HETEROADAMANTANES AND THEIR DERIVATIVES.

13.* SYNTHESIS OF 1-AZAADAMANTANE AND SOME DERIVATIVES OF IT

A. I. Kuznetsov and A.-M. Béér

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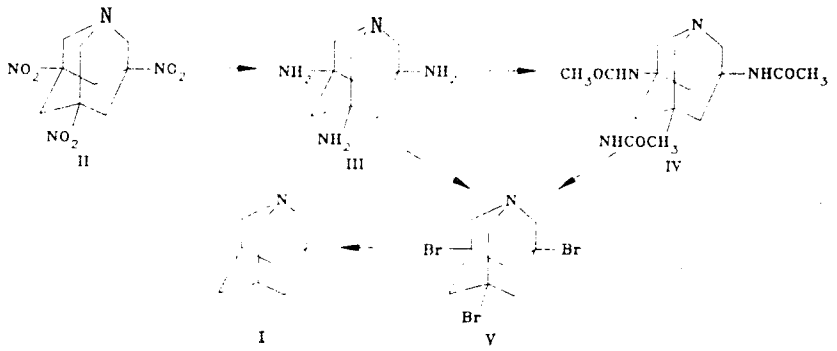
3,5,7-Tribromo-1-azaadamantane is made by the action of sodium nitrite on 3,5,7-triamino-1-azaadamantane in concentrated hydrobromic acid. The reduction of this compound with hydrazine hydrate in the presence of a nickel catalyst gives 1-azaadamantane.

1-Azaadamantane I and its derivatives with functional groups in bridgehead positions are difficult to prepare and virtually unstudied. The previously described 3,5,7-trinitro-1-azaadamantane (II) [2, 3] can serve as the starting compound for their syntheses. Compound II is obtained by the action of formaldehyde on the initial, unisolated product of the reduction of picric acid with sodium borohydride and then of ammonia [3].

The reduction of trinitroazaadamantane, II, with hydrazine hydrate over a nickel catalyst leads to the formation of 3,5,7-triamino-1-azaadamantane (III), which was obtained previously, in lesser yield, by the reduction of compound II with tin(II) chloride [2]. The action of acetic anhydride on triamine III gives 3,5,7-triacetylamino-1-azaadamantane (IV), which separates as an acetate, as shown by the presence in its IR spectrum of amide and carboxyl group absorption bands at 1640 and 1740 cm^{-1}, respectively.

Substitutive deamination of triaminoazaadamantane III with sodium nitrite in concentrated hydrobromic acid gives 3,5,7-tribromo-1-azaadamantane (V) [4], which is also formed by heating triamide IV in concentrated hydrobromic acid.



The analogous transformation under identical conditions is also characteristic of 1-acetylaminoadamantane [5].

By reducing tribromoazaadamantane V with hydrazine hydrate in the presence of Raney nickel in the procedure we described previously for the synthesis of 1,3,5-triazaadamantane [6], 1-azaadamantane is obtained. Completion of the last step finishes the development of a new procedure for preparing 1-azaadamantane.

*For Communication 12, see [1].

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EXPERIMENTAL

The IR spectra were recorded on a Specord IR-71 instrument in mineral oil, the PMR spectra, on a Bruker WM-250 instrument in $CDCl_3$ with HMS as an internal standard. The elementary analyses of the new compounds for C, H, N, and Br corresponded to the calculated values.

3,5,7-Trinitro-1-azaadamantane (II). A solution of 9.08 g (240 mmoles) of sodium borohydride in 45 ml of water is added dropwise, with stirring, to a suspension of 12.0 g (52 mmoles) of 2,4,6-trinitrophenol in 300 ml of a 1.5% aqueous solution of NaOH at a temperature of 10-13°C. The mixture is held at this temperature for 20 min after which 28 ml of 34% formalin and of concentrated orthophosphoric acid are added simultaneously, drop by drop. As a result, the pH of the reaction mixture is lowered to 8.5. By adding orthophosphoric acid, the pH is brought to 5.0 and the mixture is stirred without cooling for 2 h. The precipitate settling out is filtered off, and 8.34 g of a mixture of the cis and trans isomers of 1,3,5-trinitro-1,3,5-trihydroxymethylcyclohexane is obtained. This is stirred with 400 ml of water for 1 h. To the suspension that is formed, 8.3 ml of 10% aqueous ammonia is added dropwise at 10°C, and the mixture is stirred for 5 h as the temperature is gradually raised to room temperature. The deposit that forms over 2 days is filtered off and extracted with acetone. The acetone solution is passed through a thin layer of Al_2O_3 and evaporated. The resultant product is purified by sublimation. Yield 0.96 g (8% based on the picric acid) of trinitroazaadamantane II. T_{mp} 267.5-268.0°C. According to [3], T_{mp} is 267.0-267.5°C. IR spectrum: 1540, 1345 cm^{-1} (NO_2). PMR spectrum: 3.42 (6H, s, 3 NCH_2C), 3.00 and 2.80 ppm (6H, 2 d, 3 CCH_2C, J_{AB} = 13 Hz).

3,5,7-Triamino-1-azaadamantane (III). Over a period of 12 h, 8 ml of hydrazine hydrate is added, with stirring, to a mixture of 5.0 g (27.4 mmoles) of azaadamantane II, 100 ml of isopropyl alcohol, and 0.1 g of Raney nickel while the temperature of the reaction mixture is held at 50°C (±5°C), a fresh portion of catalyst being added every 4 h. The nickel is filtered off, the filtrate evaporated, and the residue recrystallized from toluene. The yield is 3.05 g (91%) of triaminoazaadamantane III, T_{mp} 87.0-88.0°C. According to [2], T_{mp} is 88.0-90.0°C. IR spectrum: 3350-3010 cm^{-1} (NH_2). PMR spectrum: 2.65 (6H, s, 3 NCH_2C), 1.59 (6H, s, 3 CCH_2C), 2.24 ppm (2H, s, NH_2).

3,5,7-Triacetylamino-1-azaadamantane Acetate (IV, $C_{17}H_{28}N_4O_5$). A mixture of 0.55 g (3 mmoles) of azaadamantane III and 5 ml of acetic anhydride is boiled for 3 h, 5 ml of ethyl alcohol is added, and, after being boiled for another 15 min, the mixture is evaporated to dryness. The residue is washed with 3 × 3 ml of toluene. The yield is 1.0 g (95%) of the acetate of triacetylaminoazaadamantane IV, T_{mp} 233.0°C (with decomp.). IR spectrum: 3240, 3040, 1740, 1640 cm^{-1} (COOH and CONH).

3,5,7-Tribromo-1-azaadamantane (V, $C_9H_{12}Br_3$). **A.** A mixture of 1.0 g (5.5 mmoles) of compound III and 10 ml of concentrated HBr is cooled to 0-5°C and a solution of 1.8 g (26.1 mmoles) of sodium nitrite in 4 ml of water is added to it with stirring over a period of 0.5 h. Stirring is continued without cooling for 2 h. The mixture is neutralized with a 40% solution of alkali and extracted with chloroform (5 × 20 ml). The extract is passed through a thin layer of silica gel and the solvent evaporated. The product is purified by sublimation. The yield is 0.67 g (32%) of tribromoazaadamantane V, T_{mp} 156-157°C. PMR spectrum: 3.32 (6H, s, 3 NCH_2C), 2.89 and 2.86 ppm (6H, 2 d, 3 CCH_2C, J_{AB} = 2.2 Hz).

B. A mixture of 0.6 g (1.6 mmoles) of azaadamantane acetate IV and 4 ml of concentrated HBr is boiled for 20 h, evaporated down, and the residue dissolved with potash and extracted with chloroform. The extract is passed through a thin layer of silica gel, the solvent evaporated, and the residue sublimed. The yield is 0.26 g (42%) of tribromoazaadamantane V, completely identical with that obtained by procedure **A**.

1-Azaadamantane (I). A mixture of 0.5 g (1.3 mmoles) of compound V, 0.16 g (3.9 mmoles) of NaOH, 0.1 g of Raney nickel, and 20 ml of ethyl alcohol is heated to boiling, and 2 ml of hydrazine hydrate in 3 ml of ethyl alcohol is added to it gradually with stirring. After 9 h, the nickel is filtered off and the filtrate evaporated. The residue is extracted with hot acetone (5 × 5 ml), the solvent distilled off, and the residue sublimed. The yield is 0.152 g (84%) of compound I. T_{mp} 254-255°C (in a sealed capillary). According to [7], T_{mp} is 255-256°C. PMR spectrum: 3.00 (6H, s, 3 NCH_2C), 1.95 (6H, s, 3 CCH_2C), 1.65 ppm (1H, s, ≡CH).

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