Synthesis of the Four Stereoisomers of 4-Aminoadamantane-2-carboxylic Acid, Rigid Analogues of γ-Aminobutyric Acid

By **Robin M. Black**, Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire SP4 0JQ

Synthetic routes to the four stereoisomers of 4-aminoadamantane-2-carboxylic acid are described. π Route cyclisations to 2,4-disubstituted adamantanes are expanded to obtain 4_{eq}- and 4_{ax}-acetamidoadamantan-2-ones. These are converted into acetamido-nitriles using tosylmethyl isocyanide and subsequently hydrolysed to three of the amino-acids. The diaxial isomer is prepared by a stereospecific nitrene insertion reaction. Mass spectra of the amino-acids and their ethyl esters are reported.

MANY derivatives of adamantane have been screened for biological activity following the discoveries of the antiviral [1] and dopaminergic [2] properties of 1-aminoadamantane, and also the enhanced potencies observed in several simple drug derivatives containing an adamantyl moiety.[3] Almost all of these studies have used the adamantane nucleus simply as a relatively compact highly lipophilic group likely to facilitate the penetration of drug molecules through lipid membranes or to provide a stronger association with lipophilic sites on receptor molecules. Surprisingly, few examples have been reported where the unique rigid stereochemistry of adamantane has been used to provide a lipophilic framework for the attachment of pharmacophoric groups in fixed conformations. Thus Lavrova *et al.*[4] prepared isomeric derivatives of 1-hydroxy-4-dimethylaminoadamantane as rigid anticholinergics, more recently 2-phenyl-2-(1-piperidyl)adamantane has been examined as a rigid analogue of phencyclidene [5] and simple 1,2-substituted adamantane analogues of tetrodotoxin have been prepared.[6] The possibilities for using isomeric 2,4- or 2,6-disubstituted adamantanes as rigid conformational analogues appear to have been ignored.

γ-Aminobutyric acid (GABA) is now recognised as the major inhibitory neurotransmitter in the mammalian central nervous system and several laboratories,[7] especially those of Johnston and Krogsgaard-Larsen have reported the syntheses of many conformationally restricted but flexible analogues of GABA in an effort to determine the conformation(s) preferred by the receptor(s).

This paper describes the syntheses of the four stereoisomers of 4-aminoadamantane-2-carboxylic acid, analogues of GABA with four conformationally different rigid carbon skeletons.

RESULTS AND DISCUSSION

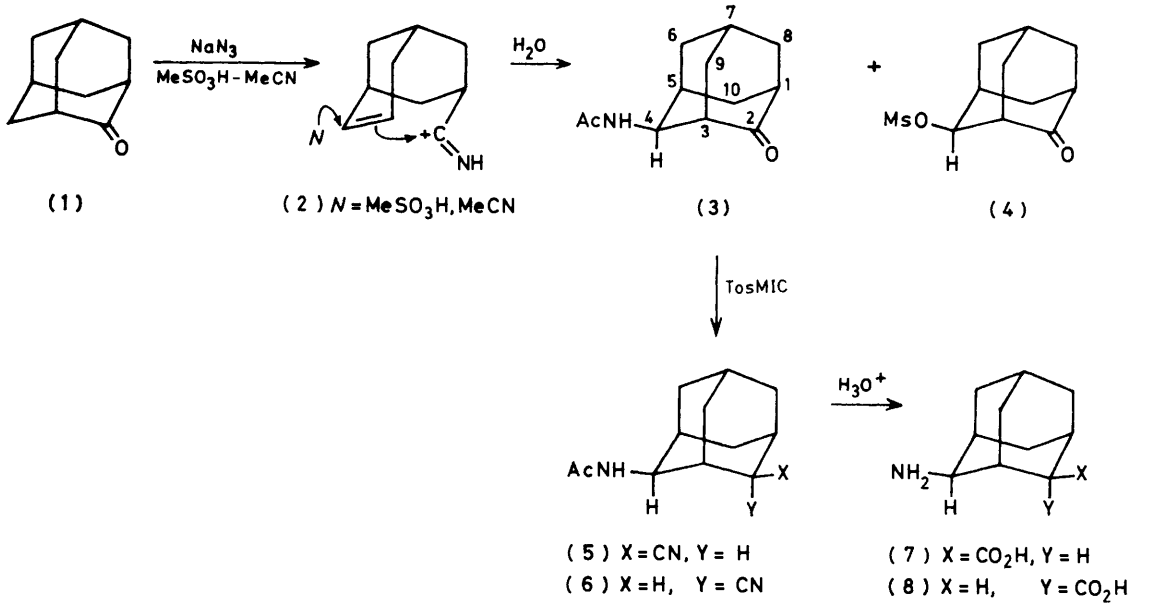
Since the recent introduction of the reagent tosylmethyl isocyanide [8] it has become relatively easy to convert ketones into carboxylic acids through the addition of one carbon unit. A convenient route to three of the isomeric 4-aminoadamantane-2-carboxylic acids seemed, therefore, to be the conversion of 4_{eq}- and 4_{ax}-acetamidoadamantan-2-one into the 4-acetamidoadamantane-2-carbonitriles and subsequent hydrolysis of the latter to the amino-acids.

The Schmidt reaction of adamantanone (1) gives a variety of products depending on the reaction conditions and, particularly, on the acid used. When methanesulphonic acid was used as acid and solvent [9a] the major kinetically determined product 4_{eq}-methylsulphonyloxyadamantan-2-one (4) resulted from a π route cyclisation [9b] of the protonated Schmidt fragmentation product *endo*-bicyclo[3.3.1]non-6-ene-3-carbonitrile (2). Under these conditions methanesulphonic acid was effectively the only nucleophile participating in the cyclisation. Addition of acetonitrile as solvent should present a competing nucleophile, the nitrile nitrogen as in a Ritter reaction,[10] and under appropriate conditions 4_{eq}-acetamidoadamantan-2-one (3) should be the major product. In the event, addition of sodium azide to adamantanone in acetonitrile and methanesulphonic acid (5 : 1, v/v) and storage for 5 days at room temperature gave a 43% yield of compound (3) after two recrystallisations of the crude reaction product (Scheme 1). The ^{1}H n.m.r. spectrum of the crude product indicated that compounds (3) and (4) were formed in a ratio of *ca.* 4 : 1. Also formed were *endo*-bicyclo[3.3.1]non-6-ene-3-carbonitrile (16% isolated) and small amounts of 4_{ax}-acetamidoadamantan-2-one (*eq* : *ax* *ca.* 19 : 1 by g.l.c.). Configurational assignments were consistent with the higher chemical shift observed for the axial C-4 proton of the equatorial isomer.[9a,b]

Treatment of compound (3) with tosylmethyl isocyanide gave approximately equal amounts (ratio 54 : 46 by g.l.c.) of the 2_{eq} and 2_{ax}-carbonitriles (5) and (6), separated by chromatography on silica gel. Configurations were assigned from the ^{1}H n.m.r. spectra based on the relative chemical shifts of the axial C-4 protons, (5) δ 4.03 (*eq*-CN) and (6) δ 4.38 (*ax*-CN). The axial C-4 proton in (6) lies parallel to the axial C≡N linkage and should, therefore, be subject to an anisotropic deshielding effect.[11]

Finally, hydrolysis of the nitriles with 5N-sulphuric acid and isolation by ion-exchange chromatography afforded good yields of 4_{eq}-aminoadamantane-2_{eq}-carboxylic acid (7) and 4_{eq}-aminoadamantane-2_{ax}-carboxylic acid (8). The strength of acid used for the hydrolysis was important since the use of hydrobromic in acetic acid [12] resulted in significant amounts (5—10%) of epimerisation about C-2.

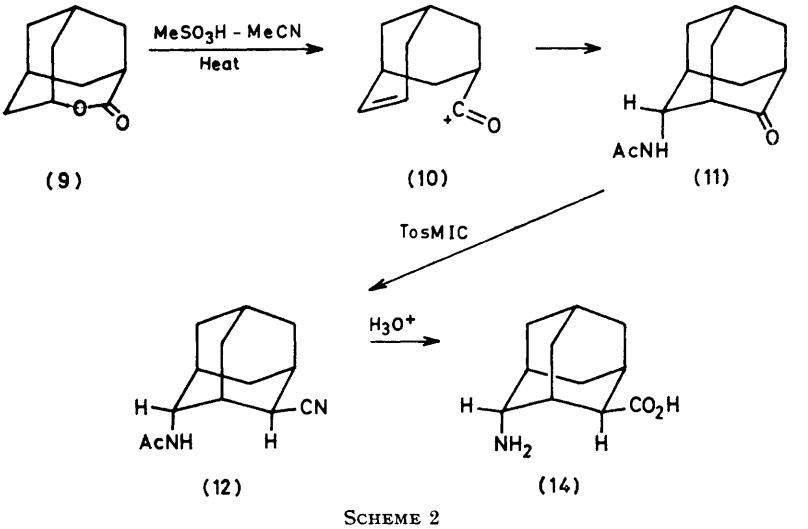
When π cyclisations to 4-hydroxyadamantanone



SCHEME 1

derivatives are performed under conditions of thermodynamic control the reverse stereochemistry is found and axial products predominate. Thus McKervey *et al.*[9b] showed that treatment of 4-oxahomoadamantan-5-one (9) with methanesulphonic acid at 90 °C for 1 h afforded a mixture containing the axial and equatorial mesylates in a ratio of 6 : 1 *via* a π cyclisation of the acylium ion (10). When the lactone (9) was heated under reflux with methanesulphonic acid in acetonitrile (Scheme 2) a slow reaction ensued yielding after a week a mixture containing the axial and equatorial 4-acetamido-derivatives in a ratio of *ca.* 5.5 : 1, unchanged lactone (*ca.* 17%), and small amounts of the mesylates (<10%). Again the lower solubility of the amide allowed the pure axial isomer (11) to be isolated in 30% yield after two recrystallisations of the crude product. Attempts to increase the speed of the reaction by using sulphuric acid resulted in extensive polymerisation of the solvent.

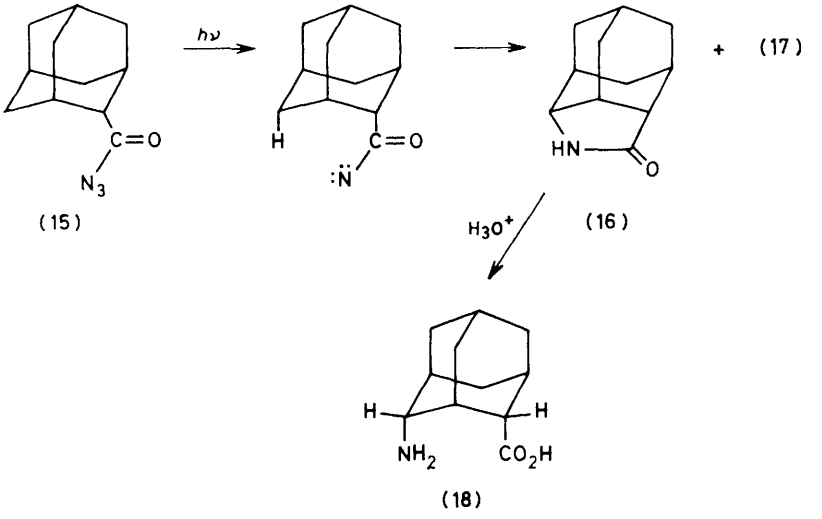
Treatment of compound (11) with tosylmethyl isocyanide gave, as expected, predominantly the equatorial nitrile (12) (*eq*-CN : *ax*-CN *ca.* 6 : 1 by g.l.c.), the formation of the diaxial isomer (13) probably resulting from equilibration of the products[8] rather than reagent attack from an axial direction. Hydrolysis of (12) gave 4_{ax}-aminoadamantane-2_{eq}-carboxylic acid (14).



SCHEME 2

Although small quantities of the diaxial acetamidonitrile were available from the preceding pathway, a more satisfactory stereospecific route to the diaxial amino-acid exploited the stereochemical requirements for intramolecular nitrene insertion[13] (Scheme 3). Thus photolysis of 2-adamantylcarbonyl azide (15) (prepared by conventional procedures from the acid) yielded a

mixture containing approximately equal amounts of the lactam (16) and 2-adamantyl isocyanate (17) the competing Curtius rearrangement product. After a facile separation by chromatography the lactam was rapidly hydrolysed with 6N-hydrochloric acid to the diaxial amino-acid (18). An analogous carbene insertion reaction has been used to synthesise ethanoadamantan-3-one.[14] This unambiguous synthesis of the diaxial acid confirmed the configurational assignment of (12). All four acids were converted into their lipophilic ethyl esters for *in vivo* pharmacological testing.



SCHEME 3

The electron-impact mass spectra of the isomeric acetamidoadamantanones and those of the acetamidonitriles were qualitatively similar. In contrast, the four amino-acids showed qualitative and quantitative differences in their spectra allowing (8; $2_{ax},4_{eq}$) and (18; $2_{ax},4_{ax}$) to be uniquely identified. The amino-acids (7; $2_{eq},4_{eq}$) and (14; $2_{eq},4_{ax}$) produced almost identical spectra containing in addition to M^+ a base-peak at *m/e* 177 (loss of H_2O) and a major ion at 149 (proably loss of HCO_2H). The amino-acid (8; $2_{ax},4_{eq}$) gave the molecular ion as the base peak with intense ions at *m/e* 178 and 149. The diaxial amino-acid (18) showed ions similar to (7) but also an intense ion at *m/e* 99, observable in the mass spectrum of lactam (16). Furthermore, compound (18) was clearly distinguishable by its chemical ionisation (isobutane) mass spectrum from the almost total absence (<1%) of a MH^+ species. The base peak at *m/e* 178 corresponded to loss of water, protonation presumably facilitating cyclisation to the lactam (16). All the other amino-acids showed 100% MH^+ ions. The mass spectra of the ethyl esters derived from the acids also exhibited major differences. Those with equatorial CO_2Et [*m/e* 194 (*ca.* 30%), 177 (100%), and 149 (*ca.* 90%)] gave similar spectra as did those with axial CO_2Et [*m/e* 194 (100%), 177 (<5%), and 149 (<10%)]. Thus the configuration of CO_2Et appears to determine the appearance of the mass spectrum.

EXPERIMENTAL

^1H N.m.r. spectra were measured at 100 Hz with a JEOL JNM-MH-100 spectrometer and $SiMe_4$ as internal standard. I.r. spectra were recorded in KBr discs on a Perkin-Elmer 157 spectrometer. Mass spectra were obtained using a VG 70-70 instrument at 70 eV, the eight most intense ions excluding isotope peaks are recorded. G.l.c. refers to analysis on 5% OV1 on Gas-chrom. Q. Melting points were determined in sealed capillary tubes and are uncorrected. Acetonitrile was dried over and distilled from calcium hydride. Organic extracts were dried over $MgSO_4$.

4_{eq}-*Acetamidoadamantan-2-one* (3).—Sodium azide (3.0 g) was added as portions during 45 min to a stirred ice-cooled solution of adamantanone (6.0 g, 40 mmol) in dry acetonitrile (250 ml) and methanesulphonic acid (50 ml). The ice-bath was removed, stirring continued for 5 h, and the solution then stored for 5 days at room temperature (20—25 °C). After evaporation of the solvent the residue was poured onto ice–water to yield a white precipitate, which on extraction with light petroleum (40—60 °C) yielded *endo*-bicyclo[3.3.1]non-6-ene-3-carbonitrile (0.93 g), m.p. 172—176 °C (from light petroleum). The spectral data were similar to those published.[6e] The remaining aqueous phase was neutralised with sodium hydrogencarbonate, extracted with dichloromethane, and the combined extracts washed with water and dried. Removal of the solvent gave a white crystalline residue which was recrystallised twice from ethyl acetate to yield 4_{eq}-acetamidoadamantan-2-one (3.36 g, 41%), m.p. 165—169 °C (Found: C, 69.75; H, 8.25; N, 6.55. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%), $\nu_{max.}$ 3 260, 1 718, 1 640, and 1 538 cm^{-1}; δ ($CDCl_3$) 7.22 (1 H, d, NH), 4.18 (1 H, m, 4-H), 2.02 (3 H, s, CH_3), and 2.75—1.6 (12 H, m, remaining adamantyl H); *m/e* 207 (M^+, 25%), 179 (100), 164 (21), 148 (19), 120 (40), 79 (62), 78 (26), and 43 (62).

4_{eq}-*Acetamidoadamantane*-$2_{eq}/2_{ax}$-*carbonitriles* (5) and (6).—Potassium t-butoxide (4.0 g) was added as portions during 5 min to a stirred ice-cooled suspension of (3) (2.07 g, 10 mmol) and tosylmethyl isocyanide [15] (2.6 g, 13 mmol) in dry dimethoxyethane (50 ml) and absolute ethanol (1 ml) under nitrogen. Stirring was continued for 30 min without

cooling and then for 4 h at 40 °C. Most of the solvent was evaporated and the residue poured onto ice–water containing a slight excess of hydrochloric acid. After neutralisation with sodium hydrogencarbonate the mixture was extracted with dichloromethane and the extracts washed, dried, and concentrated to yield an oil. Chromatography over silica gel with chloroform plus 2% ethanol produced three main fractions the first of which yielded a white solid (0.19 g), m.p. 156—159 °C with spectral properties similar to those quoted [16] for 4-tosyloxazole. The second fraction gave a white crystalline solid (0.798 g) which recrystallised from ethyl acetate to give pure 4_{eq}-acetamidoadamantane-2_{eq}-carbonitrile (5) (0.687 g, 31.5%), m.p. 195—198 °C (Found: C, 71.7; H, 8.25; N, 12.7. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31; N, 12.83%), $\nu_{max.}$ 3 310, 2 247, 1 645, and 1 550 cm^{-1}; δ ($CDCl_3$) 6.24br (1 H, d, NH), 4.03 (1 H, m, 4-H), 3.01 (1 H, m, 2-H), 2.04 (3 H, s, CH_3), and 2.36—1.5 (12 H, m, remaining adamantyl H); *m/e* 218 (M^+, 100%), 176 (40), 175 (82), 159 (21), 91 (14), 79 (14), 60 (22), and 43 (26).

Concentration of the third fraction yielded 4_{eq}-acetamidoadamantane-2_{ax}-carbonitrile (6) (0.788 g), recrystallised from ethyl acetate (0.651 g, 30%), m.p. 194—196 °C (Found: C, 71.45; H, 8.35; N, 12.75. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31; N, 12.83%), $\nu_{max.}$ 3 310, 2 247, 1 650, and 1 553 cm^{-1}; δ ($CDCl_3$) 6.38br (1 H, d, NH), 4.38 (1 H, m, 4-H), 3.06 (1 H, m, 2-H), 2.04 (3 H, s, CH_3), and 2.4—1.5 (12 H, m, remaining adamantyl H); *m/e* 218 (M^+, 94%), 176 (38), 175 (100), 159 (24), 91 (25), 79 (26), 60 (31), and 43 (37).

4_{eq}-*Aminoadamantane*-2_{eq}-*carboxylic Acid* (7).—A solution of compound (5) (1.0 g) in 5N-sulphuric acid (50 ml) was heated under reflux for 48 h. After cooling the solution was extracted twice with dichloromethane and the aqueous phase passed through an Amberlite IR 120 (H^+) column. The column was washed with water until neutral and then the amino-acid eluted with 1M-ammonium hydroxide. Concentration to dryness gave a white crystalline solid which recrystallised from aqueous acetone to give hydrated compound (7) (0.717 g, 76%), m.p. 279—281 °C (decomp.) (Found: C, 64.7; H, 9.0; N, 6.9. $C_{11}H_{17}NO_2 \cdot \frac{1}{2}H_2O$ requires C, 64.68; H, 8.88; N, 6.86%), $\nu_{max.}$ 3 125—2 000br, 1 567, and 1 383 cm^{-1}; δ (D_2O) 3.52 (1 H, m, 4-H) and 2.56—1.4 (13 H remaining adamantyl H); *m/e* 195 (M^+, 31%), 194 (31), 178 (40), 177 (100), 149 (90), 91 (43), 56 (36), and 30 (65).

The ethyl ester hydrochloride salt was prepared by passing dry hydrogen chloride through a gently boiling ethanolic solution of the acid (0.300 g) for 3 h and recrystallisation of the residue from ethanol–ethyl acetate (0.275 g, 69%), m.p. 271—272 °C (decomp.) (Found: C, 59.85; H, 8.45; N, 5.35. $C_{13}H_{22}ClNO_2$ requires C, 60.10; H, 8.54; N, 5.39%), $\nu_{max.}$ 2 857br and 1 739 cm^{-1}; δ ($CDCl_3$) 8.68br (3 H, NH_3^+), 4.20 (2 H, q, CH_2CH_3), 3.53 (1 H, m, H-4), 2.8—1.5 (13 H, m, remaining adamantyl H), and 1.28 (3 H, t, CH_2CH_3); *m/e* 223 (M^+, 33%), 177 (100), 151 (38), 150 (63), 149 (97), 91 (52), 79 (34), and 30 (45).

4_{eq}-*Aminoadamantane*-2_{ax}-*carboxylic Acid* (8).—A solution of compound (6) (0.700 g) in 5N-sulphuric acid (35 ml) was treated as for compound (7) to give the hydrated amino-acid (0.455 g, 70%), m.p. 283—285 °C (decomp.) (from water) (Found: C, 64.75; H, 8.9; N, 6.8. $C_{11}H_{17}NO_2 \cdot \frac{1}{2}H_2O$ requires C, 64.68; H, 8.88; N, 6.86%), $\nu_{max.}$ 3 030—2151br, 1 555, and 1 400 cm^{-1}; δ (D_2O) 3.60 (1 H, m, 4-H), 2.64 (1 H, m, 2-H), and 2.5—1.5 (12 H, m, remaining adamantyl H); *m/e* 195 (M^+, 100%), 194 (77), 178 (62), 149 (72), 93 (40), 82 (41), 56 (48), and 30 (61).

Ethyl ester hydrochloride (84%), m.p. 213—215 °C (from ethanol–ether) (Found: C, 59.95; H, 8.35; N, 5.4%. $C_{13}H_{22}ClNO_2$ requires C, 60.10; H, 8.54; N, 5.39%), $\nu_{max.}$ 2 807br and 1 739 cm^{-1}; δ ($CDCl_3$) 8.3br (3 H, NH_3^+), 4.17 (2 H, q, CH_2CH_3), 3.74 (1 H, m, 4-H), 2.88—1.45 (13 H, m, remaining adamantyl H), and 1.28 (3 H, t, CH_3CH_3); *m/e* 223 (M^+, 7%), 194 (100), 178 (12), 148 (21), 91 (8), 79 (6), 56 (6), and 30 (8).

4_{ax}-*Acetamidoadamantan*-2-*one* (11).—A solution of 4-oxahomoadamantan-5-one [9b] (9) (10 g) in methanesulphonic acid (50 ml) and dry acetonitrile (500 ml) was heated under reflux for 7 days. After removal of the solvent the residue was poured onto ice–water, neutralised with sodium hydrogencarbonate and the mixture extracted with dichloromethane. The extracts were washed, dried, and concentrated to yield a crystalline residue. Two recrystallisations from ethyl acetate yielded compound (11) (3.9 g, 30%), m.p. 175—178 °C (Found: C, 69.3; H, 8.3; N, 6.75. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%), $\nu_{max.}$ 3 300, 1 720, 1 640, and 1 534 cm^{-1}; δ ($CDCl_3$) 6.52 (1 H, d, NH), 4.46 (1 H, m, 4-H), 1.96 (3 H, s, CH_3), and 2.7—1.7 (12 H, m, remaining adamantyl H); *m/e* 207 (M^+, 56%), 179 (100), 164 (30), 137 (26), 120 (55), 79 (36), 56 (27), and 43 (45).

4_{ax}-*Acetamidoadamantane*-2_{eq}/2_{ax}-*carbonitriles* (12) *and* (13).—Potassium t-butoxide (5.3 g) was added portionwise during 5 min to a stirred ice-cooled solution of compound (11) (2.76 g, 13.3 mmol) and tosylmethyl isocyanide (3.5 g, 18 mmol) in dry dimethoxyethane (60 ml) and ethanol (1.33 ml) under nitrogen. The reaction was treated, worked up and chromatographed as for compounds (5) and (6). After elution of 4-tosyloxazole (0.252 g) the second fraction gave crude 4_{ax}-acetamidoadamantane-2_{ax}-carbonitrile (13) (0.243 g), recrystallised from ethyl acetate (0.198 g, 7%), m.p. 173—175 °C (Found: C, 71.45; H, 8.35; N, 12.75. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31; N, 12.83%), $\nu_{max.}$ 3 257, 2 183, 1 640, and 1 546 cm^{-1}; δ ($CDCl_3$) 6.44 (1 H, br, NH), 4.18 (1 H, m, 4-H), 2.89 (1 H, m, 2-H), 2.05 (3 H, s, CH_3) 2.6—1.6 (12 H, m, remaining adamantyl H); *m/e* 218 (M^+, 100%), 176 (40), 175 (91), 159 (16), 136 (14), 91 (14), 60 (14), and 43 (15).

Further elution of the column gave 4_{ax}-acetamidoadamantane-2_{eq}-carbonitrile (12) (1.746 g) which was recrystallised from ethyl acetate (1.549 g, 54%), m.p. 160—163 °C (Found: C, 71.35; H, 8.3; N, 12.65%. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31; N, 12.83%), $\nu_{max.}$ 3 300, 2 183, 1 640, and 1 548 cm^{-1}; δ ($CDCl_3$) 6.50br (1 H, d, NH), 4.12 (1 H, m, 4-H), 3.15 (1 H, m, 2-H), 2.03 (3 H, s, CH_3), and 2.5—1.5 (12 H, m, remaining adamantyl H); *m/e* 218 (M^+, 100%), 176 (52), 175 (58), 159 (20), 117 (16) 91 (19), 60 (26), and 43 (72).

4_{ax}-*Aminoadamantane*-2_{eq}-*carboxylic Acid* (14).—A solution of compound (13) (1.0 g) in 5N-sulphuric acid (40 ml) was treated as for compound (7) to give the amino-acid (0.591 g, 66%), m.p. 294—295 °C (decomp.) (from aqueous acetone) (Found: C, 67.35; H, 8.75; N, 7.15. $C_{11}H_{17}NO_2$ requires C, 67.66, H, 8.78, N, 7.17%), $\nu_{max.}$ 3 030—2 151br, 1 535, and 1 380; δ (D_2O) 3.62 (1 H, m, 4-H), 2.52 (1 H, m, 2-H), and 2.48—1.4 (12 H, m, remaining adamantyl H); *m/e* 195 (M^+, 29%), 194 (28), 178 (39), 177 (100), 149 (82), 133 (28), 91 (37), and 30 (53).

Ethyl ester hydrochloride (75%), m.p. 249—251 °C (decomp.) (from ethanol–ethyl acetate) (Found: C, 59.9;

H, 8.45; N, 5.4%. $C_{13}H_{11}ClNO_2$ requires C, 60.10; H, 8.54; N, 5.39%), $\nu_{max.}$ 2 857br and 1 733 cm^{-1}; δ ($CDCl_3$) 8.56br (3 H, NH_3^+), 4.15 (2 H, q, CH_2CH_3), 3.58 (1 H, m, 4-H), 3.12 (1 H, m, 2-H), 2.64 (1 H, m, 3-H), 2.5—1.4 (11 H, m, remaining adamantyl H), and 1.24 (3 H, t, CH_2CH_3); *m/e* 223 (M^+, 31%), 177 (100), 151 (36), 150 (53), 149 (89), 91 (48), 79 (29), and 30 (46).

Adamantane-2-carbonyl Azide (15).—A stirred solution of adamantane-2-carboxylic acid [8,12] (3.6 g, 20 mmol) in thionyl chloride (20 ml) was heated under reflux for 1 h. Removal of the thionyl chloride gave crude adamantane-2-carbonyl chloride as a colourless oil (4.38 g). The crude acid chloride in acetone (15 ml) was added dropwise during 20 min to a stirred, ice-cooled solution of sodium azide (2.2 g) in water (7 ml) and acetone (5 ml). Stirring was continued for a further 30 min at 0—5 °C and the reaction mixture was then extracted with ether. The combined extracts were washed successively with water, 5% sodium hydrogencarbonate and water, dried, and concentrated to yield the colourless crystalline azide (3.96 g, 96%), m.p. 25.5—27.5 °C (Found: C, 64.2; H, 7.45; N, 20.4%. $C_{11}H_{15}N_3O$ requires C, 64.37; H, 7.37; N, 20.47%), $\nu_{max.}$ 2 132 and 1 706 cm^{-1}; δ ($CDCl_3$) 2.60 (1 H, m, 2-H) 2.31 (2 H, m), and 2.1—1.4 (12 H).

4-*Azatetracyclo*[6.3.1.$0^{2,6}$.$0^{5,10}$]*dodecan*-3-*one* (16).—A solution of compound (15) (3.92 g) in dry acetonitrile (450 ml) was flushed with nitrogen, cooled to 0—5 °C in an ice-salt bath, and then irradiated under nitrogen for 4 h with a Hanovia medium-pressure mercury lamp. Removal of the solvent gave a crystalline residue shown to contain two major components by t.l.c. Elution over silica gel with chloroform gave 2-adamantyl isocyanate (17) (1.391 g, 41%), m.p. 81—85 °C (Found: C, 74.7; H, 8.6; N, 7.9%. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%), $\nu_{max.}$ 2 212 cm^{-1}; δ ($CDCl_3$) 3.78 (1 H, m, 2-H) and 2.5—1.5 (14 H, m).

Further elution with chloroform–5% methanol gave the lactam (16) (1.601 g, 47%), m.p. 275—277 °C, from light petroleum (Found: C, 74.5; H, 8.45; N, 8.05%. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%), $\nu_{max.}$ 3 226 and 1 695; δ ($CDCl_3$) 7.26br (1 H, NH), 3.56 (1 H, m, 5-H), and 2.5—1.3 (13 H, m); *m/e* 177 (M^+, 100%), 176 (18), 99 (76), 93 (33), 92 (46), 91 (34), 80 (26), and 79 (31).

4_{ax}-*Aminoadamantane*-2_{ax}-*carboxylic Acid* (18).—A solution of compound (16) (1.0 g) in 6N-HCl (50 ml) was heated at 90 °C for 3 h. Concentration to dryness gave a white crystalline residue which was purified on Amberlite IR-120 (H^+) as for compound (7) to give the diaxial amino-acid (0.854 g, 78%), m.p. 269—272 °C (decomp.) (Found: C, 67.7; H, 8.85; N, 7.2. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.78; N, 7.17%), $\nu_{max.}$ 3 030—2 151br, 1 504, and 1 400; δ (D_2O) 3.49 (1 H, m, 4-H), 2.78 (1 H, m, 2-H), and 2.5—1.56 (12 H, m); *m/e* 195 (M^+, 56%), 177 (100), 149 (47), 99 (95), 93 (50), 92 (58), 91 (54), and 79 (62).

The ethyl ester, isolated as the free base (65%), had m.p. 62—64 °C (Found: C, 69.85; H, 9.4; N, 6.15. $C_{13}H_{21}NO_2$ requires C, 69.92; H, 9.48; N, 6.27%), $\nu_{max.}$ 3390, 3 322, and 1 724; δ ($CDCl_3$) 4.16 (2 H, q, CH_2CH_3), 3.12 (1 H, m, 4-H), 2.68—1.4 (13 H, m), 1.27 (3 H, t, CH_2CH_3), and 1.20 (2 H, s, NH_2); *m/e* 223 (M^+, 8%), 194 (100), 178 (13), 148 (24), 91 (11), 79 (9), 56 (10), and 30 (10).

[1/710 *Received 5th May*, 1981]

REFERENCES

[1] W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffman, *Science*, 1964, **144**, 862.

[2] For a review see E. V. Bailey and T. W. Stone, *Arch. Int. Pharmacodyn. Ther.*, 1975, **216**, 246.

[3] For a review see R. C. Fort, jun., 'Adamantane, The Chemistry of Diamond Molecules,' Studies in Organic Chemistry, ed. P. Gassman, Marcel Dekker, New York, 1976, vol. 5, ch. 7.

[4] L. N. Lavrova, N. V. Klimova, M. I. Shar'yan, D. N. Ibadova, D. A. Kharkevich, and A. P. Skoldinov, *Khim. Farm. Zh.*, 1977, **11**, 36 (*Chem. Abstr.*, 1977, **87**, 52852).

[5] P. Geneste, J. M. Kamenka, S. N. Ung, P. Hermann, R. Goudal, and G. Trouiller, *Eur. J. Med. Chem. Chim. Ther.*, 1979, **14**, 301; A. Gabrielevitz, Y. Kloog, A. Kalir, D. Balderman, and M. Sokolovsky, *Life Sci.*, 1980, **26**, 89.

[6] W. L. F. Armarego and P. G. Tucker, *Aust. J. Chem.*, 1979, **32**, 1805.

[7] R. D. Allan, G. A. R. Johnston and B. Twitchin, *Aust. J. Chem.*, 1979, **32**, 2517; P. Krogsgaard-Larsen and T. Roldskov-Christiansen, *Eur. J. Med. Chem. Chim. Ther.*, 1979, **14**, 157; J. P. O'Donnell, D. A. Johnson and A. J. Azzaro, *J. Med. Chem.*, 1980, **23**, 1142; for a review see G. A. R. Johnston, R. D. Allan, S. M. E. Kennedy and B. Twitchin in 'GABA Neurotransmitters,' eds. P. Krogsgaard-Larsen, J. Scheel-Krüger, and H. Kofod, Munksgaard, Copenhagen, 1978, p. 149.

[8] O. H. Oldenziel, D. van Leusen, and A. M. van Leusen, *J. Org. Chem.*, 1977, **42**, 3114.

[9] (*a*) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, 1970, **35**, 4109; (*b*) D. Faulkner and M. A. McKervey, *J. Chem. Soc. C*, 1971, 3906; (*c*) J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 1969, 3517; (*d*) V. L. Narayanan and L. Setescak, *J. Heterocycl. Chem.*, 1970, **7**, 841; (*e*) R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 1970, 671.

[10] J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**, 4045.

[11] L. M. Jackman and S. Sternhell, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, 1969, 2nd edn., p. 93.

[12] H. Stetter and V. Tillmans, *Chem. Ber.*, 1972, **104**, 735.

[13] For example see W. V. Curran and R. B. Angier, *J. Org. Chem.*, 1969, **34**, 3668.

[14] D. Farcasiu, H. Bohm, and P. von R. Schleyer, *J. Org. Chem.*, 1977, **42**, 96.

[15] B. E. Hoogenboom, O. H. Oldenziel, and A. M. van Leusen, *Org. Synth.*, 1977, **57**, 102.

[16] J. R. Bull and A. Tuinman, *Tetrahedron*, 1975, **31**, 2151.