

## SYNTHESIS OF 1-AZAADAMANTANE AND ITS DERIVATIVES\*

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A simplified synthesis of 1-azaadamantane from 1,3,5-tris(hydroxymethyl)cyclohexane has been accomplished by passing its vapours together with ammonia over alumina. Some salts as well as also some quaternary salts of 1-azaadamantane have been prepared.

1-Azaadamantane is one of the nitrogen analogues of adamantane which for its relative difficult synthesis has so far not been sufficiently investigated in respect to its reactivity as well as to its physiological activity. In continuation of earlier work<sup>1,2</sup>, we aimed at the preparation of 1-azaadamantane by a more simple procedure. The starting material, as in the previous case<sup>1,2</sup>, was 1,3,5-trimethylbenzene which on oxidation afforded 1,3,5-benzenetricarboxylic acid from which both the methyl and ethyl esters were prepared and by their hydrogenation the corresponding esters of 1,3,5-cyclohexanetricarboxylic acid. Reduction of the ester with lithium aluminium hydride gave 1,3,5-tris(hydroxymethyl)cyclohexane which in contrast to the previous described purification by distillation, where on processing a larger quantity polymerization may easily occur, was now purified by extraction with dioxane followed by crystallisation. 1,3,5-Tris(hydroxymethyl)cyclohexane purified in this way was directly converted to 1-azaadamantane by passing it in a current of ammonia over  $Al_2O_3$ . The yields of 1-azaadamantane at different temperatures and different space velocities are given in Table I. From 1-azaadamantane thus obtained a number of quaternary salts listed in Table II have been prepared.

## EXPERIMENTAL

The melting points are uncorrected.

1,3,5-Benzenetricarboxylic acid was prepared by oxidation of 1,3,5-trimethylbenzene (195 g) with potassium permanganate (2 kg) in water (5 litres) at 80°C. The work-up was identical with the previously described procedure<sup>1,2</sup>. The acid was recrystallised from hot water; m.p. 380°C, yield 67%. (Ref.<sup>1,2</sup> gives m.p. 280°C which is evidently a misprint, since the right m.p. is 380°C).

\* Part III in the series Nitrogen Compounds of Adamantane; Part II: This Journal 38, 1101 (1973).

*Trimethyl 1,3,5-benzenetricarboxylate* was prepared by esterifying 1,3,5-benzenetricarboxylic acid with methanol and gaseous hydrogen chloride; m.p. 145°C, yield 74%. Ref.<sup>3</sup> gives m.p. 145–146°C.

*Trimethyl 1,3,5-cyclohexanetricarboxylate* was prepared by hydrogenation trimethyl 1,3,5-benzenetricarboxylate in the presence of  $\text{PtO}_2$ ; m.p. 46°C, yield 95%. Ref.<sup>4</sup> gives m.p. 43–45°C.

*1,3,5-Tris(hydroxymethyl)cyclohexane*. To a solution of lithium aluminium hydride (17 g) in ether (500 ml) triethyl 1,3,5-cyclohexanetricarboxylate<sup>2</sup> (40 g) in ether (150 ml) was slowly, dropwise added with continuous stirring. The mixture was heated for 4 h and then allowed to stand undisturbed overnight. The reaction product was decomposed with water (30 ml) and ethanol (60 ml) under continuous stirring. The resulting precipitate was filtered off with suction and washed with boiling ethanol. The ethanolic extracts were combined and evaporated to dryness. The residue was then extracted in a Soxhlet apparatus with dioxane. After concentrating the solution, 1,3,5-tris(hydroxymethyl)cyclohexane crystallised; m.p. 111–112°C, yield 77%. The reduction of the methyl ester by the same procedure takes place in 55% yield.

*1-Azaadamantane*. This compound was prepared catalytically in a flow apparatus consisting of a glass reactor packed with glass spheres. In the broadened part of the reactor of 12 mm diameter the catalyst bed was situated. Below the reactor was attached a freezing trap immersed in a cooling bath at a temperature of  $-20^\circ\text{C}$ . 1,3,5-Tris(hydroxymethyl)cyclohexane was fed from an oblique glass reservoir mounted at the top of the reactor under simultaneous introduction of ammonia (35 ml/min). The temperature was measured with a thermocouple extending into the middle of the catalyst bed. Example of the experiment. The reactor containing as catalyst  $\text{Al}_2\text{O}_3$  (4 g) of 0.8–1.0 mm grain size (Chemické závody ČSSP, Záluží) was heated in electric furnace to  $300^\circ\text{C}$  for one hour, while a steady stream of ammonia is passed from a cylinder. The reaction products were collected in methanol (2 ml) contained in the freezing trap immersed in the cooling bath. 1,3,5-Tris(hydroxymethyl)cyclohexane was fed in the above manner (from the glass reservoir by gently striking it) at a rate of one g every two hours. When the reaction was over, ammonia was passed into the reactor for another hour. After the temperature of the freezing

TABLE I  
Dependence of 1-Azaadamantane Content on Reaction Temperature

Experiment	Temperature $^\circ\text{C}$	Feeding rate $\text{mmol}^{-1} \text{ h kg cat.}$	1-Azaadamantane mass-% <sup>a</sup>
1	250	0.174	—
2	300	0.174	1.9
3	325	0.174	6.7
4	350	0.174	4.0
5	375	0.174	9.5
6	350	0.697	8.2
7	300	0.697	8.6
8	300	1.393	6.4

<sup>a</sup> 1-Azaadamantane content determined by gas chromatography using the direct method.

TABLE II  
Survey of the Quaternary 1-Azaadamantane Salts Prepared

Quaternary 1-azaadamantane salt	Mol. weight	M.p., °C	Calculated/found, %			
			Br	N	Br	N
1-Methyl-1-azoniaadamantane iodide	279.2	>400 decomp.	—	5.02 <sup>a</sup>	—	5.01
1-Ethyl-1-azoniaadamantane bromide	246.2	>400 decomp.	32.46	5.69	32.33	5.40
1-Propyl-1-azoniaadamantane bromide	260.1	>400 decomp.	30.73	5.38	30.80	5.45
1-Isopropyl-1-azoniaadamantane bromide	260.1	>400 decomp.	30.75	5.38	30.45	5.70
1-Butyl-1-azoniaadamantane bromide	274.3	>400 decomp.	29.13	5.11	29.31	5.20
1-Pentyl-1-azoniaadamantane bromide	288.3	318—320	27.72	4.86	27.21	5.00
1-Hexyl-1-azoniaadamantane bromide	302.3	298—300	26.44	4.63	26.33	4.45
1-Allyl-1-azoniaadamantane bromide	258.2	284—285	30.95	5.42	31.36	5.23
1-Benzyl-1-azoniaadamantane chloride	263.7	342—344	—	5.31 <sup>b</sup>	—	5.13
1-Hydroxyethyl-1-azoniaadamantane chloride	217.7	>400 decomp.	—	6.43 <sup>c</sup>	—	6.34
1-(2-Bromoethyl)-1-azoniaadamantane bromide	325.1	246—247	49.16	4.31	48.80	4.63
1-(6-Bromohexyl)-1-azoniaadamantane bromide	381.2	200—201	41.93	3.67	41.45	3.73
1,6-(Hexamethylene)-bis(1-azoniaadamantane bromide)	518.4	293—294	30.83	5.40	30.35	5.46

<sup>a</sup> Calculated: 45.46% I, found: 46.00% I. <sup>b</sup> Calculated: 13.44% Cl, found: 13.21% Cl. <sup>c</sup> Calculated: 16.28% Cl, found: 16.24% Cl.

trap had been equalized with the ambient temperature, the liquid in the trap was worked up. The reaction products dissolved in methanol were acidified with dilute hydrochloric acid (1 : 3) and subjected to steam distillation. In this way were removed the neutral components formed during the reaction. Concentrated sodium hydroxide solution was then added dropwise and the mixture again steam distilled. The distillate which contains volatile bases was neutralised with hydrochloric acid and then evaporated under reduced pressure to dryness. The residue was treated with 10 ml of benzenesulphonyl chloride and 10 ml of sodium hydroxide. The mixture was heated, then shaken in a shaking funnel to the loss of the sulphochloride odour, and finally it was subjected to steam distillation. The distillate was titrated with 0.1M-HCl to methyl red, filtered with active charcoal, and evaporated. The residue was dissolved in water, treated with ether and the base set free with sodium hydroxide. After filtering, the ether was distilled off through a short Vigreux column. The residue consisted of 1-azaadamantane. The molecular mass was determined on a mass spectrometer. Yield about 9%, m.p. 254—255°C (ref.<sup>1,2</sup> gives m.p. 257—258°C). The mixed melting point with a standard specimen of 1-azaadamantane is undepressed. For C<sub>9</sub>H<sub>15</sub>N (137.2) calculated: 78.77% C, 11.02% H, 10.21% N; found: 78.59% C, 11.18% H, 10.08% N.

*Hydrochloride.* A solution of 0.1 g of 1-azaadamantane in water was neutralised with dilute hydrochloric acid to methyl red, then filtered with active charcoal and evaporated. The residue

was crystallised from ethanol. The hydrochloride thus obtained did not melt up to 400°C. For  $C_9H_{16}ClN$  (173.7) calculated: 62.23% C, 9.29% H, 8.07% N, 20.41% Cl; found: 62.02% C, 9.28% H, 8.01% N, 19.95% Cl.

*Hydrobromide.* The hydrobromide prepared in a similar manner as the hydrochloride melted above 400°C. For  $C_9H_{16}BrN$  (218.2) calculated: 49.55% C, 7.39% H, 6.42% N, 36.63% Br; found: 50.04% C, 7.63% H, 6.56% N, 36.53% Br.

*The picrate* prepared from 1-azaadamantane and an ethereal solution of picric acid had m.p. 304–305°C (ethanol). For  $C_{15}H_{18}N_4O_7$  (366.1) calculated: 49.17% C, 4.92% H, 15.30% N; found: 49.18% C, 5.09% H, 15.20% N.

*Quaternary salts of 1-azaadamantane.* To a solution of 0.1 g of 1-azaadamantane in ether (10 ml) an excess of the appropriate alkyl halide or alkylene dihalide was added. The mixture was shaken and then left standing at room temperature. The reaction time depended on the reactivity of the alkyl halide. Most rapidly reacted alkyl halides with a short straight chain (the precipitate was deposited immediately or after a short while), and the slowest reacted alkyl halides with a branched chain (isopropyl bromide required several days). The resulting precipitate was washed several times with ether and dried. In this manner were prepared the quaternary salts presented in Table II.

*1,6-(Hexamethylene)bis(1-azoniaadamantane bromide).* 1-Azaadamantane (0.1 g) was dissolved in benzene (5 ml) and the solution was treated with 1,6-dibromohexane (0.09 g), whereupon the mixture was heated in a sealed tube at 200°C for 4 h. The resulting product was filtered off with suction, on the filter washed with hot benzene and dried; m.p. 293–294°C. For  $C_{24}H_{42}Br_2N_2$  (518.4) calculated: 5.40% N, 30.83% Br; found: 5.46% N, 30.35% Br.

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