# PREPARATION OF AMINO DERIVATIVES OF SOME NITROGEN-CONTAINING HETEROCYCLES

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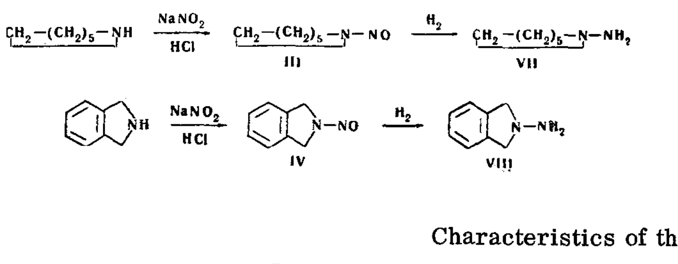
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 1, pp. 140–141, 1968

UDC 547.758:542.941.4.7'942.4

This paper presents a description of the preparation of compounds containing a primary amino group in the side chain and a tertiary nitrogen atom in the ring, starting from hexamethyleneimine and isoindoline.

At present a large number of physiologically active compounds with nitrogen-containing heterocycles in their molecular structure are known. In particular, pharmacological preparations are obtained from hexamethyleneimine as well as from isoindoline [1,2]. N-Alkyl derivatives of hexamethyleneimine [3,4] and of acylindolines [5] possess repelling activity. Some esters of hexamethylenedithiocarbamic acid are poisonous to soil nematodes [6]. Hexamethyleneimine, obtained as a secondary product in the manufacture of hexamethylenediamine, is an available initial compound. The simple methods which have been proposed for the preparation of primary amines, with nitrogen-containing five- and seven-membered heterocycles, may prove interesting in the search for new physiologically active preparations. The reduction of compounds I–IV was formerly accomplished either with $LiAlH_4$ [7] or under pressure with hydrogen and reduced nickel or cobalt catalyst in ethanol in the presence of ammonia. More satisfactory results were obtained by catalytic hydrogenation.



EXPERIMENTAL

**N-(β-Cyanoethyl)hexamethyleneimine (I).** The reaction was conducted by the same method developed for obtaining N-(β-cyanoethyl) piperidine [8]. To hexamethyleneimine was added a small excess (11–11.5%) of acrylonitrile, and after the evolution of heat had ceased, the mixture was heated in a sealed glass ampule for 6–16 hr at 100° C. Yield of I, 85–90%, colorless, transparent liquid boiling at 94°–95° C (4.5 mm), at 113° C (8.5 mm); $n_D^{20}$ 1.4763. The iodomethylate of I melts at 153–154° C (ex methanol). Found, %: C 40.99; 40.91; H 6.65; 6.62; N 9.26; 9.53; I 43.26; 43.37%. Calculated for $C_9H_{19}N_2$, %: C 40.80; H 6.48; N 9.52; I 43.20%.

**N-(β-Cyanoethyl) isoindoline (II).** To 3.85 g (0.0322 mole) of indoline 2.56 g (0.048 mole) of acrylonitrile was added gradually and the heat in a sealed glass ampoule for 9 hr at 100° C. This yields 3 g (54.2%) of a white, crystalline product which darkens in the air, boils at 161–163° C (5 mm), and melts at 81°–83° C (ex acetone).

**N-Nitrosohexamethyleneimine (III).** To a mixture of 89.5 g (0.905 mole) of hexamethyleneimine, 75 ml of conc. HCl, and 26 ml of water were added at 70° C and under stirring during the course of 1 hr, 65 g of $NaNO_2$ in 95 ml of water. Stirring was continued for 2 hr at 70° C, the upper layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were dried over calcined $Na_2SO_4$ and distilled under vacuum. Yield 101.4 g (88.3%) III, boiling at 138° C (34 mm)*, 119° C (17 mm); $n_D^{20}$ 1.4975. Found, %: N 22.04; 22.00%; Calculated for $C_6H_{12}N_2O$, %: N 21.75%.

**N-Nitrosoindoline (IV).** To a mixture of 8.25 g (0.0695 mole) of isoindoline, 8 ml of conc. HCl, and 2 ml of water at 80° C a solution of 10 g of $NaNO_2$ in 15 ml of water was added with stirring in the course of 30 min. The precipitate was filtered off and recrystallized from alcohol. Yield 4.9 g (59.5%) of IV, mp. 95°–96° C**.

**N-Aminohexamethyleneimine (VII).** To a solution of 26 g of III in 50 ml of dry ether, a suspension of 7.6 g of $LiAlH_4$ in 200 ml of dry ether was added with stirring at a temperature about 38° C, the mixture boiled for 2 hr and allowed to stand overnight. After adding in succession 8 ml of water, 6 ml of a 20% solution of NaOH, and 28 ml of water, the mixture was filtered and the precipitate washed

Characteristics of the Amines Obtained

| Compound | Hydrogen conditions | | | Mp., ° C | Bp., ° C (pressure, mm) | $n_D^{20}$ | Yield, % |
|---|---|---|---|---|---|---|---|
| | Temperature, ° C | Initial pressure, atm | Catalyst | | | | |
| V | 100 | 155 | Co | — | 116 (4) | 1.4831 | 97.8 |
| VI | 80 | 100 | Ni | 98–99 | — | — | 74.5 |
| VII | 120 | 125 | Ni | — | 95 (55) | 1.4853 | 61.2 |
| VIII | 95 | 100 | Co | — | 110 (26) | 1.5670* | 65.0 |

* $n_D^{19}$

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*According to the literature, III boils at 136–138° C (34 mm) [8].

**According to the literature, IV melts at 95–97° C [9].

with ether. By distillation were eliminated 6.7 g of unreacted III and 4.85 g (21%) of amine VII, boiling at 95° C (55 mm), $n_D$ 1.4853*.

**Catalytic Reduction.** The reaction was conducted in a revolving steel autoclave with a volume of 0.25 liter. The catalyst was separated by decantation and the solution was distilled under vacuum. The purity of the amines was controlled by titrating a sample of the amines in aqueous alcohol with 0.1 N HCl. The table summarizes the hydrogenation conditions, the yields and the constants of the amines obtained.

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6 March 1966

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*According to the literature, VII boils at 94–96° C (55 mm) [8].