

SEVERAL TRANSFORMATIONS OF 3-BENZYL-9-CARBETHOXYMETHYL-3,9-DIAZABICYCLO[3.3.1]NONANE

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The transformations of 3-benzyl-9-carbethoxymethyl-3,9-diazabicyclo[3.3.1]nonane (I) were studied. The dichloride of 9-(β -chloroethyl)-3,9-diazabicyclo[3.3.1]nonane, which is readily cyclized in the basic form to 3,9-diazatricyclo[3.3.1.2^{3,9}]undecane (V), was synthesized by reduction of I with LiAlH_4 and debenzylation with subsequent replacement of the hydroxy group, in the alcohol formed, by chlorine. An unusual cleavage of the carboxymethyl residue to form the nitrogen-unsubstituted dichloride of 3,9-diazabicyclo[3.3.1]nonane (XI) occurs on treatment with thionyl chloride of the acid obtained by saponification and debenzylation of I.

3-Benzyl-9-carbethoxymethyl-3,9-diazabicyclo[3.3.1]nonane (I) was described in one of our previous communications [1]. In order to use this substance for the synthesis of tricyclic systems, we have studied several transformations of I. By reduction of I with lithium aluminum hydride with subsequent debenzylation of the 3-benzo-9-(β -hydroxyethyl)-3,9-diazabicyclo[3.3.1]nonane (II) and subsequent hydrogenation over a palladium catalyst we obtained 9-(β -hydroxyethyl)-3,9-diazabicyclo[3.3.1]nonane (III) in an overall yield of 74%. Treatment of III with thionyl chloride made it possible to readily transform it to the dihydrochloride of 9-(β -chloroethyl)-3,9-diazabicyclo[3.3.1]nonane (IV). Compound IV readily undergoes cyclization under mild conditions by treatment with aqueous alkaline solutions or potassium carbonate without heating. The 3,9-diazatricyclo[3.3.1.2^{3,9}]undecane (V) formed* is characterized by the absence in the IR spectrum of an absorption from 3300–3500 cm^{-1} from the valence vibrations of the NH group.†

In order to synthesize the tricyclic compound X, which contains a carbonyl function in the α position with respect to the nitrogen of the carbonyl function,‡ I was transformed to 9-carbethoxymethyl-3,9-diazabicyclo[3.3.1]nonane (VIII) by catalytic debenzylation with palladium. The free base IX was isolated from the dichloride VIII. Compound IX was also obtained by saponification of ester I with subsequent debenzylation of the dihydrochloride of 3-benzyl-9-carboxymethyl-3,9-diazabicyclo[3.3.1]nonane (VII).

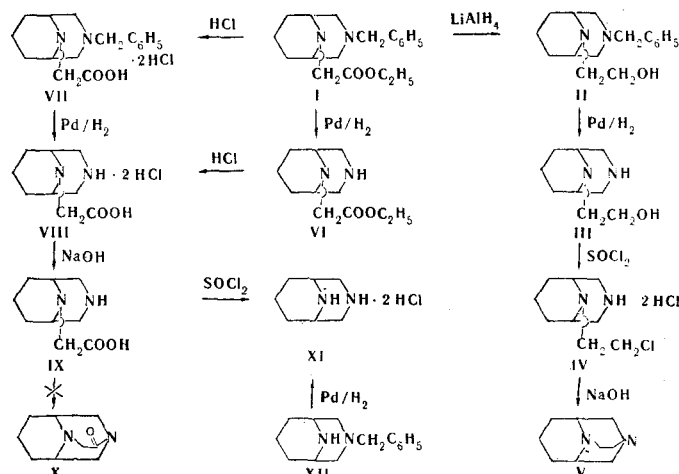
The carboxyl group of IX participates in the formation of an inner salt, as attested to by the shift of the carbonyl absorption in the IR spectra from 1735 cm^{-1} for the dihydrochloride (VIII) to 1630 cm^{-1} for the free acid IX. The high melting point (200–201°) and the low reactivity of the carbonyl group are apparently associated with the salt-forming character of compound IX. Thus, for example, substance IX is quantitatively, potentiometrically titrated as a monobasic acid only in dimethylformamide using an alkaline solution in a mixture of methanol and benzene. Compound IX does not undergo esterification on heating with alcoholic hydrogen chloride or with a mixture of alcohol and concentrated sulfuric acid and does not form,

*A report of the synthesis of V [2] was reported while this work was being accomplished.

†The IR spectra were obtained with a UR-10 recording spectrophotometer in the form of mulls in mineral oil. The PMR spectra were obtained with a YNB-100 spectrophotometer in solutions in CDCl_3 with a TMS (tetramethylsilane) internal standard. We are obliged to thank Yu. N. Sheinker, L. M. Alekseeva, and Yu. I. Pomerantsev for their assistance in carrying out the spectral investigations.

‡ Unsuccessful attempts to synthesize this type of compound on the basis of the cyclization of 8-carbethoxymethyl-3,8-diazabicyclo[3.2.1]octane have recently been described by Cignarella et al. [3].

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under the usual conditions, an acid chloride with thionyl chloride or phosphorus oxychloride.

An unusual reaction – cleavage of the carboxymethyl residue and formation of a nitrogen-unsubstituted dihydrochloride of 3,9-diazabicyclo[3.3.1]nonane (XI) [4] – occurs on treatment of acid IX, heated to 90–100°, with thionyl chloride. The structure of XI was confirmed by IR and PMR spectral data and by comparison of this compound with a known sample of XI synthesized from 3-benzyl-3,9-diazabicyclo[3.3.1]nonane (XII) by means of its debenzylation. The samples of XI obtained by both methods had identical IR spectra, and mixtures of their picrates did not give a melting point depression.

The question of the mechanism of this cleavage of the carboxymethyl residue in the 9-carboxymethyl-3,9-diazabicyclo[3.3.1]nonane (IX) requires additional study. It is possible that cleavage of the side chain to form, initially, CO and HCOH occurs under these conditions. This sort of reaction has not been described for the well-known *m*-carboxymethyl derivatives of the piperidine and piperazine series.

EXPERIMENTAL

3-Benzyl-9-(β-hydroxyethyl)-3,9-diazabicyclo[3.3.1]nonane (III). 3-Benzyl-9-carbethoxymethyl-3,9-diazabicyclo[3.3.1]nonane (I) [7.2 g (23 mmole)] was reduced with 1.36 g (35 mmole) of lithium aluminum hydride in ether (160 ml) to give 5.03 (82.1%) of II in the form of a colorless liquid with bp 155–156° (0.4 mm) and n_D^{20} 1.5485. Found %: C 74.20; H 9.16; N 11.03. C₁₆H₂₄N₂O. Calculated %: C 73.80; H 9.21; N 10.74.

9-(β-Hydroxyethyl)-3,9-diazabicyclo[3.3.1]nonane (III). Compound II [5.9 g (23 mmole)] was debenzylated by hydrogenation in the presence of palladium chloride (0.5 g of palladium chloride, 1 ml of water, 0.8 ml of hydrochloric acid) in alcohol (100 ml). About 750 ml of hydrogen was absorbed. The precipitate was filtered together with the catalyst, and the residue was washed with hot water until the dihydrochloride of III was completely dissolved; the aqueous ethanol solutions were evaporated in vacuo to dryness. The dihydrochloride of III was purified by dissolving in absolute alcohol with subsequent evaporation of the alcoholic solution in vacuo to give 5 g (90.5%) of colorless crystals with mp 267–269° (decomp.). Found %: Cl 29.12; N 11.66. C₉H₁₈N₂O · 2HCl. Calculated %: Cl 29.16; N 11.52.

Base III. This was obtained in the form of colorless crystals with mp 41–43° and bp 120–122° (2 mm). Found %: C 63.25; H 10.90; N 16.62. C₉H₁₈N₂O. Calculated %: C 63.48; H 10.65; N 16.45.

Dihydrochloride of 9-(β-Chloroethyl)-3,9-diazabicyclo[3.3.1]nonane (IV). Compound III [12.9 g (53 mmole)] of the dihydrochloride of III was refluxed for 12 h with a mixture of 120 ml of thionyl chloride and 120 ml of chloroform. The resulting precipitate was filtered, washed with chloroform and ether, and dried in a vacuum desiccator to give 13.7 g (98.7%) of a white, finely crystalline substance that was practically insoluble in the usual organic solvents and had mp 258–260° (decomp.). Found %: Cl 40.20; N 10.64. C₉H₁₇ClN₂ · 2HCl. Calculated %: Cl 40.65; N 10.70.

3,9-Diazabicyclo[3.3.1.2^{3,9}]undecane (V). Compound IV [5 g (19 mmole)] was mixed with 5 ml of water, 10 ml of 40% sodium hydroxide was added with cooling, and the mixture was thoroughly mixed and extracted with ether. After drying the extract and removal of solvent the residue was distilled in vacuo to give 1.55 g (53.2%) of a colorless, transparent liquid with bp 82–84° (1 mm) with n_D^{20} 1.5281. Found %: C 70.76; H 10.71;

N 18.39. $C_9H_{16}N_2$. Calculated %: C 71.00; H 10.58; N 18.40. The dihydrochloride of V was obtained in the form of colorless crystals with mp 294–296° (decomp.). Found %: C 47.70; H 8.35; Cl 31.27; N 12.44. $C_9H_{16}N_2 \cdot 2HCl$. Calculated %: C 48.00; H 8.05; Cl 31.49; N 12.44. The monopicrate of V was obtained in the form of yellow crystals with mp 243–245° (decomp.). Found %: C 47.13; H 5.07; N 18.26. $C_9H_{16}N_2 \cdot C_6H_3N_3O_7$. Calculated %: C 47.24; H 5.02; N 18.36.

9-Carboxymethyl-3,9-diazabicyclo[3.3.1]nonane (VI). Compound I [10.68 g (35 mmole)] was debenzylated by hydrogenation in the presence of palladium chloride (1 g of palladium chloride, 2 ml of water, and 1.6 ml of hydrochloric acid) in ethanol (200 ml). About 1000 ml of hydrogen was absorbed. The reaction mass was treated as described above to give 9.5 g (94.3%) of the dihydrochloride of VI with mp 172–174° (decomp.). Found %: Cl 24.91; N 9.91. $C_{11}H_{20}N_2O_2 \cdot 2HCl$. Calculated %: Cl 24.86; N 9.82.

Base VI. This was a colorless liquid with bp 125–127° (4 mm) and n_D^{20} 1.4954. Found %: C 61.88; H 9.36; N 13.09. $C_{11}H_{20}N_2O_2$. Calculated %: C 62.23; H 9.54; N 13.19.

3-Benzyl-9-carboxymethyl-3,9-diazabicyclo[3.3.1]nonane Dihydrochloride (VII). Compound I [10.63 g (35 mmole)] was refluxed for 3 h with 110 ml of 18% hydrochloric acid, the solution was treated with charcoal, filtered, and evaporated in vacuo. Acetone was added to the caramel-like mass, the mixture was stirred, and the precipitate was filtered to give 10.4 g (84.9%) of VII in the form of white crystals with mp 235–236° (decomp.). Found %: Cl 20.45; N 7.94. $C_{16}H_{22}N_2O_2 \cdot 2HCl$. Calculated %: Cl 20.42; N 8.06.

9-Carboxymethyl-3,9-diazabicyclo[3.3.1]nonane Dihydrochloride (VIII). A. Compound VI [1.45 g (6.8 mmole)] was refluxed for 3 h with 15 ml of 18% hydrochloric acid. The colorless solution was evaporated the residue was triturated with acetone, filtered, and dried in a vacuum desiccator to give 1.55 g (88.5%) of white crystals with mp 245–247° (decomp.). Found %: C 41.74; H 7.09; Cl 27.67; N 11.21. $C_9H_{16}N_2O_2 \cdot 2HCl$. Calculated %: C 42.03; H 7.05; Cl 27.57; N 10.89.

B. Compound VII [20.7 g (59 mmole)] was hydrogenated in ethanol (400 ml) in the presence of 2 g of palladium chloride dissolved in 4 ml of water and 3.2 ml of hydrochloric acid. About 2200 ml of hydrogen was absorbed. The reaction mass was treated as in the case of the preparation of VI to give 14.6 g (93.5%) of VIII in the form of colorless crystals with mp 245–247° (decomp.). No melting point depression was observed for a mixture of this sample with the substance obtained by method A. Found %: C 42.00; H 7.18; Cl 27.75; N 10.85. $C_9H_{16}N_2O_2 \cdot 2HCl$. Calculated %: C 42.03; H 7.05; Cl 27.57; N 10.89.

9-Carboxymethyl-3,9-diazabicyclo[3.3.1]nonane (IX). Compound VIII [2 g (7.78 mmole)] was mixed with 20 ml of water; and 15.5 ml (15.5 mmole) of 1 N sodium hydroxide was added. The resulting solution was evaporated to dryness, and the residue was dried at 100° and refluxed with 30 ml of absolute ethanol for 30 min. The resulting sodium chloride was removed by filtration, the alcoholic filtrate was again evaporated, and the residue was dissolved in absolute alcohol. The solution was treated with charcoal, filtered, and 0.85 g of colorless crystals with mp 200–201° was isolated from the filtrate with ether. Found %: N 15.20. $C_9H_{16}N_2O_2$. Calculated %: N 15.20.

3,9-Diazabicyclo[3.3.1]nonane Dihydrochloride (XI). A. Compound IX [3 g (16 mmole)] was heated in a flask to 90–100°, and 30 ml of boiling thionyl chloride was added with stirring. All of the precipitate dissolved in 30 min. The mixture was then cooled to 70° and held at that temperature for 3 h. The excess thionyl chloride was then distilled in vacuo, and benzene was added twice to the residue with subsequent distillation. Absolute ethanol (30 ml) was added to the dry substance, and the mixture was refluxed for 3 h. The precipitate was filtered, refluxed with 30 ml of absolute ethanol, and again filtered. The precipitate was washed with absolute ether and dried in a vacuum desiccator to give 2.62 g (81%) of XI with mp 321–323° (decomp.). A dipicrate, which crystallized with two water molecules and had mp 227–228°, was obtained from the dihydrochloride by treatment with aqueous sodium picrate. Found %: C 38.07; H 3.83; N 18.46. $C_7H_{14}N_2 \cdot 2C_6H_3N_3O_7 \cdot 2H_2O$. Calculated %: C 37.99; H 3.88; N 18.05. The dihydrochloride of XI was again obtained from the dipicrate by the usual method and had mp 331–331.5° (decomp.). Found %: C 42.56; H 8.26; Cl 35.97; N 13.85. $C_7H_{14}N_2 \cdot 2HCl$. Calculated %: C 42.21; H 8.28; Cl 35.61; N 14.07.

B. 3-Benzyl-3,9-diazabicyclo[3.3.1]nonane (XII) [1] [5 g (23 mmole)] was hydrogenated in ethanol (100 ml) in the presence of 0.5 g of palladium chloride dissolved in 1 ml of water and 0.8 ml of hydrochloric acid. The usual treatment gave 3.7 g (80.5%) of XI with mp 321–324°. Compound XI was converted into a dipicrate with mp 226–228° identical to that described above (method A) by treatment with aqueous sodium picrate.

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