AZAINDOLE DERIVATIVES

XXXVI.* DIRECTION OF CLEAVAGE OF THE C–N BOND DURING CLOSING OF THE PYRROLINE RING WITH ALKYLBUTYLAMINES

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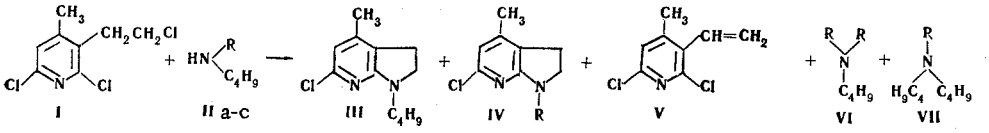
An increase in the C–N bond strength in a series of N-alkyl substituents (methyl < ethyl < hexyl < butyl) was established from a study of N-dealkylation processes during the synthesis of substituted 7-azaindoles from 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine and unsymmetrical alkylbutylamines.

In previous communications of this series [2-4] we described the general method for the synthesis of aza- and diazaindolines based on the reaction of 2-(or 4-)chloro-3-(β-chloroethyl)pyridines and 4-chloro-5-(β-chloroethyl)pyrimidines with primary or secondary amines. In the process, it was shown that closing of the pyrroline ring in the case of secondary amines proceeds with subsequent N-dealkylation, similar to the Hofmann cleavage of quaternary salts.

Correlation of previously published results [5] makes it possible to assert that a number of general principles of the thermal cleavage of quaternary ammonium salts are observed in the indicated processes: in all cases, the C–N bonds included in the five-membered ring are broken with greater difficulty than the exocyclic bonds; benzyl residues are cleaved more readily than alkyl residues, and the latter are cleaved more readily than aryl residues. In addition, the direction of cleavage of the C–N bonds when secondary amines with different alkyl substituents on the nitrogen are used in the reaction has not been studied at all. The dependence of the N-dealkylation processes on the alkyl chain length has not been adequately elucidated in the classical Hofmann cleavage of quaternary salts.

In this connection, we investigated the reactions of 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine (I) with alkylbutylamines (IIa-c).



I, IIa-c, III, IV, V, VI, VII

IIa R=CH_3; b R=C_2H_5; c R=n-C_6H_{13}

The starting alkylbutylamines (IIa-c) were synthesized via the general method in [6] from butylamine by means of acylation and subsequent reduction of the N-butylamides with lithium aluminum hydride. The reactions of I with alkylbutylamines IIa-c were carried out in an autoclave at 140° for 7 h using 2 moles of amine per mole of I. Treatment of the reaction mass accomplished the isolation and preparative separation of substances of nonbasic character – starting I and its dehydrohalogenation product, 2,6-dichloro-3-vinyl-4-methylpyridine (V). The quantitative ratios of the bases (II-IV, VI, and VII) in the remaining mix-

*See [1] for Communication XXXV.

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ture were determined by gas-liquid chromatography (GLC), after which they were preparatively separated, purified, and their individual components were characterized. The results of preparative separation of the substances were compared with the GLC data.

As in other cases [2], when I was reacted with strong bases such as alkylbutylamines, closing of the azaindole ring was accompanied by competitive dehydrohalogenation. The yields of the 2,6-dichloro-3-vinyl-4-methylpyridine (V), formed as a result of dehydrohalogenation, were 46.3-47.5% for all of the II studied. In addition, definite amounts of I were recovered unchanged under the reaction conditions selected. The steric hindrance to nucleophilic attack of II at the α position of I increased with lengthening of the alkyl chains, and the amount of recovered I increased from 24.5% for IIa to 30% for IIb and 33% for IIc. The yields of 7-azaindoline derivatives decreased accordingly.

It was most interesting to elucidate the direction of cleavage of the C–N bonds during cleavage of the unsymmetrical quaternary salts obtained as the intermediates in the synthesis of 7-azaindolines. A study of this process by means of GLC and preparative separation of the reaction products indicated that in the case of methylbutylamine (IIa) and ethylbutylamine (IIb) the lower alkyl groups are practically unambiguously cleaved, and the single azaindoline derivative in these experiments was 1-butyl-4-methyl-6-chloro-7-azaindoline (III). In the reaction of I with hexylbutylamine (IIc), the N-dealkylation was ambiguous: cleavage of both the N-butyl and the N-hexyl bonds was observed. The presence of both possible azaindolines – III and 1-hexyl-4-methyl-6-chloro-7-azaindoline (IVc) – was established in the products by GLC; the amount of III was, on the average, twice that of IVc. The structure of IVc was confirmed by an independent synthesis of this compound from I and hexylamine.

The results of GLC analysis of the tertiary aliphatic amines are in agreement with these data. The latter compounds are formed, as previously shown [7], by the reaction of the alkylchloride, formed during the N-dealkylation, with excess secondary amine. In fact, both possible tertiary amines – dibutylhexylamine (VIIc) and dihexylbutylamine (VIc) – were detected by GLC in the products of the reaction of I with IIc. Compound VIc was identical to an authentic sample obtained from IIc by acylation with caproyl chloride and subsequent reduction of the N-hexyl-N-butylcaproamide with lithium aluminum hydride. At the same time, the formation of only one corresponding dialkylbutylamine (VIa or VIb) occurred with the lower alkylbutylamine (IIa, b).

These investigations indicated that for these processes the strength of the N-alkyl bonds increases in the order methyl < ethyl < hexyl < butyl. The lower alkyl residues are cleaved more readily than the butyl residue. On passing to a hexyl substituent the difference in the C–N bond strength between N-alkyl residues decreases. Nevertheless, the N-hexyl group is cleaved somewhat more readily than the N-butyl group. The explanation of this phenomenon requires further investigation.

EXPERIMENTAL

GLC analysis was carried out with a Fractovap chromatograph with a thermal-conductivity detector; the column length was 2 m, and the stationary phase was E-301 silicone elastomer applied in 20% quantities on Chromosorb W; the gas carrier was helium, and the flow rate was 12 liters/h; the column temperature was 190°; the sensitivity of the method was less than 1% of substance.

Reaction of 2,6-Dichloro-3-(β-chloroethyl)-4-methylpyridine (I) with Methylbutylamine (IIa). A mixture of 4.48 g (0.02 mole) of I and 3.48 g (0.04 mole) of IIa [6] was heated for 7 h in an autoclave at 140°. Benzene (100 ml) was then added, and the basic substances were extracted with three 50-ml portions of 18% hydrochloric acid. The benzene layer was separated, dried with potassium carbonate, dried in vacuo, and distilled. Two fractions were collected: the first fraction was 2,6-dichloro-3-vinyl-4-methylpyridine (V) in the form of a colorless liquid with bp 140-143° (14 mm) and n_D^{20} 1.5696 [the yield was 1.9 g(47.5%)]; the second fraction [1.1 g (24.5%)] was starting I with bp 174-177° (14 mm) and mp 68-69°.

The hydrochloric acid solution was made alkaline with 50% potassium carbonate. The base was extracted with ether, dried with potassium carbonate, and, after GLC analysis, was evaporated and distilled in vacuo to give 0.8 g (17.8%) of 1-butyl-4-methyl-6-chloro-7-azaindoline (III) [2] with bp 149-153° (1.5 mm), n_D^{20} 1.5507, and retention time 12.2 min (GLC). 1,4-Dimethyl-6-chloro-7-azaindoline (IVa) was not detected in the reaction products by GLC.

Reaction of I with Ethylbutylamine (IIb). This reaction was carried out as above with 5 g (0.02 mole) of I and 4.5 g (0.04 mole) of IIb to give 1.9 g (46.3%) of V, 1.5 g (30%) of I, and 0.6 g (12.6%) of III. 1-Ethyl-4-methyl-6-chloro-7-azaindoline was not detected in the reaction products by GLC. Distillation of the basic substances in this experiment gave 1.5 g of a mixture of ethylbutylamine (IIb) and diethylbutylamine (VIb) with bp 109-137°. The mixture was refluxed for 3 h with 10 ml of acetic anhydride, 25 ml of ether was added, and VIb was extracted with three 10-ml portions of 10% hydrochloric acid. The ether layer was washed with water and 50% potassium carbonate, dried with potassium carbonate, evaporated, and the residue was vacuum distilled to give 1 g of N-acetylethylbutylamine in the form of a colorless liquid with bp 127-129° (50 mm) and n_D^{20} 1.4486. The compound was quite soluble in the usual organic solvents and slightly soluble in water. Found %: N 9.7. $C_8H_{17}NO$. Calculated %: N 9.8. The hydrochloric acid solution of VIb was made alkaline, and the base that formed was extracted with ether and converted to the picrate by addition of an alcoholic solution of picric acid. The picrate (VIb) obtained had mp 46-47° (from methanol) and was identical to that previously described [8]. Found %: N 15.8. $C_8H_{19}N \cdot C_8H_{19}N_3O_7$. Calculated %: N 15.6.

Hexylbutylamine (IIc). A mixture of 23.8 g (0.32 mole) of butylamine and 22 g (0.16 mole) of caproyl chloride [9] was refluxed for 3 h in 200 ml of anhydrous benzene and 100 ml of water was added. The benzene layer was separated, dried with magnesium sulfate, and evaporated. The residue was distilled, and the fraction with bp 165-167° (20 mm) was collected to give 26 g (95%) of N-butylcaproamide in the form of a colorless liquid that was quite soluble in the usual organic solvents. Found %: C 69.8; H 12.2; N 8.2. $C_{10}H_{21}NO$. Calculated %: C 70.1; H 12.2; N 8.1. A solution of 24 g (0.14 mole) of N-butylcaproamide in 250 ml of absolute ether was added to 16 g (0.42 mole) of lithium aluminum hydride in 200 ml of absolute ether, and the mixture was refluxed for 15 h. The usual workup gave 20 g (91%) of IIc with bp 81-83° (10 mm), n_D^{20} 1.4250,* and retention time 2.0 min (GLC).

Similarly, 6 g (69%) of hexylamine with bp 60-61° (70 mm) and n_D^{20} 1.4255 was obtained by reduction of 10 g (0.08 mole) of caproamide [11] with 9.5 g (0.25 mole) of lithium aluminum hydride in 300 ml of ether-tetrahydrofuran (1 : 3) (refluxed for 16 h).†

Reaction of I with Hexylbutylamine (IIc). The method was similar to that used for the reaction of I with methylbutylamine (IIa) and gave 3.5 g (46.6%) of V, 3 g (33.3%) of I, 0.9 g of IIc; a mixture of tertiary amines (0.4 g) consisting, according to GLC, of dihexylbutylamine (VIc), with retention time 5.5 min, and dibutylhexylamine (VIIc), with retention time 2.8 min; and 1 g of a mixture of 7-azaindolines IVc and III. According to GLC, the overall yield of III was 7.2%, while that of IVc was 3.5%.

Dihexylbutylamine (VIc). Caproyl chloride [5.4 g (0.04 mole)] was added to a solution of 6.3 g (0.04 mole) of hexylbutylamine and 8.1 g (0.08 mole) of triethylamine in 200 ml of anhydrous benzene. The mixture was refluxed for 3 h, and the triethylamine-hydrochloride precipitate was filtered and washed with benzene. The benzene solution was extracted with two 50-ml portions of 2% hydrochloric acid followed by two 40-ml portions of 50% potassium carbonate, washed with water, and dried with magnesium sulfate. The benzene was evaporated, and the residue was distilled to give 8.3 g (81.3%) of N-butyl-N-hexylcaproamide in the form of a colorless liquid with bp 167-172° (5 mm) and n_D^{20} 1.4491, which was quite soluble in the usual organic solvents. Found %: C 75.5; H 12.8; N 5.5. $C_{16}H_{33}NO$. Calculated %: C 75.3; H 12.9; N 5.5; O 6.3. A solution of 7.6 g (0.3 mole) of N-butyl-N-hexylcaproamide in 150 ml of absolute ether was added to a suspension of 3.5 g (0.9 mole) of lithium aluminum hydride in 75 ml of absolute ether, and the mixture was refluxed for 10 h. The usual workup gave 6 g (84.5%) of VIc with bp 139-142° (10 mm) and n_D^{20} 1.4405 in the form of a colorless liquid that was quite soluble in the usual organic solvents. Found %: C 79.7; H 14.4; N 5.8. $C_{16}H_{35}N$. Calculated %: C 79.6; H 14.5; N 5.8.

1-Hexyl-4-methyl-6-chloro-7-azaindoline (IVc). A mixture of 4.2 g (0.018 mole) of I and 3.8 g (0.036 mole) of hexylamine was heated in an autoclave for 7 h at 140°; the basic and nonbasic substances were separated, and the benzene solution yielded 0.7 g (19.8%) of V and 1.5 g (36.7%) of I. Workup of the hydrochloric acid solution after removal of I and V yielded 1.3 g (28%) of IVc with bp 135-137° (1 mm). Compound IVc was an oily substance with n_D^{20} 1.5361 and retention time 27.3 min (GLC) that was quite soluble in the usual organic solvents and insoluble in water. Found %: C 66.5; H 8.0; Cl 13.9; N 11.3. $C_{14}H_{21}ClN_2$. Calculated %: C 66.5; H 8.3; Cl 14.0; N 11.1.

*The synthesis of this compound by a more complex scheme from benzylhexylamine was described in [10].
†Hexylamine was previously obtained by the reduction of nitrohexane with a nickel catalyst [12].

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