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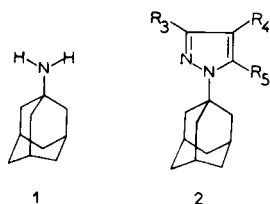
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Received May 20, 1983

Using 1-adamantylhydrazine as starting material, a series of 1-(1-adamantyl)pyrazoles has been prepared. Electrophilic reactivity (bromination and nitration) and nucleophilic reactivity (quaternarization) have been studied. Proton nuclear magnetic resonance spectra of all the new compounds are recorded.

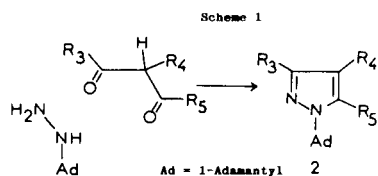
*J. Heterocyclic Chem.*, **21**, 249 (1984).

Since the discovery [1] of the antiviral properties of Amantadine **1**, a very large number of drugs containing an adamantyl group have shown biological activity. However a careful review through *Chemical Abstracts* of March 1983 indicated that no examples of the structurally related 1-(1-adamantyl)pyrazoles **2**, are known.



	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>3'</sub>
<b>a</b>	H	H	H	H
<b>b</b>	Me	H	Me	H
<b>c</b>	H	Br	H	H
<b>d</b>	H	NO <sub>2</sub>	H	OH
<b>e</b>	Me	NO <sub>2</sub>	Me	OH
<b>f</b>	Me	H	NH <sub>2</sub>	H
<b>g</b>	H	Br	H	OH

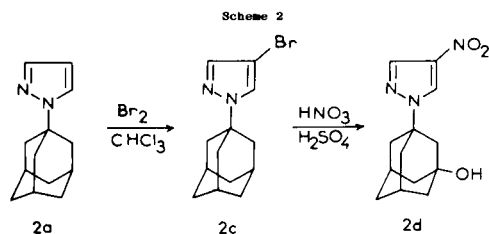
This preliminary paper deals with the synthesis and some aspects of the reactivity of a number of 1-(1-adamantyl)pyrazoles **2**. Spectral evidence for each of the structures is briefly discussed. For products **2a**, **2b** and **2f**, a general method of building pyrazoles (Scheme 1) by treating 1-adamantylhydrazine with a suitable  $\beta$ -dicarbonyl compound [2] was used which gave satisfactory yields. Our attempts to introduce the adamantyl group directly into the pyrazole nucleus with 1-bromoadamantane were unsuccessful.



The reaction of 1-adamantylhydrazine with 3-aminocrotonitrile could afford two isomers: 1-(1-adamantyl)-3-methyl-5-amino and 1-(1-adamantyl)-3-amino-5-methyl pyrazole, but under the experimental conditions used, only the 5-amino isomer was obtained, as supported by proton and carbon-13 nuclear magnetic resonance (Table 1).

Nitration of the 1-(1-adamantyl)pyrazoles **2a** and **2b** with nitric acid-sulfuric acid gave **2d** and **2e**, respectively. In addition to the expected nitration of the 4 position of the 1-substituted pyrazole, oxidation of the 3' position of the adamantyl group attached to the nitrogen of the heterocyclic ring occurred. It is known that adamantane can be transformed into 1-hydroxyadamantane with fuming sulfuric acid by transfer of hydride to the sulfuric acid [3].

To check the possibility that the sulfuric acid ( $d = 1.84$ ) used in the nitration reaction was responsible for that oxidation, we submitted the 1-(1-adamantyl)-4-bromopyrazole **2c** to the conditions used in that nitration, in order to obtain compound **2g**. Instead of **2g**, 1-(1-adamantyl-3-ol)-4-nitropyrazole **2d** was obtained due to the replacement of the 4-bromo by a nitro group in addition to the expected oxidation reaction [4] (Scheme 2).



The quaternary salt **2h** was obtained by alkylation of 1-(1-adamantyl)pyrazole with methyl fluorosulfonate in anhydrous dichloromethane [5].

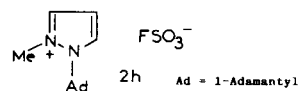


Table 1  
PMR Spectral Data for 1-(1-Adamantyl)pyrazoles (in  $\delta$  deuteriochloroform)

Compound No.	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>3'</sub>	Adamantyl group	J <sub>3,4</sub>	J <sub>4,5</sub>	J <sub>3,5</sub>
<b>2a</b>	7.48 (t)	6.22 (t)	7.52 (t)	—	1.77 (bm, 6H), 2.17 (bm, 9H)	2.41	2.74	—
<b>2b</b>	2.16 (s)	5.73 (s)	240 (s)	—	1.71 (bm, 6H), 2.23 (bm, 9H)	—	0.6	—
<b>2c</b> [a]	7.47 (d)	—	7.50 (d)	—	1.73 (bm, 6H), 2.10 (bm, 9H)	—	—	0.75
<b>2d</b>	8.08 (bs)	—	8.22 (d)	2.18 (s)	1.65 (m, 2H), 1.72-1.85 (m, 4H)	—	—	0.6
				[b]	1.95-2.25 (m, 6H), 2.35-2.58 (bm, 2H)			
<b>2e</b>	2.45 (s)	—	2.81 (s)	2.58 (s)	1.64 (bt, 2H), 1.80 (d, 4H) 2.15-	—	—	—
				[b]	2.40 (m, 8H)			
<b>2f</b>	3.50 (b)	5.35 (s)	2.15 (s)	—	1.74 (bm, 6H), 2.20 (d, 3H) 2.28	—	—	—
					(bs, 6H)			
<b>2h</b> [c]	8.50 (d)	6.89 (t)	8.59 (d)	—	1.73 (bs, 6H), 2.30 (bs, 9H)N-Me:	3.0	3.15	1.05
					4.38(s) J <sub>Me-H<sub>3</sub></sub> : 0.45			

b: broad, s: singlet, d: doublet, t: triplet, m: multiplet

[a] In hexadeuteriodimethylsulfoxide R<sub>3</sub>, 7.50, R<sub>5</sub>, 7.98, adamantyl group, 1.70 (bm, 6H), 2.07 (bm, 9H). [b] This signal exchanges with deuterium oxide. [c] This compound was not soluble in deuteriochloroform and the spectra was registered in hexadeuteriodimethylsulfoxide.

The pmr data given in Table 1 confirm the structures of the several derivatives synthesized. A more careful nuclear magnetic resonance study is now in progress that will be published soon. In order to prove that compound **2f** was the 5-amino isomer, carbon-13 nmr spectroscopy was used since the resonance of the methyl group is indicative of the 3 or 5 position [6]: methyl 13.82, C-3 143.12, C-4 91.59, C-5 146.65; adamantane carbons 29.24, 35.70, 40.76.

The mass spectra of the different products confirmed their structures, and except for 1-(1-adamantyl)pyrazole itself, the parent peak arises from the fragmentation of the azole-adamantane bond.

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured with a Perkin Elmer 257 spectrophotometer in potassium bromide unless otherwise specified. The mass spectra were measured with a Hitachi Perkin Elmer RMU-6M mass spectrometer at 75 eV. The pmr spectra were obtained with Varian EM 390 (90 MHz) in the solvents indicated. Chemical shifts and coupling constants were measured in ppm ( $\delta$ ) and J (Hz) with respect to tetramethylsilane.

### 1-(1-Adamantyl)pyrazole (**2a**).

A mixture of 7 g (0.029 moles) of 1-adamantylhydrazine dihydrochloride, 6.7 ml (0.040 moles) of 1,1,3,3-tetramethoxypropane in 14 ml of water and 4.6 ml of ethanol was heated under reflux with stirring during 2 hours. After cooling the ethanol was evaporated under vacuum and the residue was treated with a solution of 2 g of sodium carbonate in 2 ml of water. The precipitate was filtered off and washed with 30 ml of ethyl ether. The filtrate water was extracted with ethyl ether and the ethereal solutions were combined, dried over anhydrous sodium sulfate, and treated with active charcoal. The ether was evaporated under vacuum and the product recrystallized in ethanol-water to give **2a** (63% yield) mp 51-53°; ir:  $\nu$  (cm<sup>-1</sup>) 3150, 3130, 3110, 2920, 2855, 2870, 1505, 1455, 1400, 1375, 1360, 1350, 1325, 1315, 1275, 1230, 1190, 1185, 1115, 1110, 1100, 1060, 1045, 955, 925, 875, 840, 820, and 750; ms: m/e (relative intensity) 203 (17), M<sup>+</sup> 202 (100), 145 (53), 135 (23), 131 (5.5), 121 (5), 120 (16.5), 119 (43), 108 (6.5), 107 (15), 106 (6.5), 105 (16.5), 94 (18), 93 (43), 92 (56.5), 91

(60), 81 (21.5), 80 (15), 79 (66.5), 78 (25), 77 (63), 69 (30), 68 (21.5), 67 (26.5), 66 (16.5), 65 (30), 55 (21.5), 54 (13), 53 (41.5), 52 (21.5), and 51 (18).

Anal. Calcd. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>: C, 77.2; H, 9.0; N, 13.8. Found: C, 77.4; H, 9.4; N, 13.8.

### 1-(1-Adamantyl)-3,5-dimethylpyrazole (**2b**).

A mixture of 6 g (0.025 moles) of 1-adamantylhydrazine dihydrochloride and 2.57 ml (0.025 moles) of acetylacetone in 50 ml of ethanol were heated under reflux for 3 hours. After cooling, the solvent was removed under vacuum leaving as a residue 1-(1-adamantyl)-3,5-dimethylpyrazole hydrochloride. The residue was then dissolved in a minimal quantity of water and neutralized with aqueous potassium carbonate yielding a white precipitate which was extracted with chloroform. After evaporation of the solvent, the solid residue was recrystallized in ethanol-water to give **2b** (95% yield) mp 81-83°; ir:  $\nu$  (cm<sup>-1</sup>) 2920, 2890, 2860, 1555, 1450, 1420, 1390, 1360, 1315, 1295, 1280, 1215, 1190, 1155, 1110, 1045, 1030, 985, 850, 820, 795, 785, and 750; ms: m/e (relative intensity) 231 (10), M<sup>+</sup> 230 (48), 173 (12), 148 (12.5), 147 (20), 136 (13), 135 (100), 122 (27.5), 107 (12.5), 105 (7.5), 97 (25), 96 (12.5), 95 (10), 93 (39), 92 (24), 91 (26), 81 (12.5), 80 (7.5), 79 (9), 78 (26), 67 (21), 66 (7.5), 65 (11), 56 (6), 55 (16) and 53 (15).

Anal. Calcd. for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>: C, 78.2; H, 9.6; N, 12.2. Found: C, 77.8; H, 9.9; N, 11.8.

### 1-(1-Adamantyl)-4-bromopyrazole (**2c**).

To a solution of 2 g (0.0098 moles) of 1-(1-adamantyl)pyrazole (**2a**) in 50 ml of chloroform, 1 ml of bromine was added and the mixture was heated under reflux for 2 hours. After cooling, the solvent was evaporated off and the solid obtained was recrystallized from ethanol-water to give **2c**, (95% yield) mp 90-91°; ir:  $\nu$  (cm<sup>-1</sup>) 3150, 2940, 2930, 2910, 2860, 1455, 1410, 1385, 1375, 1360, 1350, 1325, 1295, 1280, 1230, 1175, 1130, 1110, 990, 955, 845, 820, 795, and 700; ms: m/e (relative intensity) M<sup>+</sup> 282 (42), 280 (43), 225 (7), 223 (7), 148 (32.5), 146 (34), 136 (11), 135 (100), 134 (42), 121 (7.5), 119 (8.5), 109 (12.5), 105 (9), 93 (39), 92 (27), 91 (24), 82 (38), 81 (16), 80 (38), 79 (43), 78 (12), 77 (23), 68 (23), 67 (19), 66 (6.5), 65 (10), 56 (7), 55 (12), 53 (11), 52 (6.5), 51 (6.5), and 41 (38).

Anal. Calcd. for C<sub>13</sub>H<sub>17</sub>BrN<sub>2</sub>: C, 55.5; H, 6.1; N, 10.0; Br, 28.4. Found: C, 55.3; H, 6.2; N, 10.12; Br, 28.7.

### 1-(1-Adamantyl-3-ol)-4-nitropyrazole (**2d**).

A mixture of 10 ml of nitric acid (d = 1.38) and 10 ml of sulfuric acid (d = 1.84) was added carefully and with external cooling to a solution of

2 g (0.0098 moles) of 1-(1-adamantyl)pyrazole (**2a**) in 20 ml of sulfuric acid. The reaction was stirred for 12 hours at room temperature, neutralized with a saturated solution of potassium carbonate and extracted with chloroform. The organic layer was dried over sodium sulfate and the solvent removed under vacuum. The resulting product was recrystallized in ethanol-water to give **2d** (77% yield) mp 131°; ir:  $\nu$  ( $\text{cm}^{-1}$ ) 3290, 3180, 3140, 2940, 2935, 2870, 1540, 1510, 1420, 1365, 1338, 1320, 1225, 1150, 1120, 1090, 1015, 1005, 980, 965, 938, 900, 875, 850, 825, 765, and 760; ms: m/e (relative intensity) 264 (7), M<sup>+</sup> 263 (44), 247 (29), 206 (30.5), 190 (9.5), 151 (24), 150 (79), 149 (16.5) 136 (8), 135 (64.5), 134 (53), 133 (6), 132 (6.5), 121 (11), 119 (7), 114 (29), 109 (11), 108 (29), 107 (24.5), 106 (12), 105 (14.5), 97 (41), 96 (5.5), 95 (52.5), 94 (14), 93 (82), 92 (100), 91 (38), 83 (6.5), 82 (7), 81 (24), 80 (12.5), 79 (53), 78 (13), 77 (38), 69 (9), 68 (6.5), 67 (28.5), 66 (7.5), 65 (18), 59 (6), 58 (8), 57 (6.5), 56 (11.5), 55 (24.5), 54 (7.5), 53 (21), 52 (13), and 51 (7.5).

*Anal.* Calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C, 59.3; H, 6.5; N, 15.9. Found: C, 59.5; H, 6.6; N, 15.9.

#### 1-(1-Adamantyl-3-ol)-3,5-dimethyl-4-nitropyrazole (**2e**).

To a cooled solution of 1.5 g (0.0065 moles) of 1-(1-adamantyl)-3,5-dimethylpyrazole (**2b**) in 20 ml of sulfuric acid ( $d = 1.84$ ) was added a mixture of 10 ml of nitric acid ( $d = 1.38$ ) and 10 ml of sulfuric acid ( $d = 1.84$ ). The reaction was stirred overnight at room temperature and neutralized with a saturated solution of potassium carbonate and extracted with chloroform. The organic layer was dried over sodium sulfate and the solvent removed under vacuum. The product obtained was recrystallized in ethanol-water to give **2e** (86% yield), mp 109°; ir:  $\nu$  ( $\text{cm}^{-1}$ ) 3480, 2925, 2870, 1560, 1500, 1460, 1415, 1390, 1355, 1310, 1215, 1150, 1130, 1105, 1085, 1005, 945, 835, 775, and 760; ms: m/e (relative intensity) M<sup>+</sup> 291 (18), 152 (11), 151 (100), 150 (8), 142 (27), 141 (18.5), 133 (5), 125 (13), 109 (9), 108 (8), 107 (15.5), 106 (7), 105 (5), 96 (6), 95 (56.5), 94 (9), 93 (66.5), 92 (66.5), 91 (18), 82 (5.5), 81 (14.5), 80 (5.5), 79 (15.5), 77 (16.5), 67 (14), 66 (8.5), 65 (11), 59 (8), 58 (8.5), 55 (14), and 53 (9.5).

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>: C, 61.8; H, 7.3; N, 14.4. Found: C, 61.1; H, 7.2; N, 14.0.

#### 1-(1-Adamantyl)-3-methyl-5-aminopyrazole (**2f**).

A mixture of 2 g (0.0084 moles) of 1-adamantylhydrazine dihydrochloride and 0.8 g (0.009 moles) of  $\beta$ -aminocrotonitrile EGA in 30 ml of ethanol were heated under reflux for 12 hours. After cooling, the solvent was removed under vacuum. The product **2f** was isolated by liquid column chromatography on silicagel 60 Merck (70-230 mesh ASTM) using

chloroform as eluent (40% yield), mp 156°; ir (chloroform):  $\nu$  ( $\text{cm}^{-1}$ ) 3445 ( $\nu$  as NH<sub>2</sub>), 3380 ( $\nu$  s NH<sub>2</sub>), 3000, 2920, 2860, 1620, 1555, 1495, 1450, 1390, 1370, 1360, 1350, 1315, 1110, and 1020; ms: m/e (relative intensity) 232 (11.5), M<sup>+</sup> 231 (66), 174 (19), 136 (14), 135 (100), 123 (12), 107 (11), 98 (8), 93 (27), 91 (12), 81 (9.5), 79 (32), 77 (12), 67 (15), 55 (9.5), 53 (7), and 41 (15.5).

*Anal.* Calcd. for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>: C, 72.7; H, 9.1; N, 18.2. Found: C, 72.9; H, 9.2; N, 18.0.

#### 1-(1-Adamantyl)-2-methylpyrazolium fluorosulfonate (**2h**).

Methyl fluorosulfonate (1 ml, 0.012 moles) was added to a solution of 0.5 g (0.0025 moles) of 1-(1-adamantyl)pyrazole (**2a**) in 100 ml of dry dichloromethane and the reaction mixture was stirred at room temperature. After 48 hours a white solid precipitated, it was filtered off and washed thoroughly with dry ethyl ether to yield the dry salt **2h** (90% yield), mp 198°; ir:  $\nu$  ( $\text{cm}^{-1}$ ) 3190, 3140, 3120, 3060, 2940, 2870, 1455, 1440, 1370, 1350, 1320, 1280, 1200, 1135, 1115, 1080, 830, 800, 780, 755, and 705.

*Anal.* Calcd. for C<sub>14</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>3</sub>S: C, 53.1; H, 6.7; N, 8.9. Found: C, 53.3; H, 6.6; N, 8.9.

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