AZAINDOLE DERIVATIVES

XXXIV*. THE INFLUENCE OF VARIOUS FACTORS ON THE REACTION OF TRICHLOROCOLLIDINE WITH DIMETHYLAMINE

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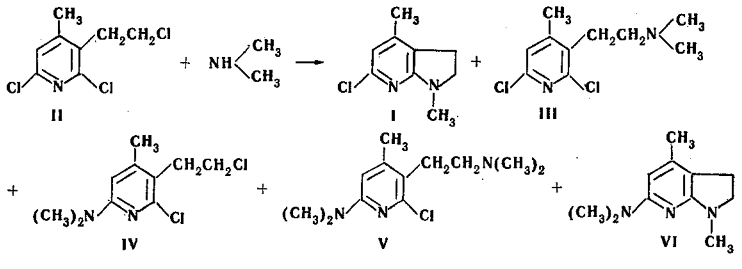
On the basis of a comparative study of the influence of various factors (ratio of the reactants, temperature, reaction time, polarity of the medium, and the catalytic action of metals) on the reaction of 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine (trichlorocollidine) with 2,6-dimethylamine, it has been shown that, in addition to 6-chloro-1,4-dimethyl-7-azaindoline, the process gives rise to various amounts, depending on the conditions of its performance, of other products: 3-(β-dimethylaminoethyl)-2,6-dichloro-4-methylpyridine, 2-chloro-3-(β-chloroethyl)-6-dimethylamino-4-methylpyridine, 2-chloro-6-dimethylamino-3-(β-dimethylaminoethyl)-4-methylpyridine, and 6-dimethylamino-1,4-dimethyl-7-azaindoline. The best method for directing the process to the formation of azaindoline derivatives is the use of highly polar solvents.

In one of the preceding papers of this series [2], the synthesis of 6-chloro-1,4-dimethyl-7-azaindoline (I) by the reaction of 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine (II) with dimethylamine was described.

A further study of this reaction has shown that, depending on the conditions of the process, various amounts of other products of the reaction of trichlorocollidine with dimethylamine are formed, in addition to I. The separation of the substances so formed was effected by the successive use of fractional distillation and salt formation at various pH values. After the separation of the unchanged II, which is practically free from basic properties and is not extracted from benzene by 18% hydrochloric acid, the mixture of basic substances was subjected to fractional vacuum distillation. This gave the high-boiling 2,6-dichloro-3-(β-dimethylaminoethyl)-4-methylpyridine (III) and 2-chloro-3-(β-chloroethyl)-6-dimethylamino-4-methylpyridine (IV). The mixture of amines boiling at a lower temperature was dissolved in ether and extracted successively with buffer solutions having pH 4 and 2, and then with 5% hydrochloric acid. The following substances passed into the respective acid solutions: 2-chloro-6-dimethylamino-3-(β-dimethylaminoethyl)-4-methylpyridine (V) (at pH 4), 6-dimethylamino-1,4-dimethyl-7-azaindoline (VI) (at pH 2), and the azaindoline I (into the 5% hydrochloric acid).



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*For Communication XXXIII, see [1].

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TABLE 1. The Reaction of Trichlorocollidine with Dimethylamine

Amount of dimethylamine (moles per mole of II)	Reaction temperature °C	Reaction time, hr	Solvent	Yield, %			
				II	I	III+IV	VI
2	140	7	Chlorobenzene	28	20	37	7
2	140	7	Ditto	27	20	36	8
2	140	7	Ditto (with the addition of copper)	25	22	37	7
3	140	7	Chlorobenzene	10	25	46	10
20	140	7	Ditto	10	14	52	12
3	140	7	Cyclohexane	19	14	58	4
3	140	7	Benzene	16	18	48	11
3	140	7	Ethanol	14	38	13	15
2	120	7	Chlorobenzene	57	10	20	9
2	190	7	Ditto	11	22	25	33
20	190	7	" "	4	13	8	63
2	140	21	" "	25	17	32	19
3	140	21	" "	9	23	38	22

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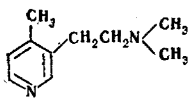
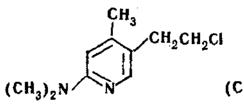
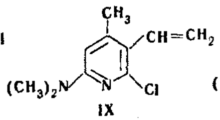
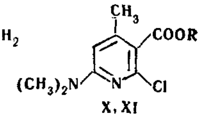
*The amount of V did not exceed 2% in any of the experiments.

Compounds III and IV have very similar properties, and therefore it was possible to separate their mixture only after dehalogenation, which gave 3-(β-dimethylaminoethyl)-4-methylpyridine (VII) and 3-(β-chlorethyl)-6-dimethylamino-4-methylpyridine (VIII). In addition to this, pure III was isolated after the treatment of the mixture of III and IV by boiling ethanolic caustic potash, with subsequent oxidation of the dehalogenation product of IV – 2-chloro-6-dimethylamino-4-methyl-3-vinylpyridine (IX) – to 2-chloro-6-dimethylamino-4-methylnicotinic acid (X).


VII


VIII


IX


X, XI

X R = H; XI R = CH_3

The acid X was characterized in the form of its methyl ester XI. The azaindoline I formed by the reaction of II with dimethylamine was also obtained by the reaction of trichlorocollidine with methylamine. In this case, the yield of I was 55%. It is an interesting fact that the azaindoline VI is formed not as the result of the reaction of I with an excess of the amine, as was found previously for other 6-amino derivatives of 7-azaindolines [3-5], but at the same time as, or before, the closure of the pyrrolidine ring. In fact, in special experiments I did not react with an excess of dimethylamine on prolonged heating to 190°C in a flask, and it was recovered quantitatively in the unchanged state.

In order to study the influence of various factors (the ratio of the reactants, the temperature, the time of the process, the polarity of the medium, and the catalytic action of metals) on the reaction of II with dimethylamine, we have developed a convenient method for the quantitative determination of compounds I-VI in the reaction mixture by gas-liquid chromatography.

In the series of experiments discussed below, after the separation and gravimetric determination of the II that had not reacted, the mixture of amines formed, without separation, was subjected to chromatographic analysis. The retention time of I was 6.5 min, VI 8.5 min, V 9.75 min, and a mixture of III and IV 15.2 min. It was shown by special experiments that the results of the gas-chromatographic analysis (see Table 1) agreed well with the results obtained by the preparative separation of the reaction products.

The composition of the reaction mixtures was investigated on a Fractovap gas-liquid chromatograph. The length of the column was 2 m, the stationary phase E-301 elastomer deposited in an amount of 20% on Chromosorb W with a grain size of 45/60 mesh with helium as the carrier gas at a rate of flow of 166 ml/min, with a column temperature of 190°C.

In an analysis of the figures in the table it can be seen that the reaction of II with dimethylamine is not affected by the material of the apparatus or by the addition of the catalyst – copper wire. At the same time, the reaction depends markedly on the polarity of the medium. On passing from cyclohexane to benzene, chlorobenzene, and further to ethanol the amount of unchanged II and of the monoaminodichloropyridines III and IV fall regularly, and the yields of the azaindolines I and VI rise in parallel. Apparently, an

TABLE 2. Reaction of Trichlorocollidine with Dibutylamine

Amount of dibutylamine, moles	Reaction temperature	Reaction time hr	Yield, %			
			II	XII	XIII	XIV
2	140	7	43	17	29	6
4	140	7	43	17	25	8
6	140	7	42	18	26	7
6	140	16	28	28	25	12
2	180	7	9	23	44	4

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*The results of the preparative separation of the substances are given by the method described previously [2].

increase in the polarity of the solvent promotes the replacement of halogens in the α position of the pyridine ring by amines with subsequent closure of the pyrroline ring. The same process is observed with a rise in the temperature, the amount of the azaindoline VI rising particularly markedly. The yields of VI also rise with an increase in the reaction time and in the amount of amine taken. At lower temperature (140°C) an increase in the amount of amine also increases the yield of monoamine-substituted dichlorocollidine.

Simpler relationships are observed in the reaction of II with dibutylamine (see Table 2). In this case, the amount of side reactions is considerably smaller [2,6,7]; the main products are 1-butyl-6-chloro-4-methyl-7-azaindoline (XII) and the product of the dehydrohalogenation of II – 2,6-dichloro-4-methyl-3-vinylpyridine (XIII). The magnitude of the excess of dibutylamine used in the reaction has practically no effect on the ratio of these products; conversely, with time the process changes in the direction of the azaindoline derivative XII and 2-chloro-3-(β-chloroethyl)-6-dibutylamino-4-methylpyridine (XIV). A rise in the temperature leads to an increase in the yield of the unsaturated compound XIII. In all cases, the yield of XIV does not exceed 12%.

A consideration of the reactions of II with dimethylamine and with dibutylamine permits the conclusion that in both cases, the replacement of the α-halogen atoms in the trichlorocollidine by a secondary amine residue is the slowest stage of the reaction, determing the rate of formation of azaindoline derivatives, and an increase in the excess of amine has little effect on this process.

The most expedient method of directing the reaction to the formation of azaindoline derivative is the use of highly polar solvents.

EXPERIMENTAL

Reaction of Trichlorocollidine (II) with Dimethylamine. A mixture of 84.8 g (0.377 mole) of II and 42 g (0.933 mole) of dimethylamine was heated in an autoclave at 140°C for 7 hr. Then 200 ml of benzene was added to the reaction mixture, and the benzene solution was washed with water, treated with 18% hydrochloric acid (3 × 50 ml), dried with potassium carbonate, and evaporated in vacuum. The residue was distilled at 174-177°C (14 mm). This gave 21.3 g (25%) of II that had not reacted. The hydrochloric acid solution was made alkaline with potassium carbonate and the liberated base was extracted with ether. The residue after the evaporation of the ether (54 g) was distilled at a residual pressure of 9 mm. Two fractions were collected: 1) bp 150-170°C, 32.1 g; 2) bp 170-177°C, mp 67-68°C, 21.1 g.

The second fraction consisted of a mixture of the two isomeric substances III and IV (found, %: C 51.5; H 6.0; Cl 30.8; N 11.9. Calculated for $C_{10}H_{14}Cl_2N_2$, %: C 51.5; H 6.0; Cl 30.5; N 12.0), which could not be separated by fractional distillation, recrystallization from petroleum ether or other solvents, or even by virtue of their basicities or the different solubilities of their salts.

The first fraction from the distillation was dissolved in 150 ml of ether and extracted with a buffer solution having pH 4.18 (2 × 50 ml). The aqueous layer was made alkaline with potassium carbonate and the base was extracted with ether. After the solvent had been evaporated off, the residue was distilled at 138-140°C (5 mm), n_D^{20} 1.5437. The yield was 1.6 g (2%) of V in the form of an oily substance readily soluble in the usual organic solvents. Hydrochloride – colorless crystals, mp 175-176°C (from ethyl acetate). The substance is readily soluble in water and alcohols, and sparingly soluble in ether, acetone, and ethyl acetate. Found, %: C 51.7; H 7.6; Cl 25.6; N 15.2. Calculated for $C_{12}H_{20}ClN_3 \cdot HCl$, %; C 51.8; H 7.5; Cl 25.5; N 15.1.

The ethereal solution after the separation of the V was extracted with a buffer solution having pH 2 (2 × 50 ml). The aqueous layer was treated in the same way as in the isolation of V. After distillation at 128-130°C (3 mm), 7.4 g (10%) of VI was obtained. The substance crystallized. Colorless crystals, mp 54-55°C (from aqueous ethanol). Soluble in ether, benzene, acetone, chloroform, and alcohols, and insoluble in water and petroleum ether. Found, %: C 69.3; H 8.5; N 22.3. Calculated for $C_{11}H_{17}N_3$, %: C 69.1; H 8.9; N 22.0.

The ethereal solution after the separation of the VI was extracted with 5% hydrochloric acid (2 × 50 ml). The hydrochloric acid solution was made alkaline with potassium carbonate, and the base was extracted with ether. The solvent was evaporated off and the residue was distilled at 149-150°C (9 mm). This gave 9.1 g (13%) of I, mp 66°C.

The ethereal solution after the separation of the V, VI, and I was dried with potassium carbonate and evaporated. This gave 12 g of II with bp 170-173°C (3 mm). The total yield of II was 33.3 g (39%).

6-Chloro-1,4-dimethyl-7-azaindoline (I). A mixture of 35 g (0.156 mole) of II and 10.2 g (0.330 mole) of methylamine was heated in a stainless steel bomb at 140°C for 7 hr. Then 50 ml of water was added to the the reaction mixture and it was extracted with benzene. The benzene solution was separated off and the I was extracted from it with 18% hydrochloric acid. After the separation of the I, the benzene solution was dried with potassium carbonate and evaporated in vacuum. Vacuum distillation of the residue yielded 0.4 g (2%) of XIII with bp 140-143°C (14 mm), n_D^{20} 1.5726 [8], and 12.8 g (36%) of II with bp 174-177°C (14 mm), mp 69°C [9]. The hydrochloric acid solution was made alkaline with potassium carbonate and the base I was extracted with ether. After the solvent had been evaporated off, the residue was distilled at 149-151°C (9 mm), giving 15.8 g (55%) of I with mp 66°C. The substance gave no depression of the melting point in admixture with an authentic sample of I.

3-(β-Dimethylaminoethyl)-4-methylpyridine (VII) and 3-(β-Chloroethyl)-6-dimethylamino-4-methylpyridine (VIII). A solution of 6 g (0.026 mole) of a mixture of III and IV in 150 ml of ethanol was treated with a boiling solution of 6 g of palladium chloride in 60 ml of 18% hydrochloric acid and hydrogenation was carried out at room temperature and an overpressure of 15-20 cm water. After the separation of the palladium, the reaction mixture was evaporated in vacuum, made alkaline with 50% potassium carbonate solution, and extracted with ether. The residue from the evaporation of the ether (4.6 g) was distilled in vacuum. Two fractions were collected: 1) bp 116-120°C (4 mm), n_D^{20} 1.5401, 1.6 g – VII. Oily substance readily soluble in the usual organic solvents and sparingly soluble in water. Found, %: N 17.1. Calculated for $C_{10}H_{16}N_2$, %: N 17.1. Hydrochloride – colorless crystals, mp 167-168°C (from acetone). The substance was readily soluble in water and alcohols, and insoluble in ether, benzene, and acetone. Found, %: C 59.5; H 8.4; Cl 17.8; N 13.7. Calculated for $C_{10}H_{16}N_2 \cdot HCl$, %: C 59.8; H 8.5; Cl 17.7; N 13.9. Fraction 2) 2.7 g, bp 132-140°C (4 mm), mp 39-40°C (from petroleum ether) – VIII. Colorless crystals, readily soluble in ether, benzene, acetone, chloroform, and alcohols, sparingly soluble in petroleum ether, and insoluble in water. Found, %: C 60.5; H 7.4; Cl 18.1; N 14.2. Calculated for $C_{10}H_{15}ClN_2$, %: C 60.5; H 7.5; Cl 17.9; N 14.1. Hydrochloride – colorless crystals, mp 165-166°C (from dioxane). The substance is readily soluble in alcohols and water, and sparingly soluble in acetone, chloroform, dioxane, and benzene. Found, %: Cl 30.3; N 11.7. Calculated for $C_{10}H_{15}ClN_2 \cdot HCl$, %: Cl 30.2; N 11.9.

2,6-Dichloro-3-(β-dimethylaminoethyl)-4-methylpyridine (III) and Methyl 2-Chloro-6-dimethylamino-4-methylnicotinate (XI). 4 g (0.017 mole) of a mixture of III and IV and 1.06 g (0.025 mole) of caustic potash in 50 ml of absolute ethanol were boiled for 5 hr. A precipitate of KCl deposited. Then the ethanol was evaporated off, 10 ml of water was added to the residue, and the mixture of organic bases was extracted with benzene. After the solvent had been distilled off, this mixture contained about 30% of IX, according to the elementary analysis for chlorine and nitrogen. 3.2 g of this material was dissolved in 50 ml of acetone and, with stirring, 2.1 g of potassium permanganate was added in portions. The precipitate of manganese dioxide that deposited was filtered off and washed with acetone. The combined acetone solutions were evaporated, and the residue was treated with 15 ml of water, and the compound III, which had not reacted with the caustic potash and potassium permanganate, was extracted with ether. Distillation of the ether yielded 2.2 g of III in the form of colorless crystals with mp 67-68°C. Ths substance is readily soluble in the majority of common organic solvents and less readily in petroleum ether, and it is insoluble in water. Found, %: C 51.6; H 6.3; Cl 30.2. Calculated for $C_{10}H_{14}Cl_2N_2$, %: C 51.5; H 6.0; Cl 30.5.

The aqueous solution containing the potassium salt of the acid X was evaporated to dryness. The residue (1 g) was esterified by boiling it three times for 3 hr each time with 30 ml of a 5% methanolic solution of hydrogen chloride with subsequent evaporation in vacuum. After the third distillation of the methanolic solution of hydrogen chloride, the residue was treated with an excess of a 50% aqueous solution of potassium carbonate and the XI was extracted with ether. The ethereal solution was dried with potassium carbonate and evaporated in vacuum. This gave 0.4 g of XI in the form of colorless crystals with mp 102-103°C (from cyclohexane). The substance is readily soluble in the majority of the usual organic solvents and is insoluble in water. Found, %: C 52.7; H 5.9; N 12.4. Calculated for $C_{10}H_{13}ClO_2N_2$, %: C 52.5; H 5.7; N 12.2.

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