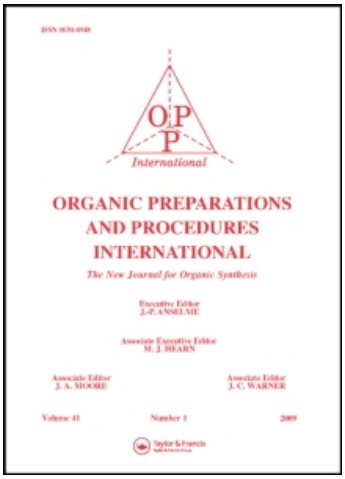

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PREPARATION OF NOVEL 2-AMINOADAMANTYL- AND 4-AMINOPROTOADAMANTYLCARBONITRILES

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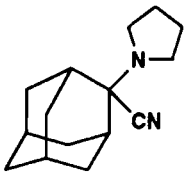
The adamantane moiety has been used extensively to modify the potency of biologically active compounds. Replacement of the cyclohexyl group of phencyclidine by the very rigid adamantyl residue results in a dramatic increase of the affinity to the muscarinic receptors.[1] Although aminoadamantylcarbonitriles are convenient precursors for adamantanoid phencyclidines, only 2-piperidinoadamantylcarbonitrile (**3**) has been reported.[2] We now describe the synthesis of polycyclic aminonitriles **1-6** using two different pathways.

One route involves the Strecker aminonitrile synthesis starting with a mixture of carbonyl compound, amine and cyanide ion (method A), while the other involves reaction of the bisulfite



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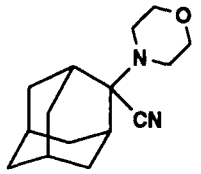

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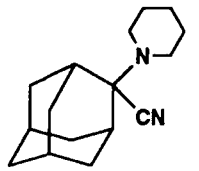

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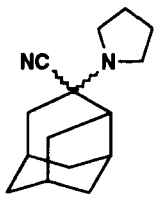

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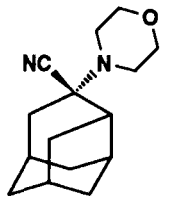

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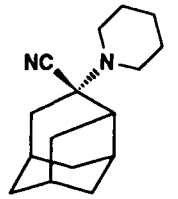

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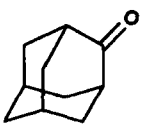
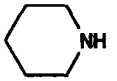
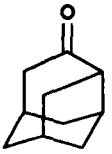
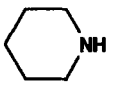
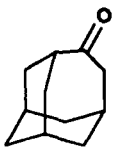
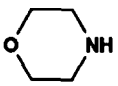
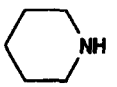
adduct of carbonyl compound with an aqueous solution of potassium cyanide and the amine (method B). In particular, we studied the reaction of 2-adamantanone, 4-protoadamantanone and 4-homoadamantanone and of their cyanohydrins with pyrrolidine, morpholine and piperidine. While compounds **1-3** were obtained by both methods A and B, compounds **4-6** could be generated only by

method B; both methods failed to convert 4-homoadamantanone to corresponding aminonitriles (Table 1). The following order of reactivity was observed with 2-adamantanone and 4-protoadamantanone

TABLE 1. Conversion of 2-Adamantanone, 4-Protoadamantanone and 4-Homoadamantanone to Aminonitriles **1-6**

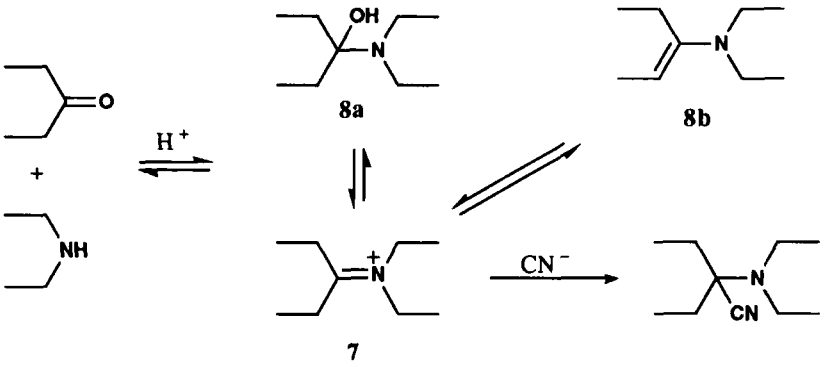
Ketone[a]	Base[a]	Method	Product	Ratio P/K[b]	Yield[c]
		A	**1**	3:1	73
		B		3.3:1	75
		A	**2**	3:1	74
		B		3.3:1	70
		A	**3**	3:1	75
		B		3.3:1	75
		A	No product		
		B	**4**	1.5:1	66
		A	No product		
		B	**5**	1:1	64
		A	No product		
		B	**6**	0.5:1	56
		A			
		B			
		A			
		B	No products		
		A			
		B			

a) All reactions were carried out in a 1:1 as well as in 1:2 ratio of ketone and base. An excess of base had no effect on the yield of products. b) The ratios product/ketone were estimated from the crude reaction mixtures. c) Yield of the isolated aminonitriles based on the reacted ketones.

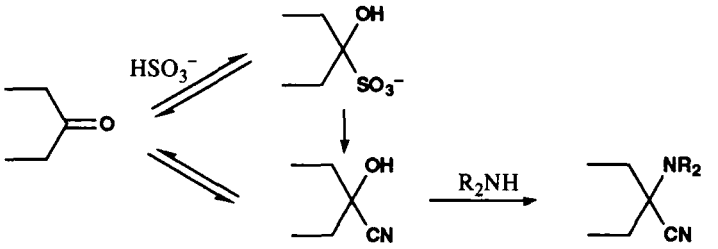
in both methods: pyrrolidine > morpholine > piperidine. The results obtained by method A could be explained through the possible formation of a cationic imine **7** (Scheme 1). However, under the reaction conditions 4-protoadamantanone and 4-homoadamantanone did not give corresponding aminonitriles. We assume a rapid equilibrium to be established between **7**, **8a** and **8b**.[3]

In contrast, when method B was employed the aminonitriles **4-6** were readily obtained in good yields (Table 1). In reactions of 4-protoadamantanone with morpholine and piperidine, only *endo*-

isomers **5** and **6** were obtained while with pyrrolidine 4-protoadamantanone reacted to give *exo*- and *endo*-**4** in a 1:10 ratio. The structure proof of all new compounds is based on spectral data and the stereochemistry of compounds **4-6** was determined by comparison of ^{13}C chemical shifts of the cyano group in the spectra of *exo*- and *endo*-protoadamantanone cyanohydrins.[4]



Scheme 1



Scheme 2

Since the mechanism of aminonitrile formation through the bisulfite addition product of ketone involves the formation of cyanohydrin as an intermediate (Scheme 2), we assume that the formation of products depends on the rate constant of dissociation of cyanohydrins.[6] The results (Table 1) imply that the rate constant of dissociation of 4-homoadamantanone cyanohydrin is higher than that of 4-protoadamantanone cyanohydrin and much higher than the rate constant of dissociation of 2-adamantanone cyanohydrin.

This was established by control experiments of the cleavage of 2-adamantanone cyanohydrin (**9**), 4-protoadamantanone cyanohydrin (**10**) and 4-homoadamantanone cyanohydrin (**11**) with piperidine. Cyanohydrin **11** was completely reverted to the corresponding ketone, while **9** and **10** gave mixtures of cyanohydrin and ketone in a 3:1 and 1:1 ratio, respectively.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were taken on JEOL FX 90Q and VARIAN GEMINI 300 spectrometers. IR spectra were recorded with a Perkin-Elmer 297 spectrophotometer, and mass spectra were taken on a

EXTREL FTMS 2001, Varian CH-7 and SHIMADZU GC-MS QP-1000 spectrometer and GLC analyses were carried out on a Varian Aerograph 1800 and Varian 3300 gas chromatograph. Melting points were determinated using Kofler stage and are uncorrected. 4-Homoadamantanone[7] and 4-protoadamantanone[8] were prepared according to the published procedures and were characterized by spectroscopic means. 2-Adamantanone was obtained from commercial sources.

General Procedures for the Synthesis of Aminonitriles 1-6

Method A.- The appropriate amine (1 or 2 mmol) and 1 ml of ice-water were mixed and pH was adjusted to 3-4 with 3N HCl. To this solution ketone (1 mmol) in 1.5 ml ethanol was added, the mixture was warmed up to reflux, and potassium cyanide (1-2 mmol) in water (2 ml) was added dropwise with efficient stirring. Reaction mixture was stirred at reflux for an additional 2-48 hrs, cooled and extracted with chloroform (3 x 10 ml). The chloroform extracts were dried over anhydrous $MgSO_4$ and the solvent was removed to afford a mixture of starting ketone and product. This mixture was separated on neutral alumina (II/III) using pentane:ether (8:2) as the eluent. The analytical samples of products **2-6** were obtained by recrystallization from ethanol, while **1** was distilled under reduced pressure.

Method B.- Potassium cyanide (1-1.5 mmol) in 2 ml of water and amine (1-2 mmol) were added to the mixture of water (1 ml), $NaHSO_3$ (1 mmol) and ketone (1 mmol). The reaction mixture was stirred at room temperature 7-14 days, extracted with chloroform (3 x 10 ml) and dried over anhydrous $MgSO_4$. After removal of the solvent the crude mixture was chromatographed on neutral alumina (II/III) using pentane:ether (8:2) as the eluent.

2-(1-Pyrrolidinyl)adamantylcarbonitrile (1), colorless oil, bp. 162-169° at 15 mmHg with decomposition. MS (m/z): 230 (M^+), 229, 202, 188, 161, 70. IR (KBr, film): 2920 (s), 2860 (m), 2820 (m), 2210 (w), 1450 (m), 1135 (m), 1100 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.64 (br. s, 2H), 2.2-1.4 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 119.5 (s, 1C), 67.0 (s, 1C), 46.2 (t, 2C), 36.9 (t, 1C), 34.2 (t, 2C), 33.8 (d, 2C), 30.2 (t, 2C), 26.2 (d, 1C), 26.0 (d, 1C), 23.2 (t, 2C). HRMS *m/z* calcd. for $C_{15}H_{22}N_2$ 230.1778, found 230.1762.
Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.34; H, 9.64; N, 12.20

2-Morpholinoadamantylcarbonitrile (2), mp. 88-92°. MS (m/z): 246 (M^+), 220, 216, 201, 188, 161, 86, 56. IR (KBr): 2980 (m), 2950 (s), 2920 (s), 2850 (s), 2210 (w), 1450 (s), 1280 (s), 1125 (s), 1010 (m), 880 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.77 (br. s, 4H), 2.58 (br. s, 4H), 2.2-1.4 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 118.6 (s, 1C), 67.1 (t, 2C), 65.9 (s, 1C), 45.9 (t, 2C), 37.2 (t, 1C), 34.5 (t, 2C), 31.5 (d, 2C), 30.1 (t, 2C), 26.3 (d, 2C). HRMS *m/z* calcd. for $C_{15}H_{22}N_2O$ 246.1727, found 246.1723.
Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; 11.37. Found: C, 73.09; H, 9.02; N, 11.42

2-Piperidinoadamantylcarbonitrile (3), mp. 83-86°, lit.[2] mp. 84°. MS (m/z): 244 (M^+), 243, 216, 215, 202, 188, 84. IR (KBr): 2980 (m), 2920 (s), 2860 (m), 2810 (m), 2210 (w), 1470 (m), 1450 (m), 1100 (m), 1000 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.0 (br. s, 2H), 2.3-1.3 (m, 22H). ^{13}C NMR ($CDCl_3$): δ 119.0 (s, 1C), 65.9 (s, 1C), 46.0 (t, 2C), 37.0 (t, 1C), 34.5 (t, 2C), 31.7 (d, 2C), 30.0 (t, 2C), 26.3 (t, 2C), 26.27 (d, 1C), 26.1 (d, 1C), 24.3 (t, 1C).

4-(1-Pyrrolidinyl)protoadamantylcarbonitrile (4), mp. 49-51°. MS (m/z): 230 (M^+), 229, 204, 203,

188, 160, 148, 121, 70. IR (KBr): 2930 (s), 2880 (m), 2810 (m), 2210 (w), 1465 (m), 1125 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.72-1.20 (m, 22H). *endo*-**4**: ^{13}C NMR ($CDCl_3$): δ 122.1 (s, 1C), 60.2 (s, 1C), 47.3 (t, 2C), 42.4 (d, 1C), 41.7 (t, 1C), 40.4 (t, 1C), 39.3 (t, 1C), 34.7 (d, 1C), 33.1 (d, 1C), 31.8 (t, 1C), 30.9 (t, 1C), 28.0 (d, 1C), 23.1 (t, 2C). *exo*-**4**: ^{13}C NMR ($CDCl_3$): δ 121.2 (s, 1C), 63.3 (s, 1C), 48.6 (t, 2C), 42.2 (d, 1C), 41.8 (t, 1C), 36.8 (t, 1C), 35.6 (t, 1C), 35.2 (d, 1C), 32.8 (d, 1C), 31.2 (t, 1C), 30.4 (t, 1C), 27.7 (d, 1C), 23.6 (t, 2C). HRMS *m/z* calcd. for $C_{15}H_{22}N_2$ 230.1778, found 230.1801.

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.08; H, 9.75; N, 12.14

4-Morpholinoprotoadamantylcarbonitrile (5), mp. 92-94°. MS (m/z): 246 (M^+), 219, 216, 188, 164, 138, 137, 126, 106, 91, 86, 79, 77, 69, 56, 55, 53. IR (KBr): 2970 (m), 2930 (s), 2860 (m), 2820 (m), 2210 (w), 1455 (m), 1290 (m), 1275 (m), 1260 (w), 1120 (s), 970 (m), 890 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.8 (t, 4H), 2.8-1.3 (m, 18H, with distinguished triplet at 2.63). ^{13}C NMR ($CDCl_3$): δ 121.3 (s, 1C), 67.0 (t, 2C), 59.9 (s, 1C), 47.1 (t, 2C), 41.9 (t, 1C), 40.2 (t, 1C), 39.8 (d, 1C), 39.4 (t, 1C), 34.8 (d, 1C), 33.3 (d, 1C), 31.8 (t, 1C), 31.0 (t, 1C), 28.3 (d, 1C). HRMS *m/z* calcd. for $C_{15}H_{22}N_2O$ 246.1727, found 246.1755.

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.95; H, 9.14; N, 11.55

4-Piperidinoprotoadamantylcarbonitrile (6), mp. 37-39°. MS (m/z): 244 (M^+), 243, 217, 202, 175, 162, 135, 91, 84, 79, 55. IR (KBr): 2930 (s), 2860 (m), 2810 (m), 2210 (w), 1470 (m), 1450 (m), 1110 (m), 960 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.8-1.3 (m, 24H). ^{13}C NMR ($CDCl_3$): δ 121.7 (s, 1C), 59.8 (s, 1C), 47.4 (t, 2C), 41.7 (t, 1C), 40.9 (t, 1C), 40.0 (d, 1C), 39.2 (t, 1C), 34.7 (d, 1C), 33.2 (d, 1C), 31.6 (t, 1C), 30.8 (t, 1C), 28.3 (d, 1C), 26.1 (t, 2C), 24.2 (t, 1C).

Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.49; H, 10.02; N, 11.34

Preparation of Cyanohydrins.- 2-Adamantanone cyanohydrin (**9**), 4-protoadamanta-none cyanohydrin (**10**) and 4-homoadamantanone cyanohydrin (**11**) were prepared according to the published procedure in 98%, 97%, and 89% overall yield, respectively, by the addition of trimethylsilyl cyanide to the corresponding ketone,[9] followed by hydrolysis with 3N hydrochloric acid.[10] 4-Cyano-4-hydroxyprotoadamantane (**10**) was obtained as a mixture of *endo*- and *exo*-isomers.[4]

4-Cyano-4-trimethylsilyloxyprotoadamantane (mixture of *endo*- and *exo*-isomers), bp. 145-147° at 15 mmHg. MS (m/z): 249 (M^+), 234, 207, 168, 131, 91, 75. IR (KBr): 2940 (s), 2880 (m), 2210 (w), 1460 (w), 1255 (s), 1120 (m), 1100 (s), 980 (m), 890 (m), 840 (m), 750 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.8-1.2 (m, 14H), 0.25 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 124.4, 123.5, 71.5, 69.3, 46.5, 45.7, 43.6, 43.1, 41.9, 39.2, 38.9, 35.4, 35.1, 34.8, 33.2, 32.6, 30.8, 30.6, 28.6, 27.4, 1.2 and 1.0. HRMS *m/z* calcd. for $C_{14}H_{23}NOSi$ 249.1543, found 249.1504.

4-Cyano-4-hydroxyprotoadamantane (10) (mixture of *endo*- and *exo*-isomers), mp. 119-121°. MS (m/z): 177 (M^+), 159, 151, 144, 135, 122, 94, 75. IR (KBr): 3420 (s), 2940 (s), 2880 (s), 2215 (w), 1460 (m), 1330 (m), 1190 (m), 1120 (m), 1090 (m), 1070 (m), 1050 (m), 1030 (m), 910 (m), 730 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.4 (s, 1H), 2.8-1.2 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 124.8, 123.9, 71.0, 68.1, 45.7, 44.8, 42.3, 42.0, 41.4, 39.3, 39.0, 35.6, 35.1, 33.5, 33.0, 32.5, 31.2, 31.0, 28.6, 27.5. HRMS *m/z* calcd. for $C_{11}H_{15}NO$ 177.1148, found 177.1140.

4-Cyano-4-trimethylsilyloxyhomoadamantane, mp. 47-49°. MS (m/z): 263 (M^+), 248, 222, 221, 173, 145, 80, 75. IR (KBr): 2960 (s), 2910 (s), 2860 (s), 2215 (w), 1450 (s), 1365 (m), 1250 (s), 1200 (m), 1090 (s), 1070 (s), 1050 (s), 1015 (m), 930 (m), 910 (m), 900 (m), 840 (s), 750 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.7 (dd, 1H), 2.28-1.58 (m, 15H), 0.24 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 124.0 (s, 1C), 76.4 (s, 1C), 51.6 (t, 1C), 43.3 (d, 1C), 37.5 (t, 1C), 36.3 (t, 1C), 35.8 (t, 1C), 32.5 (t, 1C), 30.2 (d, 1C), 29.5 (t, 1C), 26.7 (d, 2C), 0.9 (q, 3C). HRMS *m/z* calcd. for $C_{15}H_{25}NOSi$ 263.1700, found 263.1704.

4-Cyano-4-hydroxyhomoadamantane (11), mp. 122-124°. MS (m/z): 191 (M^+), 173, 164, 145, 122, 107, 93, 80. IR (KBr): 3420 (s), 2900 (s), 2850 (s), 2215 (w), 1450 (m), 1220 (w), 1200 (w), 1080 (m), 1060 (m), 1030 (m), 1000 (m), 925 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.74 (dd, 1H), 2.52 (s, 1H), 2.32-1.51 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 124.6 (s, 1C), 75.8 (s, 1C), 49.4 (t, 1C), 42.6 (d, 1C), 37.9 (t, 1C), 36.1 (t, 1C), 35.8 (t, 1C), 33.2 (t, 1C), 30.1 (d, 1C), 29.4 (t, 1C), 26.8 (d, 1C), 26.6 (d, 1C). HRMS *m/z* calcd. for $C_{12}H_{17}NO$ 191.1305, found 191.1338.

Cleavage of Cyanohydrins 9, 10 and 11 in the Presence of Piperidine.- A mixture of cyanohydrin (1 mmol), piperidine (1.5-4.0 mmol) and water (1 ml) was stirred 2.5-14 hrs and extracted with dichloromethane (3 x 5 ml). Combined dichloromethane extracts were washed with water and dried over anhydrous $MgSO_4$. The solvent was removed and residue analyzed by GLC and by ^{13}C NMR spectroscopy.

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2. U. Fotadar, *Indian. J. Chem.*, **20B**, 1006 (1981).

3. On the basis of available experimental data, we are unable to rule out which of the reversible steps is responsible in the reactions with 4-protoadamantanone and 4-homoadamantanone. See also: G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

4. *endo*- and *exo*-Protoadamantanone cyanohydrins were obtained in a 3.5:1 ratio. The stereochemistry of the addition of trimethylsilyl cyanide is in accord with the Grignard addition of MeMgI to 4-protoadamantanone which gave predominantly 4-*endo*-methyl-4-hydroxyprotoadamantane,[5a] as well as with proposed attack of cyanide ion from the more open direction.[5b]

5. (a) D. Lenoir, D. J. Raber and P. v. R. Schleyer, *J. Am. Chem. Soc.* **96**, 2149 (1974); (b) D. A. Evans, G. L. Carroll and L. K. Truesdale, *J. Org. Chem.*, **39**, 914 (1974).

6. It is known that cyanohydrins can revert to the carbonyl compounds in the presence of amines; T. D. Stewart and C. H. Li, *J. Am. Chem. Soc.*, **60**, 2782 (1938). See also: W.-M. Ching and R. G.

Kallen, *ibid.*, **100**, 6119 (1978).

7. P. v. R. Schleyer, E. Funke and S. H. Liggero, *ibid.*, **91**, 3965 (1969).
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