

CHLORINATION OF α, α' -AMINOPICOLINE

S. D. Moshchitskii, L. S. Sologub, and Ya. N. Ivashchenko

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 6, pp. 1068-1070, 1968

UDC 547.821.411.2'822.7:542.944.1

When α, α' -aminopicoline is treated with gaseous chlorine or hydrogen peroxide and hydrochloric acid, the methyl group is not affected and chlorine enters into the pyridine nucleus with the formation of 6-amino-3,5-dichloropicoline-2. A number of new chloro-substituted derivatives of pyridine have been obtained and are described.

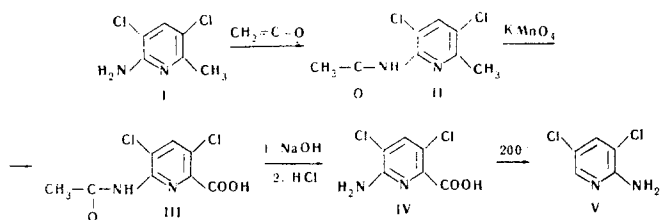
Until the present time, the direct chlorination of α -aminopicoline has not been described.

When α, α' -aminopyridine is chlorinated by gaseous chlorine, a mixture of mono- and dichloroaminopyridine is obtained at low yield [1-3]. When 15% H_2O_2 reacts with a solution of α -aminopyridine in HCl at 85-90° C, a high yield of 2-amino-5-chloropyridine is obtained [4]. It has been established that, depending on the conditions of chlorination, α -picoline gives rise to a mixture of reaction products containing different contents of chlorine up to perchloropicoline [5-9].

In our experiments, chlorination of α, α' -aminopicoline was achieved by two pathways: by the action of gaseous chlorine at different temperatures and in various solvents, and also by the action of H_2O_2 in HCl.

In all cases, the same, previously undescribed compound, 6-amino-3,5-dichloropicoline-2 (I), was obtained, and on chlorination with gaseous chlorine, the best yield (64%) was obtained when the reaction was conducted in 25% H_2SO_4 at room temperature. When α, α' -aminopicoline was treated with H_2O_2 in HCl the yield of compound I was equivalent to 90%.

The structure of the aminodichloropicoline obtained was proved by converting the compound into the well-known [2], 2-amino-3,5-dichloropyridine (V) according to the following scheme:



With acetic anhydride, compound I forms a diacetyl derivative which, on oxidation with potassium permanganate, does not form the corresponding diacetyl derivative of aminodichloropicolinic acid, but is converted into the acid IV with a very poor yield. When the latter is boiled for 30 min with acetic anhydride, the diacetyl derivative of 2-amino-3,5-dichloropyridine is formed.

On diazotization of compound I in conc HCl, 3,5,6-trichloropicoline-2 (VII) is formed with a yield of 17%, and when this process is conducted in 20% H_2SO_4 , 6-oxy-3,5-dichloropicoline-2 (VI) is obtained with almost a quantitative yield. The latter compound had previously been obtained with a yield of 40% by chlorination of 6-methyl-2-pyridone with gaseous chlorine

in an alkaline solution [10]. When compound VI was heated with phosphorus oxychloride, compound VII was formed with a yield of 80%.

EXPERIMENTAL

6-Amino-3,5-dichloropicoline-2 (I). a) Over the course of 2 hr at room temperature, gaseous chlorine was passed into a solution of 10.8 g (0.1 mole) of α, α' -aminopicoline in 20 ml of 25% H_2SO_4 . The reaction mixture was diluted with water to 100-150 ml and carefully neutralized with sodium bicarbonate to a weakly alkaline reaction. The yield of compound I was 11.4 g (64%), mp 132° C (from aqueous ethanol). The compound is soluble in the majority of organic solvents. Found, %: Cl, 40.01. Calculated for $C_6H_6Cl_2N_2$, %: Cl, 40.11.

b) Over the course of 30 min 25 ml of 25% H_2O_2 was added dropwise with stirring to a solution of 10.8 g (0.1 mole) of α, α' -aminopicoline in 100 ml conc HCl. The reaction mixture was maintained at room temperature for 1 hr and heated at 60-70° C for 15-20 min. After cooling, compound I was isolated in an analogous manner to method a) Yield, 15.9 g (90%). Picrate: mp 197° C (from ethanol)-Found, %: Cl, 17.46. Calculated for $C_6H_6Cl_2N_2 \cdot C_6H_3N_3O_7$, %: Cl, 17.48.

Hydrochloride of 6-amino-3,5-dichloropicoline-2. Over the course of 1 hr, dry HCl was passed into a solution of 17.7 g (0.1 mole) of compound I in 40 ml of absolute ethanol. After the solvent had been removed by distillation, the hydrochloride was crystallized from a mixture of ethanol and sulfuric ether, mp 188-190° C. Yield, 16 g (75%). Found, %: Cl, 50.25. Calculated for $C_6H_6Cl_2N_2 \cdot HCl$, %: Cl, 49.88.

Diacetyl derivative of 6-amino-3,5-dichloropicoline-2. A 10-ml volume of acetic anhydride was added to 1.8 g (0.01 mole) of compound I and the reaction mixture was boiled for 60-70 min. After cooling, the mixture was treated with a 10% aqueous solution of sodium bicarbonate. Yield, 1.7 g (65%), mp 136° C (from methyl alcohol). Found, %: Cl, 27.71. Calculated for $C_{10}H_{10}Cl_2N_2O_2$, %: Cl, 27.20.

6-Acetylamino-3,5-dichloropicoline-2 (II). For 2 hr, ketene was passed into a solution of 8.9 g (0.05 mole) of compound I in 200 ml absolute ether at room temperature. The separated crystals, 7.8 g (72%), were crystallized from petroleum ether (bp 80-100° C), mp 122° C. Found, %: Cl, 32.47. Calculated for $C_8H_8Cl_2N_2O$, %: Cl, 32.42.

6-Acetylamino-3,5-dichloropicolinic acid (III). In the course of 20 hr, 15.5 g of powdered potassium permanganate was gradually added to 10.8 g (0.05 mole) of compound II in 300 ml water at 70° C. The hot solution was then filtered from manganese dioxide and evaporated to 1/3 of its original volume. The solution was maintained in the refrigerator overnight and the nonreacted compound II was removed by filtration and acidified with dilute (1 : 1) HCl. On cooling, the acid III was precipitated with a yield of 5.7 g (46%), mp 162° C (acetone + petroleum ether). Found, %: Cl, 28.44. Calculated for $C_8H_8Cl_2N_2O_3$, %: Cl, 28.51.

6-Amino-3,5-dichloropicolinic acid (IV). A solution of 2.5 g (0.01 mole) of compound III in 20 ml of 5% NaOH was heated for 1 hr. After cooling, it was acidified with dilute HCl (1 : 1) and 1.9 g (96%) of compound IV was precipitated, mp 197-198° C (with decomp. from water). Found, %: Cl, 34.26. Calculated for $C_6H_4Cl_2N_2O_2$, %: Cl, 34.33.

2-Amino-3,5-dichloropyridine (V). A 0.01 mole quantity of compound IV was heated in an oil bath at 200° C for 10 min and then

distilled with steam. Mp 79–80° C (from aqueous ethanol). In the test of displacement with a known compound [2] the compound melts without depression. Found, %: Cl, 43.44. Calculated for $C_5H_4Cl_2N_2$, %: Cl, 43.55.

6-Oxy-3,5-dichloropicoline-2 (VI). A solution of 6.0 g of sodium nitrite in 20 ml water was added in portions, with vigorous shaking, to a solution of 8.9 g (0.05 mole) of compound I in 80 ml of 20% H_2SO_4 cooled to 0° C. Then, 2 hr after the addition of the last portion of sodium nitrite, the precipitate was removed by filtration. Yield of compound VI, 8.6 g (96%), mp 214–216° C (from methanol). Found, %: Cl, 39.69. Calculated for $C_6H_5Cl_2NO$, %: Cl, 39.88.

3,5,6-Trichloropicoline-2 (VII). a) A 0.01 mole quantity of the hydrochloride of compound I was dissolved in 15 ml conc HCl and finely ground sodium nitrite (1.7 g) was added in portions, with vigorous mixing, while the reaction mass was actively cooled with a mixture of ice and salt. The reaction mixture was maintained in the refrigerator overnight, then diluted in water, and the precipitate was removed by filtration. Yield, 0.33 g (17%), mp 71–72° C. Found, %: Cl, 54.26. Calculated for $C_6H_4Cl_3N$, %: Cl, 54.19.

b) A mixture of 0.9 g (0.005 mole) of compound VI and 20 ml of phosphorus oxychloride was heated in a sealed ampul for 5 hr at 180–190° C. The contents of the ampul were then transferred into a flask containing crushed ice. The precipitate was removed by filtration. Yield, 0.8 g (81%), mp 71–72° C. Found, %: Cl, 54.07. Calculated for $C_6H_4Cl_3N$, %: Cl, 54.19.

Diacetyl derivative of 2-amino-3,5-dichloropyridine. a) A 5 ml volume of acetic acid was added to 0.4 g (0.0025 mole) of compound V and the reaction mixture was heated in an oil bath at 150° C for 90 min. Acetic anhydride was then removed by distillation at reduced pressure and the residue was treated with a 10% solution of sodium bicarbonate. The resultant precipitate was removed by filtration, mp 90–92° C (from water). Found, %: Cl, 28.94. Calculated for $C_9H_8Cl_2N_2O_2$, %: Cl, 28.42.

b) A 10-ml volume of acetic anhydride was added to 2.0 g (0.01 mole) of compound IV and the reaction mixture was heated in an oil bath at 150° C for 30 min. The diacetyl derivative was precipitated in an analogous manner to method (a), mp 89–91° C. Found, %: Cl, 29.04. Calculated for $C_9H_8Cl_2N_2O_2$, %: Cl, 28.42.

REFERENCES

1. Schering Co., German patent no. 400191, 1924; C., 1, 303, 1925.
2. A. E. Chichibabin and A. F. Egorov, ZhRFKhO, 60, 683, 1928.
3. J. P. English and J. H. Clark, J. Am. Chem. Soc., 68, 458, 1946.
4. F. Friedrich, Pharmazie, 19, 677, 1964.
5. W. Sell, J. Chem. Soc., 799, 1905.
6. P. Dyson and D. Hammick, J. Chem. Soc., 781, 1939.
7. E. McBee and H. Hass, US patent no. 2516402, 1950; C. A., 45, 670, 1951.
8. E. McBee, H. Hass, and E. Hodnett, Ind. Eng. Chem., 39, 389, 1947.
9. Dow Chemical Co., British patent no. 957276, 1964.
10. M. R. Cava and N. K. Bhattacharvya, J. Org. Chem., 23, 1614, 1958.

28 August 1966

Institute of Organic Chemistry
AS UkrSSR, Kiev