

NEW PREPARATION OF 7-NITRO-1,3,5-TRIAZAADAMANTANE AND ITS DERIVATIVES OBTAINED BY HYDROGENATION AND OZONISATION*

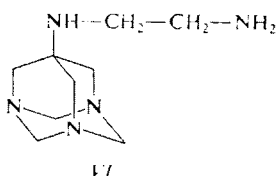
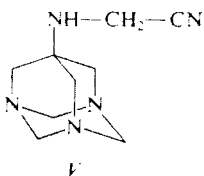
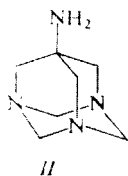
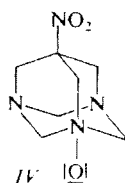
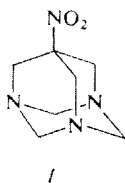
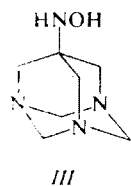
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A novel synthesis of 7-nitro-1,3,5-triazaadamantane (*I*) and some of its derivatives is described. 7-Amino (*II*) and 7-hydroxyamino-1,3,5-triazaadamantane (*III*) were obtained from the hydrogenation products of *I*. 7-Nitro-1,3,5-triazaadamantane N-oxide (*IV*) was prepared from *I*. The amine *II* was transformed into 7-(cyanomethyl)amino-1,3,5-triazaadamantane (*V*) which was reduced to 7-(2-aminoethyl)amino-1,3,5-triazaadamantane (*VI*).

This paper is a continuation of our previous study on 1,3,5-triazaadamantane derivatives with possible pharmacological activity¹ and deals with a novel preparation of 7-nitro-1,3,5-triazaadamantane² (*I*) and its hydrogenation over various catalysts. The hydrogenation of *I* over PtO₂ or Pd/C in ethanol affords solely 7-amino-1,3,5-triazaadamantane (*II*). On the other hand, the hydrogenation over Pd/C in water leads to 7-hydroxyamino-1,3,5-triazaadamantane (*III*). Preparation of quaternary salts of 7-nitro-1,3,5-triazaadamantane was successful only in the case of the lower



* Part VII in the series Nitrogen Compounds of Adamantane; Part VI: This Journal 40, 442 (1975).

homologues, *i.e.* 7-nitro-1,3-diaza-5-methylazoniaadamantane iodide and 7-nitro-1,3,5-triazaadamantane iodide.

Treatment of the nitro derivative *I* with ozone in water afforded 7-nitro-1,3,5-triazaadamantane N-oxide (*IV*) in good yield. The same compound was prepared from *I* and hydrogen peroxide in glacial acetic acid. Evaporation of a solution of the N-oxide *IV* in dilute acetic acid gave its acetate, whereas evaporation of an aqueous solution of *IV* afforded the monohydrate which only upon sublimation yielded the yellow N-oxide *IV*.

The cyanomethylation of the amine *II* with formaldehyde and sodium cyanide led to 7-(cyanomethyl)amino-1,3,5-triazaadamantane (*V*) which on reduction with lithium aluminium hydride afforded 7-(2-aminoethyl)amino-1,3,5-triazaadamantane (*VI*). The reduction of *V* with sodium gave a mixture of *II*, *VI* and 7-methylamino-1,3,5-triazaadamantane.

EXPERIMENTAL

The melting points are uncorrected. The purity of the prepared compounds was checked by gas-liquid and paper chromatography and by mass spectrometry (LKB 9000 spectrometer).

7-Nitro-1,3,5-triazaadamantane (*I*)

Formic acid (90 ml, 98–100%) and nitromethane (108 ml) were added to a mixture of hexamethylenetetramine (280 g) and 80% ethanol (1000 ml). The mixture was boiled for 4 hours and set aside overnight. The separated crystals were washed several times with water and ethanol and dried. Further amount was obtained from the mother liquors, total yield 238 g (65%). The product was crystallized from water, m.p. 314–315°C. (Ref.³ gives m.p. 315°C).

Hydrogenation of 7-Nitro-1,3,5-triazaadamantane

a) Compound *I* (0.5 g) was hydrogenated in ethanol (100 ml) over PtO₂ (0.1 g) under normal pressure at room temperature for 4 hours. The consumption of hydrogen was 238 ml. The catalyst was filtered off, the filtrate taken down, the residue dissolved in methanol and filtered. Concentration of the solution gave 0.5 g of the product, m.p. 302–304°C, which, according to gas-liquid chromatography and mass spectrometry, is identical with 7-amino-1,3,5-triazaadamantane (*IV*); no mixture melting point depression with the authentic specimen¹.

b) Compound *I* (0.5 g) was hydrogenated in ethanol (100 ml) over 3% Pd/C (0.3 g) under the same conditions as described above; after 3.5 hours the consumption of hydrogen was 213 ml. (The catalyst used had pasty consistency and contained about 50% water; it was dried in vacuo prior to use). The reaction mixture afforded 0.3 g of the amine *IV*, identical with the compound prepared in the preceding experiment.

c) Compound *I* (10 g) was hydrogenated in water (200 ml) over Pd/C (1 g) under the same conditions as described in the preceding experiment. After 1.5 hour the hydrogen consumption was 2.8 l. The catalyst was filtered off and the filtrate was concentrated to a small volume. The crystals, which separated (4 g, 43%), melted at 228°C (decomposition), and were identified (gas-liquid chromatography, mass spectrometry) as 7-hydroxyamino-1,3,5-triazaadamantane (*II*). Ref.⁴ gives m.p. 227–229°C.

7-Nitro-1,3-diaza-5-methylazoniaadamantane Iodide

A mixture of *I* (3.6 g) and methyl iodide (14 g) was kept at 40–50°C for 3 hours. The obtained product was crystallized from 50% aqueous ethanol, m.p. 258°C, yield 94%. For $C_8H_{15}IN_4O_2$ (326.1) calculated: 29.46% C, 4.63% H, 38.91% I, 17.18% N; found: 29.57% C, 4.73% H, 38.68% I, 17.35% N.

7-Nitro-1,3-diaza-5-ethylazoniaadamantane Iodide

A mixture of *I* (0.5 g) and ethyl iodide (9.5 g) was heated in a sealed ampoule to 100°C for 5 hours. The obtained yellowish compound was crystallized from 50% ethanol, m.p. 233–234°C; yield 97%. For $C_9H_{17}IN_4O_2$ (340.2) calculated: 31.78% C, 5.04% H, 37.30% I, 16.47% N; found: 31.61% C, 4.90% H, 36.92% I, 16.39% N.

7-Nitro-1,3,5-triazaadamantane N-Oxide (*IV*)

a) Ozone (approx. 3%) was introduced into a suspension of *I* (50 g) in water (500 ml) for 8 hours. The resulting solution was taken down and the residue was dissolved in boiling ethanol (750 ml). The yellow solution was filtered and allowed to crystallize. From the mother liquors another portion of the product was obtained, the total yield being 54 g (98%). The product was sublimed at 0.4–0.5 Torr and bath temperature 170°C (80%). The sublimed product was crystallized from ethanol (dioxane or pentanol) and melted then at 216°C. For $C_7H_{12}N_4O_3$ (200.2) calculated: 42.00% C, 6.04% H, 27.99% N; found: 42.03% C, 6.12% H, 27.91% N. The structure of the product (*IV*) was proved by mass spectrometry and IR spectroscopy. Its hydrogenation over PtO_2 in ethanol afforded the amine *II*.

b) To a mixture of *I* (40 g) and glacial acetic acid (100 ml) 30% hydrogen peroxide (50 ml) was added. The mixture was kept at 70–80°C for 8 hours, the acetic acid was partly evaporated *in vacuo* to half of the original volume (concentration to a smaller volume leads to an explosion). The concentrated solution was diluted with water (100 ml) and evaporated *in vacuo* on a water bath till nothing more distilled. An excess of sodium carbonate was added to the residue and the mixture was extracted with chloroform. The combined chloroform extracts were taken down and the residue crystallized from butanol, m.p. 214–215°C; no mixture melting point depression with *IV*, prepared by ozonisation.

Acetate: A solution of *IV* (0.5 g) in 50% acetic acid was evaporated, the remaining acid removed by butanol and toluene and the residue crystallized from butanol, giving 0.5 g of the product, melting at 140°C (dec.). For $C_9H_{16}N_4O_5$ (261.3) calculated: 41.53% C, 6.19% H, 21.53% N; found: 41.49% C, 6.26% H, 21.50% N.

Monohydrate: A solution of *IV* (1.0 g) in boiling water (100 ml) was cooled and the unreacted compound *IV* was filtered off. Concentration of the mother liquor afforded 0.5 g of the product, melting at about 140°C. For $C_7H_{14}N_4O_4$ (218.2) calculated: 38.52% C, 6.47% H, 25.68% N; found: 38.87% C, 6.49% H, 25.84% N. On sublimation *in vacuo* the product loses the molecule of water and affords the yellow N-oxide *IV*.

Picrate, m.p. 198–200°C (ethanol), was prepared from *IV* and picric acid. For $C_{13}H_{15}N_7O_{10}$ (429.3) calculated: 36.37% C, 3.52% H, 22.84% N; found: 36.46% C, 3.86% H, 22.47% N.

7-(Cyanomethyl)amino-1,3,5-triazaadamantane (*V*)

Concentrated hydrochloric acid (2.5 ml) was added to the compound *II* (5 g) and pH of the solution was adjusted to 5–6 by addition of dilute hydrochloric acid. Formaldehyde (37% solution,

2.5 ml) was added, the mixture was stirred for 30 minutes, sodium cyanide (2 g) was added portionwise and the mixture was again stirred for 1 hour. The hydrogen cyanide, dissolved in the reaction mixture, was driven out by a small amount of solid CO_2 and the solution was taken down *in vacuo*. The residue was dried by distilling a benzene-ethanol mixture from it and was extracted with boiling toluene (4×50 ml). Filtration and crystallization afforded 5.5 g of the product, melting at 157°C . For $\text{C}_9\text{H}_{15}\text{N}_5$ (193.5) calculated: 55.93% C, 7.82% H, 36.24% N; found: 55.89% C, 7.90% H, 36.00% N.

7-(Aminoethyl)amino-1,3,5-triazaadamantane (VI)

a) A solution of *V* (3 g) in warm dioxane (150 ml) was added dropwise in the course of 15 minutes into a boiling solution of lithium aluminium hydride (1.5 g) in dioxane (150 ml) and the mixture was boiled for 30 minutes. To the cooled mixture ethanol, followed by a concentrated NaOH solution, was added dropwise, the mixture was taken down *in vacuo*, the residue dried by distilling off butanol and extracted with boiling toluene (3×100 ml). The extracts were taken down and the residue was crystallized from a toluene-heptane (1 : 1) mixture and from benzene-hexane. The product (1.2 g) was dried over sodium and melted at $101-102^\circ\text{C}$. For $\text{C}_9\text{H}_{19}\text{N}_5$ (197.3) calculated: 54.79% C, 9.71% H, 35.00% N; found: 54.68% C, 10.01% H, 35.20% N.

b) The compound *V* (1 g) in benzene-ethanol (1 : 1) mixture (50 ml) was reduced with sodium (2 g) during 15 minutes. The mixture was decomposed with water and taken down, the residue dried by distillation of butanol and extracted three times with boiling toluene. Evaporation of the solvent afforded 0.6 g of a yellow solid consisting of *II*, 7-methylamino-1,3,5-triazaadamantane, and *VI*.

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