

Synthesis of 7-(*N*-Alkylamino)- and 7-(*N,N*-Dialkylamino)-1,3,5-Triazaadamantanes

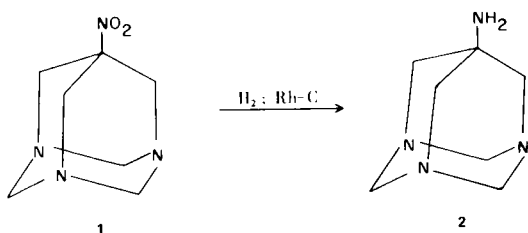
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The reductive alkylation of 7-amino-1,3,5-triazaadamantane (**2**) has been investigated leading to efficient and simple synthetic routes to some of its *N*-alkyl and *N,N*-dialkyl derivatives.

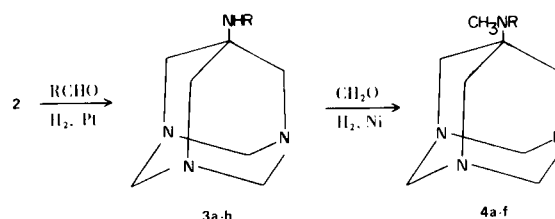
The reactant primary amine **2** has been prepared in quantitative yield from 7-nitro-1,3,5-triazaadamantane (**1**) by an improved hydrogenation procedure (rhodium-charcoal catalyst, 25-50 psi). Reported procedures for



hydrogenation of **1** with Raney nickel catalyst (at 1000 psi or with a 20:1 weight ratio of catalyst to reactant) are less convenient and provide lower yields of **2** (1,2,3). A report (2) of the synthesis of **2** by lithium aluminum hydride reduction of **1** must be questioned since the reported melting point of the product is in serious disagreement with that of authentic pure **2**.

An improved synthesis of the nitro compound **1** is described which involves simultaneous addition of paraformaldehyde and nitromethane to a refluxing methanolic solution of ammonium acetate. Yields are 47-52% when paraformaldehyde addition is slow (4-6 hours). The reaction is reported to give 70-77% yield of **1** when paraformaldehyde addition is rapid (2,3), but in our hands the yield by this procedure is only 19-21%. Hodge's experiments confirm our observations (1).

Reductive alkylation of primary amine **2** was successful with aldehydes acetaldehyde, propanal, butanal, 2-methylpropanal, pentanal, hexanal and 2,3-dimethylpentanal. Reactions were conducted in ethanol solvent with platinum catalyst (25°, 25-50 psi). The uptake of hydrogen was rapid leading to *N*-alkyl amines **3b-h** in excellent yields (92-99%); Table I. Under various reaction conditions additional aldehyde (except formaldehyde) failed to produce *N,N*-dialkyl derivatives of **2**; monoalkyl amines were



the only amine products. Also, no reductive alkylation of **2** with acetone or cyclopentanone could be realized; reactant **2** was recovered.

Formaldehyde (two mole-equivalents) reacted rapidly with **2** and hydrogen (Raney nickel catalyst) to produce the *N,N*-dimethyl derivative **4a**. Its behavior differs from that of other alkanals. None of the monomethyl compound **3a** was isolated. With freshly prepared Raney nickel W-2, catalyst (4), the yield of **4a** was 91%; a previously reported procedure, also employing Raney nickel, gave a 58% yield of **4a**, the only known *N*-alkyl derivative of **2** (1).

The reductive methylation of the *N*-alkyl compounds **3b-f** with one mole-equivalent of formaldehyde proceeded rapidly using freshly prepared Raney nickel W-2 catalyst to produce the 7-(*N*-methyl-*N*-alkylamino)-1,3,5-triazaadamantanes **4b-f**. Yields are high (90-99%); Table II). This reduction fails, however, with platinum catalyst. Under various conditions aldehydes other than formaldehyde failed to reductively alkylate **3** to form *N,N*-derivatives of **2** having different *N*-alkyl groups; reactant **3** was recovered. Amines **4a-f** are quite stable and are readily purified by vacuum distillation or sublimation. They may be crystallized from hexane in which they are quite soluble. They exhibit the interesting property of high solubility in such diverse solvents as water and benzene.

It was found that the 3-step reaction sequence **1** → **2** → **3** → **4** could be conducted without isolating the intermediates **2** and **3** and without lowering the overall yield [e.g.,

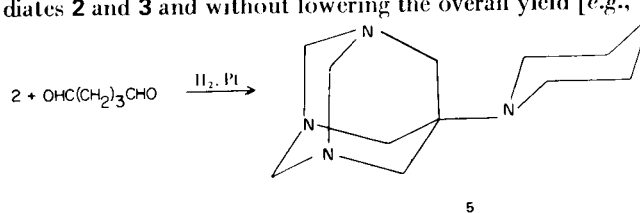


Table I

7-(*N*-Alkylamino)-1,3,5-triazaadamantanes

Cpd.	R	Yield (a) %	M.p. °C (b)	Molecular Formula	%C	Elemental Analyses			Mol wt	Found			Mol wt (c)
						Calculated %H	%N	%C		%H	%N		
<b>3b</b>	C <sub>2</sub> H <sub>5</sub>	98	126-129	C <sub>9</sub> H <sub>18</sub> N <sub>4</sub>	59.30	9.95	30.74	182.3	59.10	9.83	30.97	186	
<b>3c</b>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	95	103-104	C <sub>10</sub> H <sub>20</sub> N <sub>4</sub>	61.18	10.27	28.55	196.3	61.34	10.23	28.53	195	
<b>3d</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	99	112-114	C <sub>11</sub> H <sub>22</sub> N <sub>4</sub>	62.81	10.54	26.64	210.3	62.56	10.49	26.39	208	
<b>3e</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	97	119-120	C <sub>12</sub> H <sub>24</sub> N <sub>4</sub>	62.24	10.78	24.98	224.3	64.10	10.75	24.80	226	
<b>3f</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	93	118-120	C <sub>13</sub> H <sub>26</sub> N <sub>4</sub>	65.50	11.00	23.51	238.4	65.29	10.83	23.57	240	
<b>3g</b>	<i>i</i> -C <sub>4</sub> H <sub>9</sub>	92	154-156	C <sub>11</sub> H <sub>22</sub> N <sub>4</sub>	62.81	10.54	26.64	210.3	62.68	10.53	26.70	206	
<b>3h</b>	C <sub>7</sub> H <sub>13</sub> (d)	92	124-125	C <sub>14</sub> H <sub>28</sub> N <sub>4</sub>	66.62	11.18	22.20	252.4	66.67	11.27	22.21	250	

(a) Yield of high-purity unre-crystallized material obtained by reductive alkylation of **2**. (b) M.p. of dried, recrystallized (hexane), sublimed material used for elemental analyses (sealed capillary). (c) Molecular weight determination by vapor osmometry in benzene or chloroform solutions. (d) C<sub>7</sub>H<sub>13</sub> = C<sub>2</sub>H<sub>5</sub>CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)CH<sub>2</sub>, optically inactive mixture of diastereoisomers.

Table II

7-(*N*-Methyl-*N*-alkylamino)-1,3,5-triazaadamantanes

Cpd.	R	Yield (a) %	M.p. °C (b)	Molecular Formula	%C	Elemental Analyses			Mol wt	Found			Mol wt (c)
						Calculated %H	%N	%C		%H	%N		
<b>4a</b>	CH <sub>3</sub>	91	110-111 (d)	C <sub>9</sub> H <sub>18</sub> N <sub>4</sub>	59.30	9.95	30.74	182.3	59.53	9.78	30.84	181	
<b>4b</b>	C <sub>2</sub> H <sub>5</sub>	97	87-89	C <sub>10</sub> H <sub>20</sub> N <sub>4</sub>	61.18	10.27	28.55	196.3	61.19	10.24	28.71	195	
<b>4c</b>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	90	57-60	C <sub>11</sub> H <sub>22</sub> N <sub>4</sub>	62.81	10.54	26.64	210.3	62.65	10.59	26.48	207	
<b>4d</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	98	35-38	C <sub>12</sub> H <sub>24</sub> N <sub>4</sub>	64.24	10.78	24.98	224.3	64.05	10.78	25.06	223	
<b>4e</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	100	32-35	C <sub>13</sub> H <sub>26</sub> N <sub>4</sub>	65.50	11.00	23.51	238.4	65.28	10.81	23.34	243	
<b>4f</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	90	28-30	C <sub>14</sub> H <sub>28</sub> N <sub>4</sub>	66.62	11.18	22.20	252.4	66.80	11.10	22.25	250	

(a) Yield of unre-crystallized material obtained by reductive methylation of **3** except for **4a** prepared directly from **2**. (b) M.p. of dried, recrystallized (hexane), sublimed material used for elemental analysis (sealed capillary). (c) Molecular weight determination by vapor osmometry in benzene or chloroform solutions. (d) Lit m.p. 106-108° (1).

96% yield of **4d** (R = *n*-C<sub>4</sub>H<sub>9</sub>) from equal molar amounts of **1** and butanal].

The reductive alkylation of **2** was successful with the dialdehyde glutaraldehyde to form 7-(1-piperidyl)-1,3,5-triazaadamantane (**5**, 26% yield). Equatorial piperidyl nitrogen substitution is expected (**5**).

Structures of all amines **2-5** are supported by elemental analyses and molecular weight data (Tables I and II). The infrared spectra of carefully dried samples reveal sharp NH stretching bands near 3200 cm<sup>-1</sup> in the monoalkyl compounds **3** which bands are absent in the *N,N*-dialkyl amines **4** and **5**. The <sup>1</sup>H nmr spectra of the new compounds are also in agreement with their structures (see Experimental). In all compounds the signals for the 2, 4 and 9 methylene protons of the 1,3,5-triazaadamantane nucleus appear as an AB quartet (J ≈ 12 Hz) whereas the methylene protons of the 6, 8 and 10 positions appear as a singlet.

Reductive alkylation with sodium cyanoborohydride was conducted with **2** and acetone and with **3c** and acetaldehyde (**6**). The expected products, *N*-isopropyl and *N*-ethyl-*N*-propyl derivatives of **2**, could not be isolated in pure form although nmr spectra of the crude reaction products revealed their presence. Yields were low in these preliminary experiments and the reactions were not investigated further.

## EXPERIMENTAL

Infrared (ir) spectra were determined on a Perkin-Elmer 137 and nuclear magnetic resonance (nmr) spectra on a Varian A-60 or XL-100 instrument; tetramethylsilane was used as an internal standard in deuteriochloroform solutions unless otherwise stated. Melting points were determined in sealed capillaries and are corrected. Elemental analyses and molecular weight determinations were performed by Galbraith Laboratories, Knoxville, Tennessee.

## Aldehydes.

Aldehydes employed were commercial samples, reagent grade, distilled immediately before use except for formalin and paraformaldehyde which were used without further purification.

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

To ammonium acetate (129 g., 1.67 moles) in 200 ml. of 95% ethanol was added, slowly with stirring, through separate necks of a 1-1 4-necked flask: (1) a solution of nitromethane (33.3 g., 0.544 mole) in 50 ml. of 95% ethanol (addition time 4 hours), and (2) paraformaldehyde (111 g., 3.70 moles) (addition time 5 hours). Stirring and reflux were continued for 1 hour after addition of the paraformaldehyde was complete. Then the mixture was stirred at ambient temperature for 9 hours. The white crystalline product was filtered and washed with cold ethanol to yield 42.5 g. of **1**, m.p. 305-310° dec; lit m.p. 260-310° (1), 315° (2). The light orange filtrate was concentrated under reduced pressure at 90° to remove volatiles and yield 96.5 g. of a viscous oil mixed with crystals. The residue was dissolved in 100 ml. of hot 95% ethanol and chilled to 0° to yield 9.4 g. of additional **1**, m.p. 290-300° dec. (total yield 51.9 g., 52%). The isolated material is of high purity and may be used for reduction to the corresponding amine without further purification. If desired it may be recrystallized from water to yield long needles, m.p. 285-310°.

7-Amino-1,3,5-triazaadamantane (**2**).

7-Nitro-1,3,5-triazaadamantane (46.1 g., 0.25 mole), 175 ml. of 95% ethanol and 8.0 g. of 5% rhodium-charcoal catalyst were shaken with hydrogen in a Parr apparatus at 25° until hydrogen uptake ceased (13 hours). (The reaction bottle was refilled with hydrogen at intervals as required to keep the hydrogen pressure between 25-50 psi.) The reaction mixture was filtered with suction through *Celite* and the collected catalyst washed thoroughly with ethanol. The filtrate was concentrated to dryness under reduced pressure and the solid residue, after being ground to a powder, was pumped at 25° and 0.1 mm for 12 hours to remove traces of volatiles to yield 38.6 g. (99.5%) of high purity **2**, m.p. 216-219°; lit 213-217° (88% yield unrecrystallized) (1). The product may be recrystallized from benzene (80% recovery) to yield long needles, m.p. 214-217°; lit m.p. 218-220° (recrystallized from benzene), 69% yield (1); m.p. 300-310° (2); nmr (deuterium oxide):  $\delta$  4.70 (2, s, OH), 4.39, 3.97 (6, ABq, J = 12 Hz; 2,4,9 CH<sub>2</sub>), 3.17 (6, s, 6,8,10 CH<sub>2</sub>); TMS external standard.

7-(Pentylamino)-1,3,5-triazaadamantane (**3e**).

7-Amino-1,3,5-triazaadamantane (30.8 g., 0.2 mole), pentanal (17.2 g., 0.2 mole), platinum oxide catalyst (0.7 g.) and 150 ml. and 95% ethanol were shaken with hydrogen in a Parr apparatus at 25° (initial pressure 50 psi) until hydrogen uptake ceased (1 hour). The mixture was filtered through *Celite*, and the residue concentrated under reduced pressure to remove ethanol. The residue was dissolved in 300 ml. of benzene and dried with *Drierite* at 25°. The mixture was concentrated to dryness and the residue pumped at 0.1 mm (90°) to remove volatiles leaving 43.6 g. (97%) of high purity **3e**; the material may be purified by sublimation, without loss, m.p. 119-120°; ir (Nujol): 3300 cm<sup>-1</sup> (NH, weak); nmr (deuteriochloroform):  $\delta$  4.44, 4.08 (6, ABq, J = 12 Hz, 2,4,9 CH<sub>2</sub>), 3.29 (6, s, 6,8,10 CH<sub>2</sub>), 2.56 (2, m, CH<sub>2</sub>N of C<sub>5</sub>H<sub>11</sub>), 1.33 [7, m, NH and (CH<sub>2</sub>)<sub>3</sub>], 0.90 (3, m, CH<sub>3</sub>C).

7-(N-Alkylamino)-1,3,5-triazaadamantanes (**3b, c, d, f, g, h**).

The procedure described above for preparation of **3e** was used for preparation of other 7-(N-alkylamino)-1,3,5-triazaadamantanes

(**3b, c, d, f, g, h**) from **2** and other aldehydes (acetaldehyde, propanal, butanal, hexanal, 2-methylpropanal, and 2,3-dimethylpentanal). Analytical samples were prepared by sublimation and/or recrystallization from hexane. Yields, melting points and elemental analyses of the new substances are summarized in Table I. Their infrared and NMR spectra are similar to that of **3e** except for the N-alkyl signals.

7-(N,N-Dimethyl)-1,3,5-triazaadamantane (**4a**).

7-Amino-1,3,5-triazaadamantane (3.08 g., 0.020 mole), formalin (4.0 ml., 0.053 mole), 50 ml. of methanol and 1.2 g. of freshly prepared W-2 Raney nickel catalyst (**3**) were shaken in a Parr apparatus at 50 psi for 4 hours. The mixture was filtered through *Celite*, washed with water, and the filtrate concentrated to dryness under reduced pressure. The residue was sublimed at 100° (0.1 mm) to yield 3.3 g. (91%) of **4a**, m.p. 110-111°; lit (1) m.p. 106-108° (58% yield); ir (Nujol): revealed absence of NH bands.

7-(N-Methyl-N-pentyl)-1,3,5-triazaadamantane (**4e**).

To 7-(N-pentyl)-1,3,5-triazaadamantane (**3e**, 44.8 g., 0.20 mole) in 100 ml. of methanol was added 16 ml. of 37% formalin (0.21 mole of formaldehyde). A slight exothermic reaction occurred causing the temperature of the solution to rise to 34°. The solution was cooled to 15° and 4.0 g. of freshly prepared Raney nickel W-2 catalyst (**3**) was added. The mixture was shaken with hydrogen in a Parr apparatus until hydrogen uptake ceased (16 hours, 25°, 30-50 psi). The reaction mixture was filtered through *Celite* and the residue concentrated under reduced pressure to yield 47.6 g. (100%) of **4e**, m.p. 30-31°; distillation gave 43.9 g. (92%), b.p. 112-117° (0.1 mm) (bath temp. 150-170°), m.p. 32-35°; ir (Nujol): reveals absence of NH absorption bands; nmr (deuteriochloroform):  $\delta$  4.34, 4.00 (6, ABq, J = 12 Hz, 2,4,9 CH<sub>2</sub>), 3.33 (6, s, 6,8,10 CH<sub>2</sub>), 2.37 (2, m, CH<sub>2</sub>N of C<sub>5</sub>H<sub>11</sub>), 2.19 (s, 3, CH<sub>3</sub>N), 1.27 [6, m, (CH<sub>2</sub>)<sub>3</sub>], 0.87 (3, m, CCH<sub>3</sub>).

7-(N-Methyl-N-alkylamino)-1,3,5-triazaadamantanes (**4b, c, d, f**).

The procedure employed above for preparation of **4e** was used for preparation of other 7-(N-methyl-N-alkylamino)-1,3,5-triazaadamantanes (**4b, c, d, f**). Analytical samples were prepared by sublimation, distillation and/or recrystallization from hexane. Yields, melting points, and elemental analyses of the new substances are summarized in Table II. Their infrared and nmr spectra are similar to that of **4e** except for the N-alkyl signals.

7-(1-Piperidyl)-1,3,5-triazaadamantane (**5**).

7-Amino-1,3,5-triazaadamantane (1.54 g., 0.01 mole), 25% aqueous glutaraldehyde solution (4.0 g., 0.01 mole), 200 ml. of 95% ethanol and 0.2 g. of platinum oxide catalyst were shaken in a Parr apparatus at 25° (50 psi) until hydrogen uptake ceased (3 hours). The mixture was filtered and the filtrate concentrated to yield a white solid residue which was extracted with 40 ml. of hot hexane leaving 1.1 g. of gummy insoluble material. The extract was concentrated to remove solvents leaving 1.1 g. of crude **5**, m.p. 140-170°; recrystallization from hexane gave flat prisms (0.57 g., 26%, m.p. 160-170°); further recrystallization gave an analytical sample, m.p. 166-172°; ir (Nujol): revealed absence of NH bands; nmr (deuteriochloroform):  $\delta$  4.44, 4.06 (6, ABq, J = 12 Hz, 2,4,9 CH<sub>2</sub>), 3.44 (6, s, 6,8,10 CH<sub>2</sub>), 2.60 (4, m, CH<sub>2</sub>N of piperidyl), 1.49 (6, m, 3,4,5 CH<sub>2</sub> of piperidyl).

*Anal.* Calcd. for C<sub>12</sub>H<sub>22</sub>N<sub>4</sub>: C, 64.82; H, 9.97; N, 25.20; mol. wt. 222.33. Found: C, 64.69; H, 10.15; N, 25.12; ml. wt. 218 (osometry in chloroform).

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