

## 1,3,5-TRIAZAADAMANTANE AND ITS DERIVATIVES\*

V. GALÍK, M. ŠAFÁŘ, Z. KAFKA and S. LANDA

*Laboratory of Synthetic Fuels,**Institute of Chemical Technology, 166 28 Prague 6*

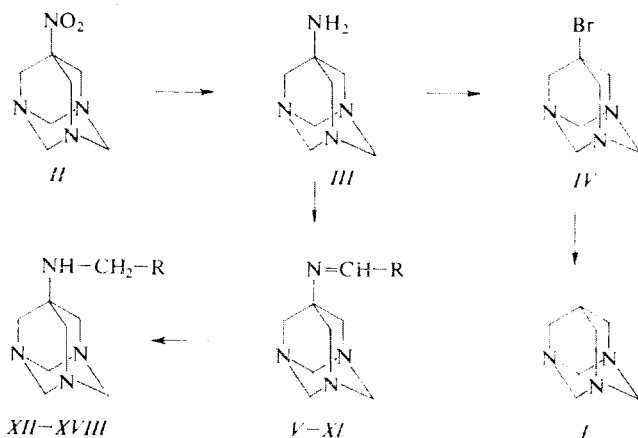
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A new synthesis of 1,3,5-triazaadamantane (*I*) is described starting with 7-nitro-1,3,5-triazaadamantane (*II*) which was reduced with zinc to 7-amino-1,3,5-triazaadamantane (*III*). The latter served as starting material for the preparation of corresponding bromo derivative *IV* and chloro derivative *IVa* which on dehalogenation with zinc afforded *I*. From 7-amino-1,3,5-triazaadamantane a series of aldimines was prepared, affording corresponding amines on hydrogenation.

In connection with the study of nitrogen analogues of adamantane<sup>1</sup> with a possible physiological activity we now prepared 1,3,5-triazaadamantane (*I*) by a new route. 7-Nitro-1,3,5-triazaadamantane (*II*) served as starting material which was prepared from formaldehyde, ammonium acetate and nitromethane. Reduction of *II* with zinc in alkaline medium gave 7-amino-1,3,5-triazaadamantane (*III*). Reduction with aluminum amalgam takes place with the same yield. Reduction of 7-nitro-1,3,5-triazaadamantane with lithium aluminum hydride is described in a patent<sup>2</sup>. Reaction of *III* with sulfuric acid, potassium bromide and sodium nitrite gave 7-bromo-1,3,5-triazaadamantane (*IV*). 7-chloro derivative *IVa* was also prepared in a similar manner. Dehalogenation of compound *IV* with zinc and ethanolic sodium hydroxide solution gives 1,3,5-triazaadamantane (*I*). Its reaction with aldehydes gave the following aldimines: (1,3,5-triaza-7-adamantyliminomethyl)benzene (*V*), 4-dimethylamino-(1,3,5-triaza-7-adamantyliminomethyl)benzene (*VI*), 4-chloro-(1,3,5-triaza-7-adamantyliminomethyl)benzene (*VII*), 4-methoxy-(1,3,5-triaza-7-adamantyliminomethyl)benzene (*VIII*), 4-(1,3,5-triaza-7-adamantyliminomethyl)pyridine (*IX*), 3-(1,3,5-triaza-7-adamantyliminomethyl)pyridine (*X*), 1-(1,3,5-triaza-7-adamantyliminomethyl)propane (*XI*).

On hydrogenation of these aldimines on platinum the corresponding secondary amines were obtained: 7-benzyl- (*XII*), 7-(4-dimethylaminobenzyl)-(*XIII*), 7-(4-chlorobenzyl)- (*XIV*), 7-(4-methoxybenzyl)- (*XV*), 7-(4-picoly)- (*XVI*), 7-(3-picoly)- (*XVII*), 7-(1-butyl)-amino-1,3,5-triazaadamantane (*XVIII*). Reaction with phenylisocyanate gave N-phenyl-N'-(1,3,5-triaza-7-adamantyl)urea (*XXII*).

\* Part VI in the series Nitrogen Compounds of Adamantane; Part V: This Journal 40, 174 (1975).



- V, XII; R = phenyl  
 VI, XIII; R = 4-dimethylaminophenyl  
 VII, XIV; R = 4-chlorophenyl  
 VIII, XV; R = 4-methoxyphenyl  
 IX, XVI; R = 4-pyridyl  
 X, XVII; R = 3-pyridyl  
 XI, XVIII; R = propyl

## EXPERIMENTAL

The melting points are uncorrected. The purity of all substances was checked by gas chromatography and mass spectrometry on a LKB-9000 instrument.

**7-Nitro-1,3,5-triazaadamantane<sup>2,4</sup>(II).** A mixture of 2 490 ml of 36% formaldehyde, 265.5 g of nitromethane, 1 500 ml of ethanol and 1 156.5 g of ammonium acetate was refluxed under stirring on a water bath for 10 hours, then ethanol was evaporated *in vacuo* and the remaining solution was left to stand overnight. The separated crystals were filtered off under suction and washed with ethanol. Yield 94 g (11.7%) of compound II which after crystallisation from butanol-toluene 1 : 1 melted at 300–302°C. For  $C_7H_{12}N_4O_2$  (184.2) calculated: 45.64% C, 6.56% H, 30.42% N; found: 45.59% C, 6.88% H, 30.44% N.

**7-Amino-1,3,5-triazaadamantane(III).** Substance II (50 g; 0.27 mol) was added under stirring to a solution of 75 g of sodium hydroxide, 200 ml of water and 750 ml of propanol and the mixture was stirred for 15 minutes. Activated zinc dust (100 g; 1.5 mol, washed with dilute hydrochloric acid 1 : 1, neutralized with dilute sodium hydroxide and decanted with water) was then added. The suspended substance dissolved within 15 minutes. The reaction mixture was refluxed for 5 hours, another 50 g (0.75 mol) of zinc dust were added and the mixture refluxed for 1–2 hours and allowed to stand overnight. The product was freed from the solvent by vacuum distillation. The solid residue was extracted with 200 ml of boiling benzene (7 times). The content of III in the residue was controlled by gas chromatography. The filtrates were decolorized with charcoal concentrated and allowed to crystallize. Recrystallization was carried out from benzene-heptane (1 : 1). Yield 28 g (67%), m.p. 303–305°C. For  $C_7H_{14}N_4$  (154.2) calculated: 54.52% C, 9.15% H, 36.34% N; found: 54.80% C, 9.18% H, 36.23% N.

*Reduction of compound II with aluminum amalgam:* The amalgam (prepared from 5.9 g of aluminum foil) was overlaid with 300 ml of ethanol and 10 g (54 mmol) of compound *II* were added, followed by dropwise addition of 48 ml of water under stirring and refluxing, which was continued till complete dissolution. The reaction mixture was filtered and ethanol distilled off in a vacuum. The residue was extracted with boiling tetrahydrofuran, the extract filtered and evaporated. Yield 6.8 g of compound *III*, m.p. 304–305°C, identical with a product prepared on reduction of lithium aluminum hydride or zinc dust.

*7-Bromo-1,3,5-triazaadamantane (IV).* A mixture of 20 ml 1.25M-H<sub>2</sub>SO<sub>4</sub> and 2.6 g of potassium bromide was dissolved under stirring and cooling and 1 g (6.5 mmol) of compound *III* was added and the mixture stirred at –5°C. Sodium nitrite (0.5 g; 7.2 mmol) was then added in small doses to the mixture over 1.5 hours and stirring was continued at 20°C for one hour. The solution was concentrated on a rotatory evaporator to half its volume, decomposed under cooling with a concentrated solution of sodium hydroxide (3 g), and extracted six times with 50 ml portions of benzene. The end of the extraction was followed by gas chromatography. The extraction of the dry alkaline residue is not suitable because in this case the unreacted *III* also passes into the extract. The combined benzene extracts are dried over solid potassium hydroxide, filtered and evaporated. The residue is sublimated at normal pressure at 160–170°C. The crude product may also be purified by crystallization from benzene–heptane (1 : 5). Yield 0.5 g (35%), m.p. 217–218°C (sealed capillary). For C<sub>7</sub>H<sub>12</sub>BrN<sub>3</sub> (218.1) calculated: 38.55% C, 5.54% H, 19.27% N, 36.64% Br; found: 38.95% C, 5.61% H, 18.96% N, 36.60% Br.

*7-Chloro-1,3,5-triazaadamantane (IVa).* A solution of 0.7 g (10 mmol) of sodium nitrite in 10 ml of water was added, to a mixture of 0.5 g (3.7 mmol) of compound *III*, 20 ml of HCl (1 : 5) and 2 g of NaCl, keeping the temperature below –5°C. After addition the mixture was stirred at –10°C for one hour, then evaporated *in vacuo*, extracted four times with ether and evaporated. The residue was crystallized from benzene–heptane (1 : 5). Yield 0.1 g of product which was purified for analysis by preparative gas chromatography; m.p. 224–225°C (sealed capillary). For C<sub>7</sub>H<sub>12</sub>ClN<sub>3</sub> (173.7) calculated: 48.42% C, 6.97% H, 24.20% N, 20.42% Cl; found: 48.47% C, 7.23% H, 24.03% N, 20.14% Cl.

TABLE I  
Yields of Aldimines of 7-Amino-1,3,5-triazaadamantane

No	Aldehyde, g	Amine, g	Yield, %	M.p., °C
<i>V</i>	3.5	5.0	54 <sup>a</sup>	213–214
<i>VI</i>	6.4	6.4	27 <sup>a</sup>	216–217
<i>VII</i>	1.85	2.0	63.2	218–219
<i>VIII</i>	2.3	2.0	70.6	212–213
<i>IX</i>	1.4	2.0	82.1	183–184
<i>X</i>	1.4	2.0	88.5	217–218
<i>XI</i>	4.0 <sup>b</sup>	4.0	33.3 <sup>a</sup>	120–121

<sup>a</sup> After repeated crystallizations; <sup>b</sup> freshly distilled, b.p. 72–73°C.

1,3,5-Triazaadamantane (I). A mixture of 0.5 g (2.3 mmol) of compound IV, 50 ml of ethanol, 2 g of sodium hydroxide, 1 g of zinc dust and 5 ml of water was refluxed under stirring for 4 hours. The reaction was followed by gas chromatography. The solvents were evaporated on a rotatory evaporator and the residue extracted with three 50 ml portions of benzene. The benzene extract was concentrated to a small volume and allowed to stand for crystallization. The crystals were filtered off and recrystallized from a mixture of benzene and heptane (1 : 5). Yield 0.1 g (31%) of a hygroscopic substance. For analysis the sample was purified by preparative gas chromatography, m.p. 256–258°C (sealed capillary). Lit.<sup>3</sup> gives 260°C.

TABLE II

Analyses of Aldimines of 7-Amino-1,3,5-triazaadamantane (V–XI) and 7-Alkylamino-1,3,5-triazaadamantane (XII–XVIII)

No	Formula	Calculated/Found			
		% C	% H	% N	% Cl
V	C <sub>14</sub> H <sub>18</sub> N <sub>4</sub> (242.3)	69.40	7.48	23.12	—
		69.53	7.55	23.16	—
VI	C <sub>16</sub> H <sub>23</sub> N <sub>5</sub> (285.4)	67.34	8.12	24.54	—
		67.21	8.21	24.57	—
VII	C <sub>14</sub> H <sub>17</sub> ClN <sub>4</sub> (276.8)	60.75	6.19	20.24	12.81
		60.84	6.34	20.06	12.71
VIII	C <sub>15</sub> H <sub>20</sub> N <sub>4</sub> O (272.4)	66.15	7.40	20.57	—
		65.89	7.47	20.46	—
IX	C <sub>13</sub> H <sub>17</sub> N <sub>5</sub> (243.3)	64.17	7.04	28.79	—
		64.27	7.10	28.75	—
X	C <sub>13</sub> H <sub>17</sub> N <sub>5</sub> (243.3)	64.17	7.04	28.79	—
		64.26	7.30	28.52	—
XI	C <sub>11</sub> H <sub>20</sub> N <sub>4</sub> (208.3)	63.42	9.68	26.90	—
		63.47	9.68	26.68	—
XII	C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> (244.3)	68.81	8.25	22.93	—
		68.63	8.31	22.82	—
XIII	C <sub>16</sub> H <sub>25</sub> N <sub>5</sub> (287.4)	66.86	8.77	24.37	—
		66.97	8.78	24.50	—
XIV	C <sub>14</sub> H <sub>19</sub> ClN <sub>4</sub> (278.8)	60.31	6.87	20.10	12.72
		60.53	6.82	20.34	12.70
XV	C <sub>15</sub> H <sub>22</sub> N <sub>4</sub> O (274.4)	65.66	8.08	20.42	—
		65.62	7.88	20.63	—
XVI	C <sub>13</sub> H <sub>19</sub> N <sub>5</sub> (245.3)	63.64	7.81	28.55	—
		63.98	7.78	28.60	—
XVII	C <sub>13</sub> H <sub>19</sub> N <sub>5</sub> (245.3)	63.64	7.81	28.55	—
		63.48	7.83	28.45	—
XVIII	C <sub>11</sub> H <sub>22</sub> N <sub>4</sub> (210.3)	62.82	10.54	26.64	—
		62.95	10.55	26.72	—

TABLE III  
Hydrogenation of Aldimines V—XI

No	Aldimine, g	H <sub>2</sub> , ml <sup>a</sup>	Time, h	Yield, %	M.p., °C
XII	1.0	115	2.0	80	172—173
XIII	1.0	110	2.0	80	182—183
XIV	0.5	65	3.0	60	170—171
XV	1.0	120	5.0	80	180—181
XVI	1.0	155	7.0	60 <sup>b</sup>	210—211
XVII	1.0	240	10.0	30 <sup>b</sup>	188—189
XVIII	1.0	120	6.0	40	103—104

<sup>a</sup> Hydrogenated on 0.1 g of PtO<sub>2</sub>; <sup>b</sup> An up to 50% hydrogenation of the pyridine nucleus to piperidine takes place.

*Aldimines of 7-amino-1,3,5-triazaadamantane (V—XI)* were prepared by azeotropic dehydration of a mixture of aldehyde and compound III with benzene (150—400 ml). The following aldehydes were used: benzaldehyde, 4-chloro-, 4-methoxybenzaldehyde and butyraldehyde (Lachema), 3- and 4-pyridinecarbaldehyde (Schuchardt). The reaction mixture was refluxed for 2 hours, benzene was evaporated under reduced pressure and the residue dissolved in boiling toluene-heptane (1 : 1). After filtration the solution was allowed to crystallize. Crystallization was repeated if necessary. In the case of compound XI dehydration was carried out with magnesium sulfate which was located in the cartridge of the Soxhlet extractor above the reaction flask. The substance was crystallized from hexane because the preparation is very soluble. Aldimines hydrolyse well to starting components even with air humidity. The yields are given in Table I. A list of analyses of the compounds prepared is given in Table II.

*7-Alkylamino-1,3,5-triazaadamantanes (XII—XVIII)*. They were prepared on hydrogenation of aldimines V—XI on platinum in ethanol at normal pressure of hydrogen (Table III). The products were purified by crystallization from toluene-heptane (1 : 1). A review of analyses of the compounds prepared is given in Table II.

*Hydrochloride of 7-nitro-1,3,5-triazaadamantane (XIX)*. A mixture of 1 g (5.4 mmol) of compound II and 50 ml of dilute (1 : 5) hydrochloric acid was evaporated in a vacuum to 1/10 its volume, diluted with ethanol to 50 ml volume, evaporated to a final volume of 20 ml and allowed to stand overnight. The crystals were filtered off and washed with ethanol. Yield 0.8 g (67%) of product, m.p. 210°C (decomp.). For C<sub>7</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>2</sub> (220.7) calculated: 38.10% C, 5.94% H, 25.39% N, 16.07% Cl; found: 38.24% C, 5.92% H, 25.36% N, 16.15% Cl.

*Nitrate of 7-nitro-1,3,5-triazaadamantane (XX)*. A solution of 2 g (10.8 mmol) of II in 120 ml of dilute nitric acid (1 : 5) was filtered and evaporated *in vacuo* to half its volume and then diluted with 200 ml of ethanol. The separated crystals were washed with ethanol and dried. Yield 1.7 g (63.6%) of product, m.p. 204°C (decomp.). For C<sub>7</sub>H<sub>13</sub>N<sub>5</sub>O<sub>5</sub> (247.2) calculated: 34.01% C, 5.30% H, 28.33% N; found: 33.99% C, 5.44% H, 28.34% N.

*Trihydrochloride of 7-amino-1,3,5-triazaadamantane* (XXI). A solution of *III* (0.5 g; 3.0 mmol) in 30 ml of ethanol and 1 ml of water was filtered and the filtrate acidified with 1 ml (80 mmol) of conc. hydrochloric acid and diluted with 50 ml of benzene. The mixture was evaporated *in vacuo* to a small volume and allowed to stand overnight. After filtration and washing with ethanol and benzene 0.5 g (63.2%) of product was obtained, m.p. 224°C (decomp.). For  $C_7H_{17}Cl_3N_4$  (263.6) calculated: 31.90% C, 6.50% H, 21.26% N, 40.35% Cl; found: 31.86% C, 6.62% H, 21.25% N, 39.52% Cl.

*N-Phenyl-N'-(1,3,5-triaza-7-adamantyl)urea* (XXII). A mixture of 150 ml of toluene and 1.5 g (9.7 mmol) of compound *III* was concentrated *in vacuo* to two thirds of its volume and heated at 50–60°C. After addition of 1.5 g (12.6 mmol) of phenylisocyanate and standing overnight the suspension was filtered and washed with toluene; yield 2.3 g (87%), m.p. 202°C (decomp.). Literature<sup>4</sup> gives m.p. over 200°C, with decomposition.

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