HETEROADAMANTANES AND THEIR DERIVATIVES.

4.* SYNTHESIS OF 1,3,5-TRIAZAADAMANTANE

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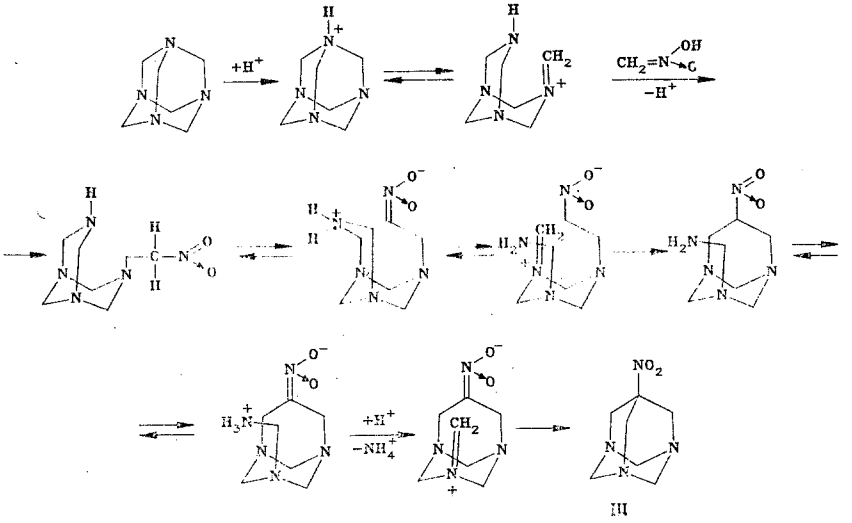
Reduction of 7-nitro-1,3,5-triazaadamantane with hydrazine hydrate in the presence of Raney nickel gave 7-hydroxyamino- and 7-amino-1,3,5-triazaadamantane, from which 7-chloro-, 7-bromo-, and 7-thiocyanato-1,3,5-triazaadamantanes were synthesized by substitutive deamination. Desulfurization of 7-thiocyanato-1,3,5-triazaadamantane in the presence of Raney nickel gave 1,3,5-triazaadamantane.

1,3,5-Triazaadamantane (I) was first synthesized thrity years ago by a complicated multistep method in 11% yield [2]. Later it was obtained by the reduction of 7-bromo-1,3,-5-triazaadamantane (II) with zinc in alkaline medium [3]. This heteroanalog of adamantane is not only theoretically important but also of definite practical interest [4] because some of its derivatives have antiviral activity [5]. It therefore became necessary to develop simpler and more convenient methods for the synthesis of triazaadamantane.

The present work presents an investigation of new methods for synthesizing triazaadamantane (I) from functional derivatives that have become readily available recently.

The starting material for the synthesis was 7-nitro-1,3,5-triazaadamantane (III), which was first obtained by the condensation of nitromethane with paraformaldehyde and ammonium acetate [6], and later by the condensation of nitromethane with hexamethylenetetramine in the presence of acetic acid [7-9]. The latter is a unique modification of the Mannich reaction in which the C–H acid component is nitromethane and hexamethylenetetramine is simultaneously the ammonium component and the source of methylene groups. On the basis of data on the mechanism of the Mannich reaction we assume that III forms by the following scheme:



III

III has been reduced to 7-amino-1,3,5-triazaadamantane (IV) by various methods [3,6-9]. We have showed that the most convenient reductant, and the easiest to use, is hydrazine hydrate; it permits the reaction to be carried out easily in the presence of a nickel catalyst

*For Communication 3, see [1].

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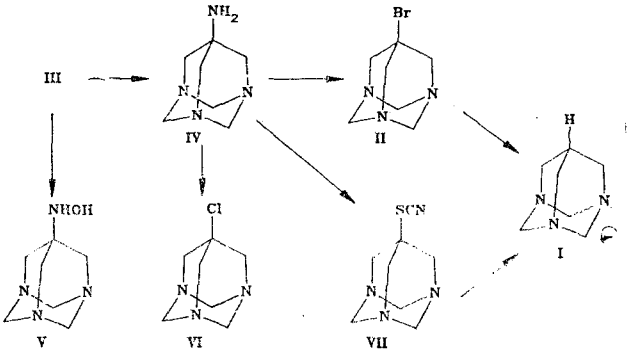
at 50° and atmospheric pressure. Reducing the temperature to 10° and reducing the hydrazine hydrate concentration by 20% gives 7-hydroxyamino-1,3,5-triazaadamantane (V) in 67% yield; it has been obtained by another method [11] in 43% yield.

In a previous study of the substitutive deamination of IV under various conditions, we found [12] that it reacts with sodium nitrite and concentrated hydrochloric or hydrobromic acid via the diazo compound and replacement of the diazo group to give 7-chloro-1,3,5-triazaadamantane (VI) in 49% yield, and the bromo compound II in 52% yield.



By an analogous route, the reaction of amine IV with sodium nitrite, potassium thiocyanate and sulfuric acid gave the hitherto unknown 7-thiocyanato-1,3,5-triazaadamantane (VII). When VII is heated with Raney nickel, desulfurization takes place easily with replacement of the thiocyanate group by hydrogen to give triazaadamantane I in 42% yield.

We have shown [13] that in the reduction of bromo compound II, hydrazine hydrate as reductant in the presence of Raney nickel gives I in quantitative yield, whereas by the previously known method [3] the yield did not exceed 31%.

The structures of the synthesized compounds were confirmed by IR and PMR spectra. The IR spectrum of IV has the characteristic absorption band of the amino valence vibrations at 3250 cm^{-1}. The presence of -NH and -OH bonds in hydroxylamine V is confirmed by the broad valence vibration bands at 3130 and 3210 cm^{-1}. In VII the thiocyanate valence vibrations appear in the 2170 cm^{-1} region.

Triazaadamantane derivatives have a quite simple and characteristic PMR spectrum. The signal of the resonance absorption of the six protons of the three N—CH_2—C methylenes appears as a singlet in the 3.10-3.80 ppm region. The signals of the six protons of the three aminal N—CH_2—N methylenes form an AB system with its center in the 4.22-4.46 ppm region (J = 12 Hz). The splitting at the singlet and doublet of the AB system in the stronger field points to further interactions among the respective protons. This signal can be assigned to protons located axially with respect to a triazacyclohexane ring, because only they are located in a "W" formation with respect to the N—CH_2—C protons.

The doublet of the AB system that is located in the weaker field corresponds to protons in an equatorial position with respect to a triazacyclohexane ring.

Furthermore the spectra of I and amine IV contain singlets in the 1.29 and 1.40 ppm regions that belong to the $C_{(7)}$ proton and the amino protons, respectively.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument, in mineral oil and KBr tablets. PMR spectra were recorded on a Jeol 4H-100 instrument in $CHCl_3$, with TMS internal standard.

7-Amino-1,3,5-triazaadamantane (IV). To a mixture of 100 g (540 mmole) of nitro derivative III (obtained according to [9]), 140 ml of water, 10 ml of isopropyl alcohol, and 8 g of freshly prepared Raney nickel was added 60 ml of hydrazine hydrate, dropwise with stirring over 2 h, so that the temperature of the reaction mixture did not exceed 40-50°. After 2 h another 2 g of catalyst was added and mixing was continued for 2 h. The nickel was filtered off, the filtrate was evaporated to dryness, and the residue was recrystallized from toluene. There was obtained 75.2 g (90.3%) of IV, mp 295-297° (sublimes). According to [3], mp 303-305°. IR spectrum: 3250 cm^{-1} (NH_2). PMR spectrum ($CHCl_3$): 1.40 (2H, s, C—NH_2); 3.16 (6H, s, N—CH_2—C); 4.03 and 4.41 ppm (6H, 2d, N—CH_2—N, J_{AB} = 12 Hz). Found: C 54.8 H 9.2 N 36.0%. M 154. $C_7H_{14}N_4$. Calculated: C 54.5; H 9.2; N 36.3%; M 154.

7-Hydroxylamino-1,3,5-triazaadamantane (V). A mixture of 2 g (11 mmole) of III, 20 ml of water, and 0.2 g of Raney nickel was cooled to 10° and 1 ml of hydrazine hydrate was added with stirring. Stirring was continued for 2 h. The nickel was filtered off. The filtrate was evaporated and extracted with 2 ml of cold water. After evaporation of the water the residue was washed free of IV with 10 ml of hot acetone, to give 1.13 g (67%) of practically pure V, mp 228-229°. According to [11], mp 228°. IR spectrum, in KBr tablet: 3130 (NH); 3210 cm^{-1} (OH). Found: C 49.6; H 8.2; N 32.5%; M 170. $C_7H_{14}N_4O$. Calculated: C 49.4; H 8.3; N 32.9%; M 170.

Removal of the acetone gave 0.48 g (31.2%) of IV, identical in IR and PMR spectra and elemental composition with IV obtained in the preceding experiment.

7-Bromo-1,3,5-triazaadamantane (II). To a mixture of 19.2 g (125 mmoles) of IV and 80 ml of concentrated hydrobromic acid cooled to 0-5° was added a solution of 9.6 g (139 mmoles) of sodium nitrite in 60 ml of water with vigorous stirring over 30 min, and stirring was continued without cooling for 30 min. The mixture was neutralized with 40% NaOH solution and extracted with chloroform (5 × 50 ml). The chloroform was distilled off and the residue was recrystallized from toluene. There was obtained 14.4 g (52.9%) of II, mp 217.5-218.5°. According to [3], mp 217-218°. PMR spectrum ($CHCl_3$): 3.78 (6H, s, N—CH_2—C); 4.27 and 4.51 ppm (6H, 2d, N—CH_2—N, J_{AB} = 12 Hz). Found: C 38.6; H 5.5; Br 36.3%; M 218. $C_7H_{12}BrN_3$. Calculated: C 38.5; H 5.6; Br 36.6%; M 218.

7-Chloro-1,3,5-triazaadamantane (VI). Similarly to the preceding procedure, a mixture of 19.2 g (125 mmole) of IV, 80 ml of conc. HCl, and a solution of 9.6 g (139 mmole) of sodium nitrite in 60 ml of water at 0-5° gave 10.76 g (49.7%) of VI, mp 224-226°. According to [3], mp 224-225°. PMR spectrum ($CHCl_3$): 3.55 (6H, s, N—CH_2—C); 4.12 and 4.40 ppm (6H, 2d, N—CH_2—N, J_{AB} = 12 Hz). Found: C 48.8; H 7.1; Cl 20.1%; M 173. $C_7H_{12}ClN_3$. Calculated: C 48.4; H 7.0; Cl 20.4%; M 173.

7-Thiocyanato-1,3,5-triazaadamantane (VII). To a mixture of 7.7 g (50 mmoles) of IV, 150 ml of 12% hydrochloric acid and 15.8 g (160 mmoles) of potassium thiocyanate cooled to 0-3° was added a solution of 4.2 g (60 mmoles) of sodium nitrite in 75 ml of water over 20 min with stirring. After mixing for 15 min the mixture was neutralized with 40% NaOH solution and extracted with chloroform (5 × 50 ml). The chloroform was distilled off and the residue was recrystallized from isopropyl alcohol. There was obtained 4.15 g (42.2%) of VII, mp 160-161°. IR spectrum: 2170 cm^{-1} (SCN). PMR spectrum ($CHCl_3$): 3.71 (6H, s, N—CH_2—C); 4.26 and 4.53 ppm (6H, 2d, N—CH_2—N, J_{AB} = 12 Hz). Found: C 49.0; H 6.2; N 28.2; S 16.5%; M 196. $C_8H_{12}N_4S$. Calculated: C 49.0; H 6.2; N 28.5; S 16.3%; M 196.

1,3,5-Triazaadamantane (I). A. A mixture of 3.76 g (17.2 mmoles) of bromo compound II, 1 g of NaOH, 0.6 g of Raney nickel, and 40 ml of ethyl alcohol was heated to boiling, and 2 ml o hydrazine hydrate was added dropwise with stirring. After 3.5 h the nickel was filtered off, the alcohol was distilled off, and the residue was extracted with hot benzene (3 × 50 ml). The benzene was distilled off and the crystalline residue was purified by vacuum sublimation. There was obtained 2.28 g (95%) of 1,3,5-triazaadamantane, mp. 256-257°. According to [3], mp 256-258°. PMR spectrum ($CHCl_3$): 1.29 (2H, s, C—H); 3.59 (6H, s, N—CH_2—C); 4.36 and 4.56 ppm (6H, 2d, N—CH_2—N, J_{AB} = 12 Hz). Found: C 60.5; H 9.6; N 29.8%; M 139. $C_7H_{13}N_3$. Calculated: C 60.4; H 9.4; N 30.2%; M 139.

B. To a boiling solution of 2 g (10 mmoles) of thiocyanato derivatives VII in 30 ml of isopropyl alcohol were added four 2-g portions of freshly prepared Raney nickel at 15-min intervals with vigorous stirring. Stirring was continued for another 30 min. The nickel was filtered off, the isopropyl alcohol was distilled off, and the residue was recrystallized from toluene. There was obtained 0.88 g (60.3%) of material identical in melting point, PMR spectrum, and elemental composition with that obtained by method A.

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TETRAZOLES.

20.* TETRAZOLIUM SALTS IN INTERPHASE CATALYSIS

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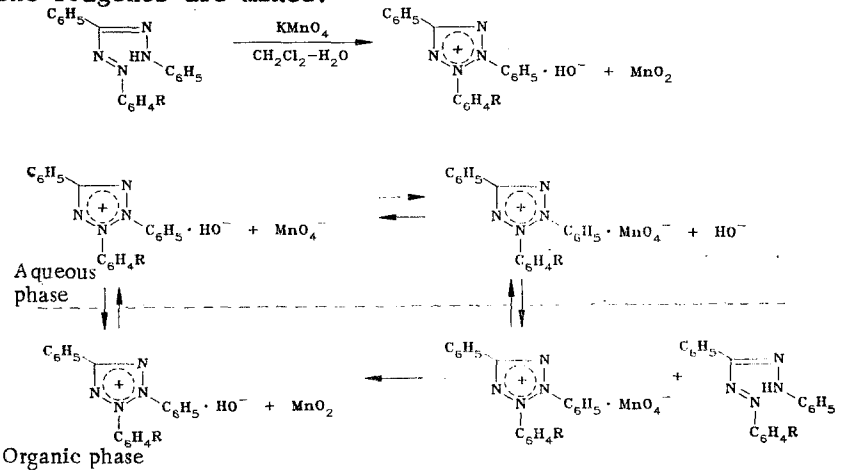
Oxidation of substituted triaylformazanes by potassium permanganate in a two-phase organic solvent–water system in the presence of catalytic amounts of tetrabutylammonium bromide gives the corresponding tetrazolium salts, which are interphase transfer catalysts in oxidation, alkylation, and esterification. From distribution coefficient data it is concluded that 2,3,5-triphenyltetrazolium chloride has less catalytic activity than 2,5-diphenyl-3-(m-nitrophenyl)-tetrazolium bromide.

The substantial interest in tetrazolium salts in recent years is related to their use in medicine [2, 3] and in new silver-free photographic materials [4]. The principal method for synthesizing tetrazolium salts is the oxidation of formazanes. In the numerous variants of this method the oxidants are alkyl nitrites [5], lead tetracetate [6], silver nitrate [7], bromine [8], and other reagents [9]. Nevertheless because of the unsatisfactory reproducibility of the results it is difficult to give preference to any of those oxidants. It was therefore of interest to study formazane oxidation by interphase catalysis. For this purpose substituted arylformazans were chosen to be oxidized at 25° by potassium permanganate in a two-phase organic solvent–water system in the presence of tetrabutylammonium bromide. Under these conditions formazane oxidation is rapid and is finished within 15-20 min after the reagents are mixed.



*Communication 19, see [1].

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