almost quantitatively by boiling the substance in ethanol for 24 hr.

As in the case of pyridine derivatives [5], the introduction of a chlorine atom into the α'-position of the N-heteroaromatic pyrimidine system somewhat lowers the capacity of the α-chlorine atom for nucleophilic substitution reactions. While in I the chlorine atom in position 4 is completely replaced by an N-ethylaniline residue even on being boiled in ethanol for 7 hr; in the analogous reaction with II under the same conditions 60% of the initial II was recovered and only 20% of VI was obtained. Heating II with N-ethylaniline at 140° C enabled the yield of VI to be raised to 69%. In connection with the greater reactivity of the halogen atoms in the α'-positions of the pyrimidine nucleus as compared with the analogous substitution in the pyridine molecule, this reaction leads not to the 6-chloro-derivative of diazaindoline but to 6-(ethylphenylamino)-1-phenyl-5,7-diazaindoline (VI). Thus, in the pyrimidine series the temperature barrier to the replacement of the second halogen atom in the nucleus by a residue of a secondary amine proved to be considerably lower than in the pyridine series, where the analogous process took place only at 300° C [5]. It is also interesting to note that, in contrast to the analogous reaction with 2,6-dihalo derivatives of pyridine, the replacement of an α'-halogen atom in the pyrimidine nucleus is not accompanied by N-dealkylation. While the reaction of 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine with N-alkylanilines from 4-methyl-1-phenyl-6-phenylamino-7-azaindoline, II and N-ethylaniline gave only VI. The NMR spectrum of VI agrees well with a bicyclic structure for this compound (figure); in addition to the signals of the protons of the N—C_2H_5 group (1.32 and 3.02 ppm), the N-phenyl substituent (6.87–7.70 ppm), and the singlet of the proton at C_4 of the 5,7-diazaindoline system, there are two triplets at 4.00 and 4.12 ppm with a spin-spin coupling constant of J = = 7.5 Hz, which are characteristic for the N—CH_2—CH_2 group of the pyrroline ring.

EXPERIMENTAL

Reaction of 4-chloro-5-(β-chloroethyl)pyrimidine (I) with N-ethylaniline. A mixture of 4.2 g (0.024 mole) of I and 2.8 g (0.024 mole) of N-ethylaniline was heated in 50 ml of boiling ethanol for 7 hr. The reaction mixture was evaporated in vacuum, and the residue was treated with 50% potassium carbonate solution and extracted with chloroform. The extract was dried with calcined potassium carbonate, and the chloroform was distilled off in vacuum. To separate the III and V, the reaction mixture (6.2 g) was chromatographed on a column of alumina (diameter 3.5 cm, height 83 cm). Elution was performed with ether. The evaporation of 2 *l* of the ethereal eluate gave 4.2 g (67.7%) of III. Colorless liquid, readily soluble in the usual organic solvents, insoluble in water, n_D^{20} 1.5908. On storage or distillation, it cyclizes. Found, %: C 64.05; H 6.25; N 16.00; Cl 13.70. Calculated for $C_{14}H_{16}ClN_3$, %: C 64.24; H 6.13; N 16.06; Cl 13.57. **Picrate**—light yellow crystals, mp 137–138° C (ethanol). Readily soluble in acetone and chloroform, and sparingly soluble in ether, alcohol, and water. Found, %: C 48.97; H 3.92; N 17.06; Cl 7.26. Calculated for $C_{14}H_{16}ClN_3 \cdot C_6H_3N_3O_7$, %: C 48.93; H 3.87; N 17.13; Cl 7.23. Further elution of the column after the isolation of the III was carried out with ethanol. From 300 ml of the ethanolic eluate was obtained 1.2 g (26.1%) of V with mp 104–105° C, giving no depression of the melting point in admixture with a sample synthesized from I and aniline [2].

4-(Ethylphenylamino)-5-vinylpyrimidine (IV). A solution of 0.25 g (0.0044 mole) of caustic potash in 10 ml of anhydrous ethanol was added to 0.5 g (0.0019 mole) of III, and the mixture was boiled for 3 hr, during which time a precipitate of potassium chloride formed. The ethanol was distilled off, 10 ml of water was added, and the mixture was extracted with chloroform. The chloroform extract was dried with potassium carbonate and evaporated in vacuum. The residue (0.3 g) was shown by paper chromatography to consist of a mixture of V and IV, with the V predominating. In order to separate the IV, which distills readily, from the V, which decomposes on heating, the mixture was subjected to vacuum distillation. The process was accompanied by marked resinification; the distillate obtained at 143–146° C/1 mm crystallized. The yield of IV was 0.16 g (37.2%). Light yellow crystals, mp 42–43° C (petroleum ether). The substance is readily soluble in ether, ethanol, acetone, benzene, and chloroform, sparingly soluble in petroleum ether, and insoluble in water. Found, %: C 74.39; H 6.80; N 18.31. Calculated for $C_{14}H_{15}N_3$, %: C 74.67; H 6.66; N 18.67.

Cyclization of III. A solution of 0.4 g (0.0015 mole) of III in 30 ml of ethanol was boiled for 24 hr, and was then evaporated to dryness in vacuum. The residue was washed with aqueous methanol. This gave 0.25 g (83.3%) of V. Colorless crystals, mp 105–106° C (aqueous methanol). The substance gave no depression of the melting point in admixture with a sample obtained by the cyclization of 5-(β-chloroethyl)-

4-phenylaminopyrimidine [2]. **The hydrochloride of V** formed colorless crystals, mp 262–263° C (ethanol). The substance is soluble in water and chloroform, sparingly soluble in ethanol, and insoluble in acetone, benzene, and ether. Found, %: C 61.38; H 5.17; N 17.68; Cl 15.33. Calculated for $C_{12}H_{11}N_3 \cdot HCl$, %: C 61.67; H 5.14; N 17.98; Cl 15.20.

Reaction of 2,4-dichloro-5-(β-chloroethyl)pyrimidine (II) with N-ethylaniline. a) A mixture of 2 g (0.01 mole) of **II** and 2.3 g (0.02 mole) of N-ethylaniline was heated at 140° C for 7 hr. The solidifying reaction mixture was treated with 50% potassium carbonate solution. The liberated base was extracted with chloroform, and the extract was dried with potassium carbonate and evaporated in vacuum. The residue (2.3 g) was distilled, and a fraction with bp 175–177° C/0.4 mm was collected, giving 1.98 g (69%) of **VI**. Colorless crystals, mp 136–137° C (methanol). The substances is readily soluble in benzene, chloroform, and ethanol, less readily in methanol, and insoluble in water. Found, %: C 75.82; H 6.32; N 17.83. Calculated for $C_{20}H_{20}N_4$, %: C 75.95; H 6.33; N 17.72. b) A mixture of 1 g (0.005 mole) of **II** and 1.15 g (0.01 mole) of N-ethylaniline was heated in 25 ml of boiling ethanol for 7 hr, and then the reaction mixture was evaporated in vacuum. The residue was treated with 50% potassium carbonate solution and extracted with chloroform. The chloroform extract was dried with potassium carbonate and evaporated in vacuum. The residue (1 g) was distilled to give 0.6 g (60%) of **II**, bp 132–135° C/4 mm and 0.3 g (20%) of **VI**, bp 175–177° C/0.4 mm (identified by a mixed melting point and IR spectrum—no absorption in the NH group region).

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