# Introduction of Pharmacophoric Groups into Polycyclic Systems. Part 3[1]. Amine Derivatives of Adamantane and Diaza-adamantane

**Peter W. Hickmott*,† and Simon Wood**
*Department of Chemistry, University of Salford, Salford M5 4WT*
**Peter Murray-Rust**
*Department of Chemistry, University of Stirling, Stirling FK9 4LA*

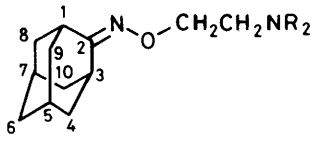
Methods for introducing various pharmacophoric amine-containing substituents into the adamantane system have been investigated. These include β-and α-aminoalkyloxyimino, β-aminoalkylidene, β-hydroxyethylamino, and β-phenylethylamino. Aminoalkyloxyimines were prepared by alkylation of the anion of adamantanone oxime with the corresponding aminoalkyl chloride, and a 2-aminoethylidene derivative was prepared by Wittig reaction of 2-dimethylaminoethyltriphenylphosphonium bromide with adamantanone. The reaction of 6-hydroxy-7-methyl-6-phenyladamantane-2,4-dione with aqueous sodium cyanide has been shown to be both regio- and stereo-selective, only the C-2 carbonyl group reacting from the most hindered direction. This is possibly due to stabilisation of the cyanohydrin by hydrogen bonding between the hydroxy and C-4 carbonyl groups. When trimethylsilyl cyanide was used in place of sodium cyanide, the reaction remained regioselective but, in the absence of hydrogen bond stabilisation, the stereoselectivity was lost and two trimethylsilyloxy cyanides were isolated, epimeric at C-2. The stereochemistry of one epimer has been determined by *X*-ray crystallography, details of which are reported here. Hydrogenation of the trimethylsilyloxy cyanides then gave the corresponding β-hydroxyamine, isolated as the hydrochloride. Finally 5,7-diphenyl-1,3-diaza-adamantan-6-one was prepared by a literature method and converted, with difficulty, into the oxime which was reduced by RedAl to the corresponding amine.

The presence of the aminoalkyl ether derivative of oximes in compounds showing a wide range of pharmacological activity, such as antispasmolytic,[2,3] antidepressant,[2,4] anticonvulsant,[4] and analgesic[3] activity, establishes its importance as an active pharmacophoric group. The beneficial effects of adamantyl substituents on the biological activity of drugs containing them,[5] and in particular the unique antiviral activity[6] and the anti-Parkinsonism[7] properties of 1-aminoadamantane, has prompted us to investigate the effect of incorporating aminoalkyloxyimino groupings into an adamantane system.

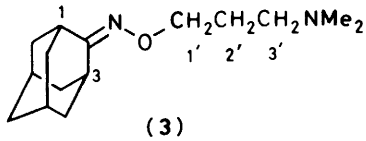
For ease of manipulation and accessibility, adamantanone oxime was chosen as the adamantane carrier molecule. The oxime anion was generated by base and converted into the aminoalkyloxyiminoadamantanes (**1**)—(**6**) by reaction with the appropriate aminoalkyl chloride, following the methodology of Budai *et al.*[3] The structures of the products obtained were confirmed by their analytical and spectroscopic data (see Table 1 and Experimental section), and require no further comment.

We have also investigated other methods of introducing amine substituents into the adamantane system, with a view to applying them to labile polyfunctional adamantane systems such as (**7**). The mild reductive amination of ketones with sodium cyanoborohydride and the corresponding amine at pH 6[8] has been shown to work well with adamantanone[9] but failed completely when applied to the labile 6-hydroxy-7-methyl-6-phenyladamantane-2,4-dione (**7**).[10] A recent modification of the Wittig reaction involving the use of 2-dimethylaminoethyltriphenylphosphonium bromide has been shown[11] to yield the corresponding 2-aminoethylidene derivative. Application of this method to adamantanone readily gave the unsaturated amine (**8**). However, since this compound showed no activity in the primary analgesic screen, unlike the aminoalkoxyimino derivatives (**1**)—(**6**), this reaction was not extended to the synthesis of other adamantane derivatives of this type.

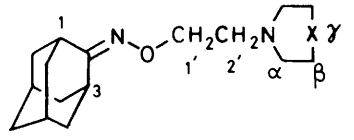
The β-hydroxy amine or substituted ethanolamine unit is another pharmacophoric group present in numerous compounds possessing biological activity.[12–14] These compounds are basically anticholinergic agents and as such are of considerable commercial interest. From the synthetic point



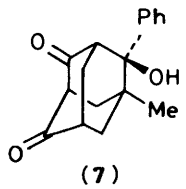
(**1**) R = H
(**2**) R = Me



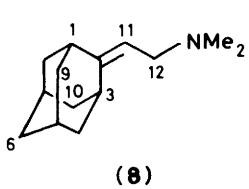
(**3**)



(**4**) X = -
(**5**) X = O
(**6**) X = $CH_2$



(**7**)



(**8**)

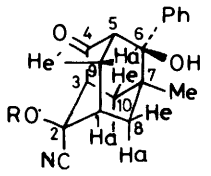
† *Present Address:* Department of Chemistry, University of Natal, King George V Avenue, Durban, Natal, 4001.

**Table 1.** Preparation of oximo ethers

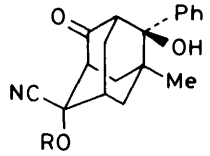
| Compd. | Method | Yield[a] (%) | B.p.[b] (°C) | Molecular formula | Molecular ion (*m/z*) Found | Calc. |
|---|---|---|---|---|---|---|
| (1) | C | 28 (64) | 55 | $C_{12}H_{21}N_2O$ | 209.1653 | 209.1653 |
| (2) | A | 39 (63) | 82 | $C_{14}H_{24}N_2O$ | 236.1888 | 236.1888 |
| (3) | A | 35 (43) | 90 | $C_{15}H_{26}N_2O$ | 250.2048 | 250.2044 |
| (4) | B | 47 (54) | 60 | $C_{16}H_{26}N_2O$ | 262.2044 | 262.2044 |
| (5) | B | 55 (68) | 90 | $C_{16}H_{26}N_2O_2$ | 278.1991 | 278.1993 |
| (6) | B | 56 (72) | 65 | $C_{17}H_{28}N_2O$ | 276.2199 | 276.2200 |

[a] Yield in parentheses is after correction for unchanged starting material. [b] At 0.5 mmHg pressure.

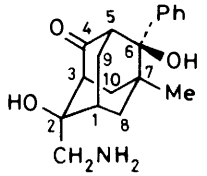
of view the ethanolamine moiety also possesses the advantage that it is readily incorporated into polycyclic ketones by reduction of the corresponding cyanohydrin. Accordingly the adamantanedione (**7**) was treated with 1 equivalent of sodium cyanide. The i.r. spectrum of the product showed nitrile and carbonyl absorptions at 2 235 and 1 705 $cm^{-1}$ respectively, confirming that only one carbonyl group had reacted. Since cyanohydrin formation is an equilibrium process[15,16] the thermodynamically more stable C-2 cyanohydrin should be favoured over the C-4 cyanohydrin in the latter case owing to developing 1,3-diaxial interactions with the bulky phenyl substituent at C-6. That only one of the two possible C-2 epimers had been formed was indicated by the absence of twinning of any of the peaks in the $^{13}C$ n.m.r. spectrum. Based on thermodynamic considerations the cyanohydrin must be



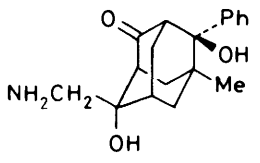

(**9**) R = H
(**10**) R = $SiMe_3$




(**11**) R = H
(**12**) R = $SiMe_3$




(**13**)




(**14**)

assigned structure (**9**), contrary to a previous assignment,[9] and this is confirmed by comparison of the $^{13}C$ n.m.r. spectrum with those of the trimethylsilyl derivatives (**10**) and (**12**), the structure of (**12**) having been confirmed by *X*-ray analysis (see later). The pertinent chemical shifts are those of the C-8, -9, and -10 carbons which are as follows: (**9**): 36.15, 29.4, and 36.15; (**10**): 35.3, 29.3, and 36.5; (**12**): 32.1, 28.7, and 32.55, respectively. This means that the C-2 carbonyl group has been approached by the cyanide anion from the more hindered direction (two developing 1,3-diaxial interactions with H *versus* one from the other direction) confirming the expectation that the C-2 stereochemistry must arise from operation of thermodynamic rather than kinetic control. This can be attributed to either better accommodation of the bulky solvated hydroxy group in

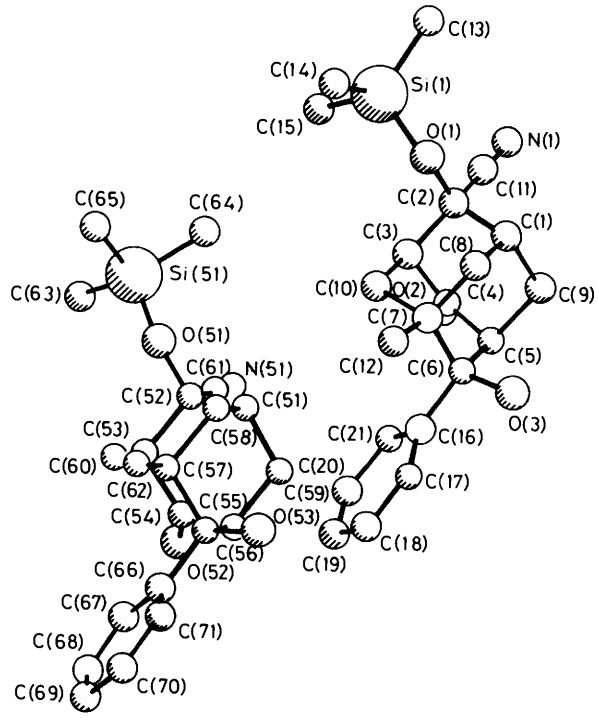



**Figure.**

(**9**) compared with (**11**), or a weak hydrogen bonding interaction with the carbonyl group in (**9**). Certainly the i.r. spectrum shows low frequency hydroxy absorption (3 300 $cm^{-1}$) which can be attributed to H-bonding.[17]

The yield of cyanohydrin (**9**) was unacceptably low (13%) and in order to improve on this the dione (**7**) was treated with trimethylsilyl cyanide.[18] This gave the trimethylsilyloxy cyanide in much better yield (68%) as a mixture of two isomers epimeric at C-2. These were separated by chromatography and their $^1H$ and $^{13}C$ n.m.r. spectroscopic data are summarised in Tables 2 and 3. These show that, apart from the C-8 and C-10 chemical shifts, there are very little differences between the two isomers and an unequivocal stereochemical assignment cannot be made. An *X*-ray crystallographic analysis of isomer (**12**) was, therefore, carried out the fractional atomic co-ordinates for which are summarised in Table 4 and the crystallographic structure and numbering illustrated in the Figure.* This clearly shows the bulky trimethylsilyloxy moiety to be *cis* orientated with respect to the C-7 methyl group (C-12 in Figure 1) and this confirms the stereochemistry depicted in structure (**12**).

The ratio of isomers (**10**):(**12**) obtained was 1:2 but, unfortunately, this was determined after purification[9] and thus will not be a true measure of the product ratio as actually formed. Nevertheless, it does serve to illustrate that, in the absence of H-bonding stabilisation, nucleophilic attack on the C-2 carbonyl group occurs from both directions in a product controlled reaction, in agreement with our previous reasoning concerning the preferential formation of cyanohydrin (**9**) rather than (**11**).

Reduction of the cyanohydrin (**9**) with lithium aluminium

* The bond lengths and angles together with the thermal parameters are available as a Supplementary publication [SUP No. 56305 (7pp.)]; for details of the Supplementary publications system see Instructions for Authors, *J. Chem. Soc., Perkin Trans.* 1, 1985, Issue 1. The structure factors are available on request from the Editorial office.

**Table 2.** $^1$H N.m.r. spectral data[a] and assignments for the two C-2 epimers of 6-hydroxy-7-methyl-4-oxo-6-phenyl-2-trimethylsilyloxyadamantane-2-carbonitrile [(**10**) and (**12**)]

| | | Isomer (**10**) | | | | Isomer (**12**) | | | |
|---|---|---|---|---|---|---|---|---|---|
| Assignment[b] | Splitting | Chemical shift | Coupling (Hz)[c] Geminal | Vicinal | W[d] | Chemical shift | Coupling (Hz)[c] Geminal | Vicinal | W[d] |
| $SiMe_3$ | s | 0.29 | — | — | — | 0.17 | — | — | — |
| 5-Me | s | 0.67 | — | — | — | 0.68 | — | — | — |
| OH | s | 1.18 | — | — | — | 1.24 | — | — | — |
| 10e-H | dt | 1.40 | 13.1 (10a-H) | 2.8 (3-H) | 2.5 (8e-H) | 1.26 | 12.4 (10a-H) | 2.5 (3-H) | 2.4 (8e-H) |
| 10a-H | dd | 1.64 | 13.1 (10e-H) | 2.6 (3-H) | — | 1.66 | 12.4 (10e-H) | 2.4 (3-H) | — |
| 8a-H | dt | 1.77 | 12.8 (8e-H) | 2.4 (1-H) | 2.0 (9e′-H) | 1.77 | 11.8 (8e-H) | 2.3 (1-H) | 2.0 (9e′-H) |
| 1-H | m | 1.93 | — | 2.4 (8a-H) | obnm | 1.98 | — | 2.3 (8a-H) | obnm |
| | | | | 2.5 (9e′-H) | (3-H, 5-H) | | | 2.4 (9e′-H) | (3-H, 5-H) |
| | | | | 2.6 (9a′-H) | | | | 2.6 (9a′-H) | |
| | | | | 3.0 (8e-H) | | | | 3.2 (8e-H) | |
| 9e′-H | dq | 2.10 | 11.8 (9a′-H) | 2.5 (1-H) | 2.0 (8a-H) | 1.83 | 12.9 (9a′-H) | 2.4 (1-H) | 2.0 (8a-H) |
| | | | | 2.4 (5-H) | | | | 2.8 (5-H) | |
| 9a′-H | dt | 2.37 | 11.8 (9e′-H) | 2.6 (1-H) | — | 2.47 | 12.9 (9e′-H) | 2.6 (1-H) | — |
| | | | | 2.8 (5-H) | | | | 2.9 (8e-H) | |
| 5-H | m | 2.47 | — | 2.4 (9e′-H) | obnm | 2.54 | — | 2.8 (9e′-H) | obnm |
| | | | | 2.8 (9a′-H) | (1-H, 3-H) | | | 2.9 (9a′-H) | (1-H, 3-H) |
| 8e-H | dt | 2.50 | 12.8 (8a-H) | 3.0 (1-H) | 2.5 (10e-H) | 2.25 | 11.8 (8a-H) | 3.2 (1-H) | 2.4 (10e-H) |
| 3-H | m | 2.80 | — | 2.8 (10e-H) | obnm | 2.87 | — | 2.5 (10e-H) | obnm |
| | | | | 2.6 (10a-H) | (1-H, 5-H) | | | 2.4 (10a-H) | (1-H, 5-H) |
| Ph | m | 7.10 | — | — | — | 7.10 | — | — | — |
| | m | 7.50 | — | — | — | 7.57 | — | — | — |

[a] 220 MHz Spectra in $C_6D_6$. [b] a and e Refer to axial and equatorial hydrogens respectively, attached to ring numbered 1, 2, 3, 10, 7, 8; a′ and e′ refer to hydrogens axial or equatorial to the 1, 9, 5, 6, 7, 8 ring. [c] Proton coupled is shown in parentheses. [d] obnm = observed (by decoupling) but not measurable.

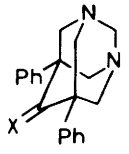
**Table 3.** $^{13}$C N.m.r. spectral data and assignments for isomers (**10**) and (**12**)

| Assignment | Splitting | Isomer (**10**) | Isomer (**12**) |
|---|---|---|---|
| $SiMe_3$ | q | 1.05 | 1.1 |
| 5-Me | q | 22.85 | 23.4 |
| C-9 | t | 29.3 | 28.7 |
| C-8* | t | 35.3 | 32.1 |
| C-7 | s | 35.6 | 35.55 |
| C-10* | t | 36.5 | 32.55 |
| C-1 | d | 38.5 | 38.3 |
| C-5† | d | 55.7 | 56.35 |
| C-3† | d | 57.4 | 56.8 |
| C-2 | s | 77.4 | 74.7 |
| C-6 | s | 78.9 | 78.85 |
| C≡N | s | 119.0 | 119.35 |
| Ph | d | 127.3 | 127.25 |
| | | 127.55 | 127.55 |
| | s | 143.7 | 143.25 |
| C-4 | s | 210.8 | 210.5 |

* Interchangeable. † Interchangeable.

hyride gave a mixture of reduction products which could not be purified. Consequently the trimethylsilyloxy cyanides (**10**) and (**12**) were each subjected to catalytic hydrogenation in order to keep the C-4 carbonyl group intact and thus prevent complications due to the introduction of an extra chiral centre at C-4. In this way the adamantane hydroxy amines (**13**) and (**14**) were obtained, as their hydrochloride salts. These compounds are not very stable, attempted conversion into the free amine by acid-base treatment resulting in decomposition; an analytically pure sample could not be obtained. However the spectroscopic data provides adequate confirmation of their structures.

Finally, we were interested in determining the effect of introducing a pharmacophoric group into a diaza-adamantane,




(**15**) X = O

(**16**) X = NOH

(**17**) X = H, $NH_2$

such as the diphenyldiaza-adamantanone (**15**) which is readily obtainable by a Mannich reaction on dibenzyl ketone.[19] Since this has been shown to possess strychnine-like activity[20] it is perhaps not surprising that no pharmacological work appears to have been carried out on this class of compound since the early 1960's. Compound (**15**) was converted, with difficulty, into the oxime (**16**) which was reduced by RedAl to the amine (**17**). The structure of the latter is confirmed by the analytical and spectroscopic data (see Experimental section). Interestingly the amine protons give signals in the $^1$H n.m.r. spectrum at exceptionally high field (δ 0.65). This must clearly be due to them lying in the shielding regions of the C-5 and C-7 phenyl substituents and indicates that these benzene rings are twisted out of the plane of the 3,4,5,6,7,10 ring in order to accommodate substituents at C-6. Perhaps not surprisingly, neither compound (**16**) or (**17**) showed any significant activity in the primary analgesic screen and since the latter showed acute toxicity to mice, no further investigation of these compounds is contemplated.

## Experimental

I.r. spectra were determined with a Perkin-Elmer 257 spectrometer as Nujol mulls; $^1$H n.m.r. and $^{13}$C n.m.r. spectra

**Table 4.** Fractional atomic co-ordinates ( × $10^4$)

| Atom | x/a | y/b | z/c | Atom | x/a | y/b | z/c |
|---|---|---|---|---|---|---|---|
| C(1) | 4 457 | 4 175 | 0 018 | C(51) | 4 831 | 3 887 | 4 851 |
| C(2) | 3 144 | 4 205 | 0 317 | C(52) | 3 573 | 3 703 | 5 232 |
| C(3) | 2 733 | 3 683 | 0 966 | C(53) | 3 492 | 3 279 | 6 020 |
| C(4) | 3 199 | 3 128 | 0 476 | C(54) | 4 303 | 2 762 | 5 669 |
| C(5) | 4 466 | 3 069 | 0 261 | C(55) | 5 543 | 2 948 | 5 383 |
| C(6) | 5 010 | 3 168 | 1 062 | C(56) | 5 996 | 3 299 | 6 098 |
| C(7) | 4 560 | 3 761 | 1 498 | C(57) | 5 161 | 3 835 | 6 389 |
| C(8) | 4 948 | 4 263 | 0 830 | C(58) | 5 235 | 4 235 | 5 570 |
| C(9) | 4 832 | 3 576 | −0 414 | C(59) | 5 604 | 3 349 | 4 576 |
| C(10) | 3 244 | 3 752 | 1 776 | C(60) | 3 918 | 3 610 | 6 730 |
| C(11) | 2 626 | 4 158 | −0 438 | C(61) | 3 102 | 3 382 | 4 547 |
| C(12) | 5 007 | 3 895 | 2 309 | C(62) | 5 481 | 4 207 | 7 128 |
| C(13) | 1 519 | 5 628 | 0 108 | C(63) | 0 499 | 3 973 | 5 759 |
| C(14) | 1 865 | 5 608 | 1 933 | C(64) | 1 863 | 4 649 | 4 182 |
| C(15) | 0 382 | 4 677 | 1 426 | C(65) | 1 545 | 5 177 | 6 016 |
| C(16) | 4 798 | 2 639 | 1 707 | C(66) | 6 082 | 2 912 | 6 898 |
| C(17) | 5 545 | 2 542 | 2 262 | C(67) | 5 383 | 2 437 | 7 205 |
| C(18) | 5 350 | 2 083 | 2 865 | C(68) | 5 523 | 2 110 | 7 898 |
| C(19) | 4 437 | 1 721 | 2 951 | C(69) | 6 366 | 2 222 | 8 344 |
| C(20) | 3 720 | 1 798 | 2 416 | C(70) | 7 055 | 2 700 | 8 040 |
| C(21) | 3 902 | 2 254 | 1 787 | C(71) | 6 930 | 3 031 | 7 332 |
| N(1) | 2 230 | 4 147 | −1 036 | N(51) | 2 729 | 3 122 | 4 064 |
| O(1) | 2 840 | 4 754 | 0 741 | O(51) | 2 899 | 4 205 | 5 507 |
| O(2) | 2 567 | 2 768 | 0 233 | O(52) | 3 954 | 2 280 | 5 539 |
| O(3) | 6 224 | 3 230 | 0 726 | O(53) | 7 096 | 3 537 | 5 692 |
| Si(1) | 1 649 | 5 150 | 1 020 | Si(51) | 1 693 | 4 485 | 5 367 |

were recorded at 90 and 20 MHz respectively, using Perkin-Elmer R32 and Varian CFT-20 spectrometers, as $CDCl_3$ solutions (unless otherwise stated) with tetramethylsilane as internal standard; accurate mass measurements were obtained with an AEI MS 902S mass spectrometer operating at 70 eV.

Adamantanone oxime was prepared by the literature method.[21] The following spectroscopic data was determined for comparison with that of the oximino ethers: $\nu_{max.}$ 3 200 (OH) and 1 670 $cm^{-1}$ (C=N); $\delta_H$ 1.75—2.05 (m, 12 H), 2.53 (br s, 1 H, 1-H), 3.60 (br s, 1 H, 3-H), and 4.65 (br s, 1 H, OH); $\delta_C$ 166.4 (s, C-2), 38.7 (t, C-6), 37.2 (t, C-4, -10), 36.35 (t, C-8, -9), 36.0 (d, C-3), 28.55 (d, C-1), and 27.7 (d, C-5, -7).

*Aminoalkyl Chlorides: General Procedure.*—The commercially available hydrochloride (0.05 mol) was dissolved in water (20 ml) and the solution basified with potassium carbonate. The solution was extracted with ether (3 × 30 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residual liquid was distilled under reduced pressure to give the following aminoalkyl chlorides: dimethylaminoethyl chloride (3.51 g, 65%), $\delta_H$ 2.30 (s, 6 H, Me), 2.66 (t, 2 H, *J* 6 Hz, $NCH_2$), and 3.61 (t, 2 H, *J* 6 Hz, $CH_2Cl$); dimethylaminopropyl chloride (4.72 g, 78%), $\delta_H$ 1.7—2.0 (m, 2 H, $CH_2$), 2.30 (s, 6 H, Me), 2.37 (t, 2 H, *J* 7 Hz, $NCH_2$), and 3.66 (t, 2 H, *J* 7 Hz, $CH_2Cl$); pyrrolidin-1-ylethyl chloride (4.20 g, 63%), $\delta_H$ 1.78 (t, 4 H, *J* 5 Hz, β-$CH_2$), 2.56 (t, 4 H, *J* 5 Hz, α-$CH_2$), 2.78 (t, 2 H, *J* 7 Hz, $NCH_2$), and 3.55 (t, 2 H, *J* 7 Hz, $CH_2Cl$); morpholinoethyl chloride (5.13 g, 69%), $\delta_H$ 2.50 (t, 4 H, *J* 4 Hz, $CH_2NCH_2$), 2.72 (t, 2 H, *J* 7 Hz, $NCH_2$), 3.62 (t, 2 H, *J* 7 Hz, $CH_2Cl$), and 3.73 (t, 4 H, *J* 4 Hz, $CH_2OCH_2$); *piperidinoethyl chloride* (4.96 g, 67%), $\delta_H$ 1.3—1.9 (m, 6 H, β- and α-$CH_2$), 2.37 (t, 4 H, *J* 4 Hz, α-$CH_2$), 2.63 (t, 2 H, *J* 7 Hz, $NCH_2$), 3.54 (t, 2 H, *J* 7 Hz, $CH_2Cl$).

*Oximino Ethers: General Procedures.—Method A.* A solution of adamantanone oxime (1.65 g, 10 mmol) in dry toluene (30 ml) was added dropwise to a stirred suspension of sodium hydride (0.48 g, 10 mmol) in dry toluene (10 ml) at 85 °C. The temperature was then raised to 130 °C for 2 h. A solution of the aminoalkyl chloride (0.011 mol) in dry toluene (5 ml) was then added dropwise. The mixture was heated for a further 6 h at 130 °C, and then cooled to 30 °C and diluted with water (10 ml). The organic layer was separated and extracted with dilute hydrochloric acid (3 × 15 ml). The acid extract was basified with ammonia solution to pH 10, extracted with ether (4 × 25 ml), and the extract dried ($MgSO_4$) and concentrated under reduced pressure. T.l.c. (ethyl acetate–ethanol, 4:1) indicated the required product at low $R_F$ value and unchanged adamantanone oxime at higher $R_F$ value. The mixtures were separated by flash chromatography using a 30 mm diameter column packed with 200 mm of silica and the same eluant. Twenty fractions (20 ml) were collected and analysed by t.l.c. The ones containing only the product were combined, concentrated, and distilled.

*Method B.* Adamantanone oxime (1.65 g, 10 mmol) was added to a solution of sodium (0.25 g, 11 mmol) in absolute ethanol (20 ml) and the mixture was heated under reflux for 0.5 h; a solution of the aminoalkyl chloride (10 mmol) in absolute ethanol (5 ml) was then added. The mixture was heated under reflux for a further 4 h after which it was cooled and the solvent removed under reduced pressure. Water (20 ml) was added to the residue and the mixture extracted with ether (4 × 20 ml). The combined ether extracts were extracted with dilute hydrochloric acid (3 × 15 ml). The combined acid extracts were basified with aqueous ammonia to pH 10, extracted with ether (4 × 25 ml), and the combined extracts dried ($MgSO_4$), and concentrated under reduced pressure. Purification was effected as in Method A.

*Method C.* Adamantanone oxime (1.65 g, 10 mmol) and 2-chloroethylamine hydrochloride (2.32 g, 20 mmol) were added to a solution of sodium (0.92 g, 40 mmol) in absolute ethanol (40 ml) at room temperature. The mixture was stirred at room temperature for 4 h after which the sodium chloride was filtered off and the filtrate concentrated under reduced pressure. Water (10 ml) was added to the residue and the mixture extracted with ether (4 × 25 ml), and the combined extracts dried ($MgSO_4$) and concentrated under reduced pressure. Purification was effected as in Method A.

Preparative details and analytical data are summarised in Table 1 and the relevant spectroscopic data are given below.

*Adamantanone* O-(2-*aminoethyl*)*oxime* (**1**), $\nu_{max.}$ 3 400 ($NH_2$) and 1 640 $cm^{-1}$ (C=N); $\delta_H$ 1.65 (br s, 2 H, $NH_2$), 1.8—2.15 (m, 12 H), 2.55 (m, 1 H, C-1), 2.97 (t, 2 H, *J* 5 Hz, 2′-H), 3.53 (br s, 1 H, 3-H), and 4.06 (t, 2 H, *J* 5 Hz, 1′-H); $\delta_C$ 166.3 (s, C-2), 74.0 (t, C-1′), 40.75 (t, C-2′), 38.5 (t, C-6), 37.1 (t, C-4, -10), 36.0 (t, C-8, -9), 35.7 (d, C-3), 29.0 (d, C-1), and 27.35 (d, C-5, -7).

*Adamantanone* O-(2-*dimethylaminoethyl*)*oxime* (**2**), $\nu_{max.}$ 1 640 $cm^{-1}$ (C=N); $\delta_H$ 1.7—2.1 (m, 12 H), 2.28 (s, 6 H, Me), 2.61 (t, overlaid by br s, 3 H, *J* 6 Hz, $NCH_2$ and 1-H), 3.50 (br s, 1 H, 3-H), and 4.13 (t, 2 H, *J* 6 Hz, $OCH_2$); $\delta_C$ 166.5 (s, C-2), 71.3 (t, C-1′), 57.95 (t, C-2′), 45.75 (q, Me), 38.9 (t, C-6), 37.45 (t, C-4, -10), 36.35 (t, C-8, -9), 36.1 (d, C-3), 29.5 (d, C-1), 27.7 (d, C-5, -7).

*Adamantanone* O-(3-*dimethylaminopropyl*)*oxime* (**3**), $\nu_{max.}$ 1 640 $cm^{-1}$ (C=N); $\delta_H$ 1.7—2.1 (m, 14 H), 2.23 (s, 6 H, Me), 2.44 (t, 2 H, *J* 6 Hz, 3′-H), 2.54 (br s, 1 H, 1-H), 3.50 (br s, 1 H, 3-H), and 4.05 (t, 2 H, *J* 6 Hz, 1′-H); $\delta_C$ 164.75 (s, C-2), 70.25 (t, C-1′), 55.75 (t, C-3′), 44.65 (q, Me), 38.2 (t, C-6), 36.81 (t, C-4, -10), 35.85 (t, C-8, -9), 35.35 (d, C-3), 28.67 (d, C-1), 27.1 (d, C-5, -7), 26.7 (C-2′).

*Adamantanone* O-(2-*pyrrolidin*-1-*ylethyl*)*oxime* (**4**), $\nu_{max.}$ 1 640 $cm^{-1}$ (C=N); $\delta_H$ 1.6—2.1 (m, 16 H), 2.57 (t overlaid by br s, 5 H, *J* 5 Hz, α-H and 1-H), 2.75 (t, 2 H, *J* 6 Hz, 2′-H), 3.56 (br s, 1 H, 3-H), and 4.18 (t, 2 H, *J* 6 Hz, 1′-H); $\delta_C$ 166.3 (s, C-2), 72.15 (t, C-1′), 54.55 (t, C-2′ and C-α), 38.8 (t, C-6), 37.45 (t, C-4, -10),

36.4 (t, C-8, -9), 36.0 (d, C-3), 29.5 (d, C-1), 27.7 (d, C-5, -7), and 23.4 (t, C-β).

*Adamantanone* O-(*2-morpholinoethyl*)*oxime* (**5**), $\nu_{max.}$ 1 640 $cm^{-1}$ (C=N); $\delta_H$ 1.7—2.1 (m, 12 H), 2.54 (t overlaid by br s, 5 H, *J* 4 Hz, α-H and 1-H), 2.66 (t, 2 H, *J* 6 Hz, 2′-H), 3.45 (br s, 1 H, 3-H), 3.70 (t, 4 H, *J* 4 Hz, β-H), and 4.15 (t, 2 H, *J* 6 Hz, 1′-H); $\delta_C$ 165.7 (s, C-2), 70.4 (t, C-1′), 66.4 (t, C-β), 56.85 (t, C-2′), 53.55 (t, C-α), 38.4 (t, C-6), 36.95 (t, C-4, -10), 36.0 (d, C-8, -9), 35.6 (d, C-3), 29.0 (d, C-1), and 27.3 (d, C-5, -7).

*Adamantanone* O-(*2-piperidinoethyl*)*oxime* (**6**), $\nu_{max.}$ 1 640 $cm^{-1}$ (C=N); $\delta_H$ 1.3—1.7 (m, 6 H, β-H, γ-H), 1.8—2.1 (m, 12 H), 2.50 (t, overlaid by br s, 5 H, *J* 4 Hz, α-H and 1-H), 2.66 (t, 2 H, *J* 6 Hz, 2′-H), 3.50 (br s, 1 H, 3-H), and 4.19 (t, 2 H, *J* 6 Hz, 1′-H); $\delta_C$ 166.4 (s, C-2), 71.0 (t, C-1′), 57.65 (t, C-2′), 54.7 (t, C-α), 38.9 (t, C-6), 37.45 (t, C-4, -10), 36.3 (t, C-8, -9), 36.1 (d, C-3), 29.5 (d, C-1), 27.7 (d, C-5, -7), 25.85 (t, C-β), 24.05 (t, C-γ).

2-(*Adamantan-2-ylidene*)-N,N-*dimethylethylamine* (**8**).—Dry and finely powdered 2-dimethylaminoethyltriphenylphosphonium bromide (3.34 g, 10 mmol; ex. Aldrich) in dry tetrahydrofuran (25 ml; distilled from $LiAlH_4$) was placed under a nitrogen atmosphere. To this stirred mixture was added butyllithium in hexane (1.75 M; 5.7 ml, 10 mmol) over 0.2 h at 0 °C. An orange solution developed and, after 0.5 h at 0 °C, a solution of adamantanone (1.5 g, 10 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to reach room temperature and then warmed to 60 °C for 20 h. On cooling the mixture was acidified with 2M-hydrochloric acid (20 ml) and the organic solvent removed under reduced pressure. The aqueous layer was extracted with ether (3 × 25 ml), in order to remove unchanged starting material, and basified with potassium carbonate and then extracted with chloroform (3 × 50 ml). The combined chloroform extracts were dried ($K_2CO_3$) and concentrated under reduced pressure. Distillation of the residual oil gave the unsaturated amine (**8**) (0.64 g, 31%), b.p. 80—81 °C/1 mmHg; $\nu_{max.}$ 1 670 $cm^{-1}$ (C=C); $\delta_H$ 1.7—2.2 (m, 12 H), 2.29 (s, 6 H, Me), 2.38 (br s, 1 H, 3-H), 2.90 (d overlaid by a br s, 3 H, *J* 7 Hz, 1-, 12-H), and 5.12 (t, 1 H, *J* 7 Hz, 11-H); $\delta_C$ 150.4 (s, C-2), 113.3 (d, C-11), 55.3 (t, C-12), 44.8 (q, Me), 40.45 (d, C-1), 39.55 (t, C-8, -9), 38.5 (t, C-4, -10), 37.0 (t, C-6), 32.0 (d, C-3), and 28.35 (d, C-5, -7) (Found: C, 81.51, H, 11.03, N, 6.76%; $M^+$, 205.1830. Calc. for $C_{14}H_{23}N$: C, 81.89, H, 11.29, N, 6.82%, *M*, 205.1830).

2,6-*Dihydroxy-7-methyl-4-oxo-6-phenyladamantane-2-carbonitrile* (**9**).—A mixture of 6-hydroxy-7-methyl-6-phenyladamantane-2,4-dione (**7**)[22] (0.54 g, 2 mmol) and sodium cyanide (0.98 g, 2 mmol) in water (65 ml) and ethanol (65 ml) was stirred for 48 h at room temperature. The mixture was diluted with water (400 ml) and the resulting solution extracted with ether (4 × 50 ml). The combined ether extracts were washed successively with 5% hydrochloric acid (200 ml), 5% aqueous sodium hydrogen carbonate (200 ml), and saturated brine (200 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallisation of the resulting white solid from chloroform gave the cyanohydrin (**9**) (0.079 g, 13%), m.p. 208—209 °C; $\nu_{max.}$ 3 475 and 3 300 (OH), 2 235 (C≡N), and 1 705 (C=O) $cm^{-1}$; $\delta_H$ [$(CD_3)_2CO$] 0.80 (s, 3 H, Me), 1.77 (m, 3 H, 8a-, 10a-, 10e-H), 2.28 (m, 2 H, 1-, 9e′-H), 2.73 (m, 2 H, 8e-, 9a′-H), 2.88 (m, 2 H, 3-, 5-H), 4.42 (br s, 1 H, 6-HO), 6.08 (br s, 1 H, 2-HO), and 7.27 (m) and 7.57 (m) (5 H, Ph); $\delta_C$ [$(CD_3)_2CO$] 211.3 (s, C-4), 145.4 (s), 128.4 (d), 127.95 (d, Ph), 120.6 (s, C≡N), 79.1 (s, C-6), 76.9 (s, C-2), 58.0 (d, C-5), 55.65 (d, C-3), 37.95 (d, C-1), 37.45 (s, C-7), 36.15 (t, C-8, -10), 29.4 (t, C-9), and 23.2 (q, Me) (Found: C, 72.48, H, 6.16, N, 4.88%; $M^+$, 297.1363. Calc. for $C_{18}H_{19}NO_3$: C, 72.71, H, 6.44, N, 4.71%; *M*, 297.1364).

6-*Hydroxy-7-methyl-4-oxo-6-phenyl-2-trimethylsilyloxyadamantane-2-carbonitrile* [(**10**) *and* (**12**)].—Trimethylsilyl cyanide (0.66 g, 6 mmol) was added dropwise with stirring to a solution of the adamantanedione (**7**) (1.62 g, 6 mmol) and zinc iodide (50 mg) in chloroform (6 ml) at 0 °C under a nitrogen atmosphere. After being stirred at room temperature for 20 h the red solution was concentrated under reduced pressure. The resulting solid was purified by medium pressure chromatography using a 60 mm diameter column packed with silica (80 g) and eluting with an ethyl acetate–light petroleum (b.p. 60—82 °C) (1:20). Two hundred fractions (20 ml) were collected and monitored by t.l.c. The appropriate fractions were combined and evaporated to give two isomers of the nitrile (**10**) and (**12**). The individual isomers were recrystallised from light petroleum (b.p. 60—80 °C) to give colourless elongated needles of (**10**) (0.461 g, 21%), m.p. 169—170 °C (Found: C, 68.1; H, 7.33; N, 3.67%; $M^+$, 369. Calc. for $C_{21}H_{27}NO_3Si$: C, 68.26; H, 7.36; N, 3.79%, *M*, 369), and (**12**) (0.914 g, 41%), m.p. 266—267 °C (Found: C, 68.35; H, 7.35; N, 3.70%; $M^+$, 369. Calc. for $C_{22}H_{27}NO_3Si$: C, 68.26; H, 7.36; N, 3.79%; *M*, 369). The spectroscopic data are summarised in Tables 2 and 3.

2,6-*Dihydroxy-7-methyl-4-oxo-6-phenyladamant-2-ylmethylamine Hydrochloride* [(**13**) *and* (**14**)].—The silylcyanohydrins (**10**) and (**12**) (0.406 g, 1.1 mmol) were each separately hydrogenated in the presence of 5% platinum oxide on charcoal (0.2 g) in absolute ethanol (50 ml) containing concentrated hydrochloric acid (0.1 ml) under an atmosphere of hydrogen. The mixtures were shaken until hydrogen absorption had ceased (*ca.* 40 h). The mixtures were then filtered through HiFlo and the filtrates concentrated under reduced pressure to give the crude solid hydrochloride. Partial purification of the latter was effected by dissolution in the minimum of methanol and addition of diethyl ether until precipitation occurred. Results obtained for each isomer were as follows.

Isomer (**13**) (0.30 g, 81%), m.p. 260—262 °C (decomp.); $\delta_H$ ($CD_3OD$–2M-NaOH; 250 MHz) 0.78 (s, 3 H, Me), 1.60 (m, 3 H, 10-, 8a-H), 1.92 (m, 1 H, 1-H), 2.25 (dq, 1 H, 9e′-H), 2.5—2.6 (m, 2 H, 8e-, 9a′-H), 2.74 (m, 2 H, 3-, 5-H), 2.93 (s, 2 H, $CH_2N$), and 7.28 (m) and 7.56 (m) (Ph); $\delta_C$($CD_3OD$) 217.6 (s, C-4), 146.2 (s), 129.1 (d), 128.2 (d, Ph), 79.6 (s, C-6), 77.8 (s, C-2), 59.0 (d, C-5), 54.9 (d, C-3), 45.5 (t, $CH_2N$), 37.1 (s, C-7), 36.7 (t, C-10), 36.6 (d, C-1), 35.4 (t, C-8), 31.1 (t, C-9), and 23.4 (q, Me) (Found: $M^+$, 301.1676. Calc. for $C_{18}H_{23}NO_3$: *M*, 301.1677).

*Isomer* (**14**) (0.28 g, 75%), m.p. 145—147 °C (decomp.); $\delta_H$($D_2O$; 90 MHz) 0.74 (s, 3 H, Me), 1.5—2.3 (m, 5 H), 2.7—2.9 (m, 4 H), 3.1 (m, 2 H), and 7.4 (m, 5 H); $\delta_C$ [$D_2O$; $Me_3Si(CD)_2CO_2Na$ internal reference] 221.55 (s, C-4), 146.3 (s), 130.1 (d, Ph), 82.1 (s, C-6), 77.65 (s, C-2), 59.0 (d, C-5), 57.3 (d, C-3), 47.6 (t, $CH_2N$), 38.2 (s, C-7), 36.5 (d, C-1), 36.3 (t, C-10), 35.4 (t, C-8), 31.2 (t, C-9), and 25.1 (q, Me) (Found: $M^+$, 301.1676. Calc. for $C_{18}H_{23}NO_3$: *M*, 301.1677).

6-*Amino-5,7-diphenyl-1,3-diaza-adamantane* (**17**).—A solution of 5,7-diphenyl-1,3-diaza-adamantan-6-one (**15**)[18] (3.04 g, 10 mmol) and hydroxylamine hydrochloride (1.4 g, 20 mmol) in a mixture of pyridine (60 ml) and ethanol (60 ml) was heated under reflux for 20 h. The mixture was cooled and the solvent removed under reduced pressure. The solid residue was stirred with pyridine (10 ml) and water (50 ml) for 0.1 h and the solid collected, washed with cold water, and recrystallised from aqueous ethanol to give the oxime (**16**) as white crystals (1.46 g, 46%), m.p. 274—275 °C; $\nu_{max.}$ 3 250 (OH), 1 600 (C=N), and 965 (N–O) $cm^{-1}$; $\delta_H$ [$(CD_3)SO$] 3.36—3.8 (br overlaid AB quartets, 8 H, 4-, 8-, 9-, 10-H), 4.03 (s, 2 H, 2-H), 7.2—7.6 (m, 10 H, Ph), and 9.78 (s, 1 H, OH); $\delta_C$ [$(CD_3)_2SO$] 158.0 (s, C-6), 144.7 (s, Ph), 142.6 (s, Ph), 127.75 (d), 127.1 (d), 126.75 (d), 125.9 (d), 125.3 (d, Ph), 71.7 (t, C-2), 63.05 (t, C-4, -8, -9, -10), 42.3 (s, C-5 or -7), 41.4 (s, C-7 or -5) (Found: C, 75.3; H, 6.7; N, 13.15%; $M^+$, 319.1684. Calc. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16%; *M*, 319.1683).

A suspension of the oxime (**16**) (0.96 g, 3 mmol) in dry tetrahydrofuran (50 ml) was added dropwise to a 70% solution of sodium bis(2-methoxyethoxy)aluminium hydride (RedA1) in benzene (4.3 ml, 15 mmol) at room temperature with stirring. The clear solution which resulted was refluxed for 2 h under nitrogen. To the cooled solution was added dropwise, with stirring, 20% aqueous sodium hydroxide (10 ml), and the mixture stirred at room temperature for 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. T.l.c. examination of the resulting solid indicated the presence of unchanged oxime and a product of higher $R_F$ value. The mixture was eluted down a 30 mm diameter flash column packed with 200 mm of silica using ethanol as eluant. Forty fractions (20 ml) were collected and the ones shown by t.l.c. to contain only the product of higher $R_F$ value, were combined and concentrated. Sublimation of the resulting solid (100 °C/0.1 mmHg) gave the amine (**17**) as a white crystalline solid (0.603 g, 66%), m.p. 180—181 °C; $\delta_H$ 0.65 (br s, 2 H, $NH_2$), 3.26—4.10 (m, 9 H, 4-, 6-, 8-, 9-, 10-H), 4.20 (s, 2 H, 2-H), and 7.2—7.5 (m, 10 H, Ph); $\delta_C$ 142.6 (s, Ph), 128.5 (d), 126.3 (d), 124.75 (d, Ph), 73.25 (t, C-2), 63.45 (t, C-8, -9), 60.8 (d, C-6), 53.0 (t, C-4, -10), and 35.3 (s, C-5, -7) (Found: C, 78.7; H, 7.65; N, 13.85%; $M^+$, 305. Calc. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76%; *M*, 305).

*Crystal Structure Determination of* 6-*Hydroxy*-7-*methyl*-4-*oxo*-6-*phenyl*-2-*trimethylsilyloxyadamantane*-2-*carbonitrile* (**12**).—The crystals were grown from light petroleum (b.p. 60—80 °C) by slow evaporation. The crystal was monoclinic with space group $P2_1/a$, $Z = 8$, where $a = 11.94$, $b = 22.62$, $c = 15.59$ Å, and $\beta = 75.75°$. The data were collected on a Stoe STADI-2 2-circle diffractometer (Mo-$K_\alpha$ radiation). The structure was solved by direct methods and refined with SHELX 76 programs.[23] The final *R* factor was 0.0733.

There are two very similar molecules (A and B) in the asymmetric unit. The number of an atom in molecule B equals the number of the corresponding atom in molecule A + 50 (for numbering of the atoms see Figure 1). This defines the framework but, although the two molecules are in a very similar orientation in the unit cell, there are differences in orientation of the phenyl and trimethylsilyl groups. The bond lengths and angles in the two independent molecules are very similar. The hydrogen of the hydroxy groups could not be found on difference maps for either molecule, and were omitted from calculations. All other hydrogens were included in the structure factor calculations with fixed temperature factors (higher for hydrogens in methyl groups). Methyl groups were refined as rigid groups with fixed bonds and angles allowed to rotate about the C–Si bond.

There is evidence for intermolecular hydrogen bonding between the hydroxy group of molecule A and the carbonyl group of the adjacent molecule A, and similarly between pairs of molecules B, of type A–A and B–B, but none of type A–B or B–A. This is indicated by the distances between the carbonyl oxygens O(2) and O(52) and the corresponding hydroxy oxygens O(3) and O(53) in the molecule described by the co-ordinates *x*, *y*, *z* and the molecule described by the co-ordinates $\frac{1}{2} + x$, $\frac{1}{2} - y$, *z*, which are 2.77 and 2.85 Å respectively. In normal packing for unit cells, these distances would be expected to be of the order 3.3—3.4 Å.[24]

There appears to be no intramolecular hydroxy-π phenyl interaction in the solid state because of the involvement of the hydroxy group with a carbonyl on a neighbouring molecule as described above. This is supported by the orientation of the hydroxy group with respect to the phenyl group as indicated by the torsion angle O(3)–C(6)–C(16)–C(17) of 38°. This is considerably smaller than the 90° expected if intramolecular hydrogen bonding were to occur.

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