Chemistry of Adamantane. Part XI (1) 1,2-Disubstituted Adamantanes. Synthesis and Reactions of Adamantano[2,1-*b*]- and Protoadamantano-[4,5-*b*][1,5]benzodiazepines

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The synthesis and reactions of adamantano[2,1-*b*]- and protoadamantano[4,5-*b*][1,5]benzodiazepines are described. 12,13-Dihydro-11a*H*-protoadamantano[4,5-*b*][1,5]benzodiazepin-12-one (**15**) rearranged to 2,3-dihydro-1-(protoadamant-4-en-4-yl)benzimidazol-2-one (**22**). This rearrangement does not proceed with 2-fluoro-5,5a,12,13-tetrahydroadamantano[2,1-*b*][1,5]-benzodiazepin-12-one (**2c**) under similar conditions due to its inability to form an olefinic bond at $C5_a$. A convenient method for the α-carboxylation of ketones using lithium diisopropylamide is also described.

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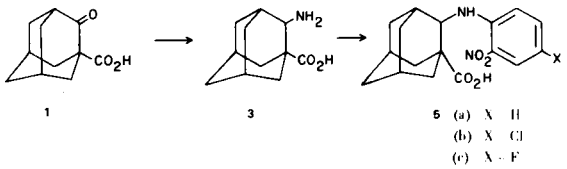
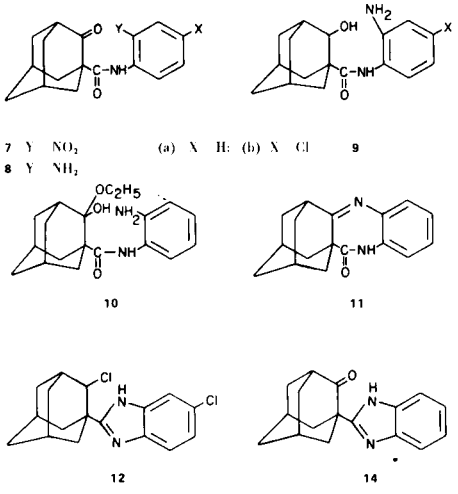
Many clinically effective antipsychotic and antidepressant drugs possess a tricyclic ring system, comprising a central seven membered ring linearly fused to two benzene rings. A hydrophilic aminoalkyl side chain is usually attached to the central ring of the tricyclic system. Our observation (1,2) that certain 1,2-disubstituted adamantane alkylamines possess antidepressant and anti-Parkinson properties, led us to design ring systems where the seven-membered ring is fused to an adamantane or protoadamantane moiety, thus replacing one of the phenyl groups as in **2** and **19**. This modification should also enhance the lipophilic character of the molecule. Since numerous psychotherapeutic agents contain a 1,5-benzodiazepine skeleton, we decided to prepare adamantano[2,1-*b*]- and protoadamantano[4,5-*b*]-[1,5]benzodiazepines, the synthesis and reactions of which are described in this paper.

In a previous communication (3) we reported a convenient method for the preparation of 2-oxo-1-adamantanecarboxylic acid (**1**) using the protoadamantane route. A synthetic route to the diazepinones (**2**) is outlined in Scheme 1. Compound **1** on reductive amination with ammonia gave 2-amino-1-adamantanecarboxylic acid (**3**), which was further characterised by its *N*-acetyl derivative (**4**). Compound **3** on reaction with an optionally substituted *o*-fluoronitrobenzene in boiling methoxyethanol in the presence of a base (triethylamine, pyridine or collidine) produced the corresponding nitroacid (**5**) in good yields. Use of refluxing xylene as a solvent gave reduced yields. Catalytic reduction of the nitro group and subsequent cyclisation of the resulting amino acid with dicyclohexyl carbodiimide (DDC) produced the desired diazepinones (**2**). The cyclisation also was effected in boiling xylene in the presence of molecular sieves. The diazepinones were characterised on the basis of spectral evidence and analyses. Further confirmation is provided by an alternative synthesis (Scheme 2). 2-Oxo-1-adamantanecarbonyl chloride (**6**), derived from **1**, on reaction with an *o*-nitroaniline gave the corresponding *N*-(2-nitro-

Scheme 1



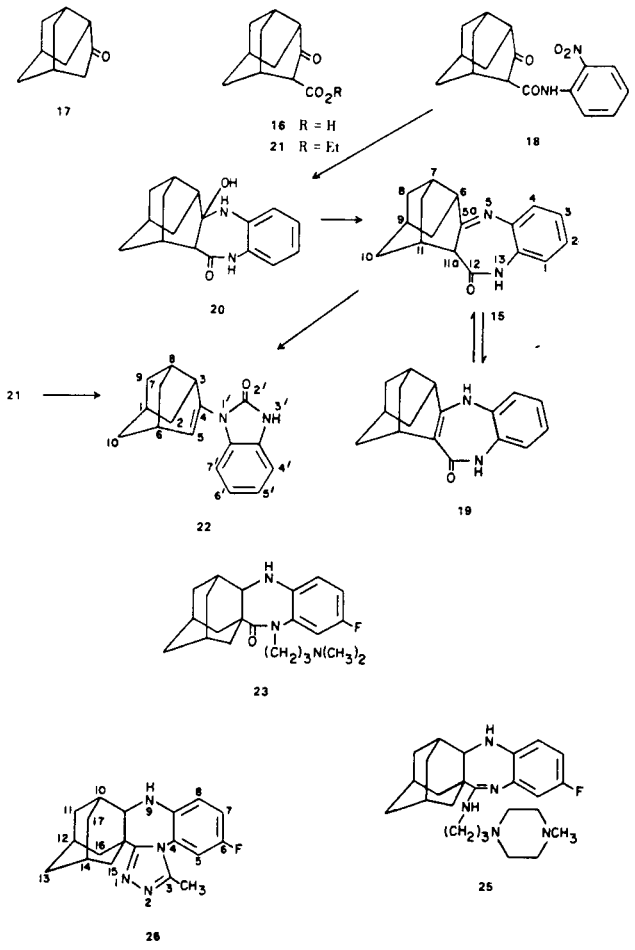
Scheme 2



phenyl)-2-oxo-1-adamantanecarboxamides (**7**). Attempted reductive cyclisation did not proceed to yield the desired lactam. Catalytic hydrogenation of **7** with 5% palladium-carbon in ethylacetate produced the aminoketones (**8**), whereas with Adams catalyst the keto group was also reduced leading to the aminols (**9**). The aminoketone (**8a**), which also was obtained by reacting **6** with 1,2-diaminobenzene, on refluxing in ethanol produced the hemiacetal

(**10**). This, without further purification, was subjected to cyclisation by heating at 130°/0.5 mm to give the cyclic imine (**11**). The appearance of a triplet at δ 0.79 and a quartet at δ 3.32 in the ^{1}H nmr spectrum suggests the formation of the intermediate ethyl hemiacetal. The molecular ion m/e 266 shown in the mass spectral analysis also suggests the formation of the imine (**11**) by thermal cyclisation. This imine on catalytic hydrogenation over 5% palladium-carbon gave the diazepinone (**2a**). The aminoketone (**8b**) was refluxed in ethanol and the solution directly hydrogenated in the presence of 5% palladium-carbon at 60 psi to give the benzodiazepinone (**2a**) with simultaneous hydrogenolysis of the chlorine substituent. Treatment of the aminol (**9b**) with phosphoryl chloride effected chlorination of the 2-hydroxyl group. This chlorine atom resists nucleophilic displacement (4). The reaction thus took the alternative facile course to give the corresponding benzimidazole (**12**) in good yield instead of producing the desired tricyclic lactam. The structure of **12** was assigned on the basis of spectral evidence. The low field appearance of a broad one-proton singlet at δ 4.89 is attributed to the adamantane H2 proton geminal to the chlorine atom. Further confirmatory evidence for the 2-substituted benzimidazole structure is provided by the characteristic absorption in the uv spectrum.

Scheme 3



Protoadamantano[4,5-*b*][1,5]benzodiazepin-12-one (**15**) was synthesised as outlined in Scheme 3. The starting 4-oxo-5-protoadamantanecarboxylic acid (**16**) was obtained by carboxylation of the anion of 4-protoadamantanone (**17**) generated by lithium diisopropylamide. Similar α-carboxylation of lactones has been reported (5). The extension of this process to **17**, where the reaction with methylmagnesium carbonate (Stiles Reagent) (6) failed, seems to offer a convenient carboxylation of ketones under mild condition at low temperatures, thus minimising the risk of subsequent decarboxylation. Bicyclo[2,2,2]octan-2-one was similarly carboxylated in 62% yield (7) an improvement on the reported procedure (8) which used Stiles reagent. Reductive amination of **16** with excess methylamine resulted mostly in decarboxylation to 4-methylaminoprotoadmantane (1). Compound **16** was readily coupled with 2-nitroaniline using DCC to give **18** which on catalytic hydrogenation underwent ring closure to the diazepinone (**15**). The structure was assigned on the basis of spectral evidence. The ^{13}C resonances at δ 47.2 and 163.5 are assigned to C11a and $C5_a$ respectively of the imine (**15**). In addition the appearance of resonances at δ 136.0 and 107.9 are attributed to C11a and C5a of the tautomeric enamine form (**19**). The doublet at δ 2.68 due to H11a in the ^{1}H nmr spectrum of **15** was absent in the spectrum of its hydrochloride. The appearance of a broad peak of δ 6.7, exchangeable with deuterium oxide, is attributed to the NH proton in **19**. The replacement of the 1645 cm^{-1} band shown in **15** by two peaks at 1600 and 1615 cm^{-1} in the ir spectrum of its hydrochloride salt also suggests the predominance of the enamine structure (**19**) in acid solution. This tautomerism also explains its reluctance to undergo hydrogenation.

A minor component was separated during chromatography of **15**. The carbinolamine structure (**20**) is suggested on the basis of spectral evidence particularly by the shift of the C5a ^{13}C nmr resonance from δ 163.5 to δ 76.0 (singlet, off resonance). A full account on the assignment of the ^{13}C nmr spectra of these compounds is in preparation (9).

The condensation of ethyl 4-oxo-5-protoadamantanecarboxylate (**21**) with 1,2-diaminobenzene in boiling toluene with a trace of *p*-toluenesulphonic acid led to the formation of the benzimidazolone (**22**). A similar reaction with ethyl 2-oxo-1-adamantanecarboxylate (**13**), did not produce the expected diazepinone (**11**) or any benzimidazolone but exclusively led to 2-(2-oxo-adamant-1-yl)-benzimidazole (**14**). This is due possibly to the relative steric hindrance at the keto function. The reaction of β-ketoesters and *o*-aryldiamines is known to give unpredictable products leading to benzodiazepinone, benzi-

midazolone, and benzimidazole depending on the relative reactivities of the ketone and ester functions and conditions employed. The derivation of *N*-alkenylbenzimidazolone is attributed to the prior formation of benzodiazepinone (10). The benzimidazolone (**22**), instead of the expected amidine, was also formed in the reaction of **15** with *N*-methylpiperazine using titanium tetrachloride as the catalyst. A similar reaction with adamantanobenzodiazepinone (**2c**) did not produce any rearranged product. This is due to the inability of **2c** to form an olefinic bond, as required for such rearrangement.

The diazepinone (**2c**) underwent the usual alkylation reaction on the amide nitrogen on treatment with an aminoalkyl halide in the presence of sodium hydride. Thus the propylamino side chain was introduced to give the compound **23**. The lactam (**2c**) when treated with phosphorus pentasulfide in pyridine gave the corresponding thiolactam (**24**), which on reaction with 1-propylamino-4-methylpiperazine produced the desired amidine (**25**). No reaction occurred with *N*-methylpiperazine due presumably to steric factors. Reaction of **24** with acethydrazide produced the adamantano[2,1-*b*][1,2,4]triazolo-[4,3-*d*][1,5]benzodiazepine (**26**).

EXPERIMENTAL

Melting points were determined with a Köfler hot stage apparatus and are uncorrected. Unless otherwise stated ir spectra were measured for potassium bromide discs with a Perkin-Elmer 457 instrument and uv spectra were measured for methanol solutions in 10 mm cells using a Unicam SP800 spectrophotometer. ^{1}H spectra for solutions in deuteriochloroform (TMS as internal reference) were measured with either a Varian A-60A spectrometer or a Brüker WH90 instrument. The latter also was used to measure the ^{13}C nmr spectra (at 22.63 MHz under both broad-band and off-resonance continous wave decoupling conditions). Mass spectra were obtained with an LKB-9000S spectrometer (isonising beam energy 20 eV). Unless mentioned otherwise the drying agent used was magnesium sulphate and column chromatography was carried out with either Sorbsil M60 grade silica gel or Florisil.

2-Amino-1-adamantanecarboxylic Acid (**3**).

Ammonia gas was passed into a solution of 2-oxo-1-adamantane carboxylic acid (**1**) (3) (10 g., 0.05 mole) in ethanol (150 ml.) for 15 minutes. The solution was hydrogenated at 60 psi in the presence of Adams catalyst (1 g.) overnight. The catalyst was filtered off and washed with hot water. The filtrate was evaporated to a white solid, which was dried under reduced pressure at 60° (10 g.), (99%), m.p. > 300° (sublimed); ir: 3100-2300, 1680, 1630, 1370 cm^{-1}; nmr (trifluoroacetic acid): δ 3.57 (1H, b, H_2), 1.30-2.15 (13H, m, skeletal).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.77; N, 7.2. Found: C, 67.6; H, 9.03; N, 7.1.

2-Acetamido-1-adamantanecarboxylic Acid (**4**).

Compound **3** with acetic anhydride and pyridine gave **4**, m.p. 260-264°; ir: 3370, 3200-2300, 1700, 1630, 1550 cm^{-1}; nmr: δ 4.27 (1H, s, H_2), 7.14 (1H, NH), 6.0-7.3 (1H, broad, COOH), 0.77-2.70 (16H, m, $COCH_3$, and skeletal).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.06; N, 5.9; O, 20.2. Found: C, 66.1; H, 8.10; N, 5.8; O, 19.9.

2-(2-Nitroanilino)-1-adamantanecarboxylic Acid (**5a**).

A mixture of 2-amino-1-adamantanecarboxylic acid (**3**) (1.0 g., 0.005 mole), 2-fluoronitrobenzene (0.7 g., 0.005 mole) and triethylamine (2 ml.) in methoxyethanol (25 ml.) was heated to reflux for 18 hours. Most of the solvent was removed and the residue was partitioned between 1*N* sodium hydroxide and diethyl ether. The aqueous solution was acidified with 2*N* hydrochloric acid and extracted into ether. The organic phase was dried and evaporated to give **5a** (1.6 g.) which was crystallised from carbon tetrachloride to give analytically pure product (1.45 g., 92%), m.p. 180-181°; ir: 3500-2250, 1680, 1500, 1340 cm^{-1}; uv: λ max 236, 435 nm (log ε 4.31, 3.76); nmr: δ 4.16 (1H, d, s in deuterium oxide, H_2; the collapse of this doublet into a singlet shows the coupling of H_2 with NH proton), 6.97 (1H, d, H_6'),8.13 (1H, dd, H_3'),6.59-7.39 (2H, m, $H_4',_5'$), 8.58 (1H, NH, exchanged in deuterium oxide), 9.96 (1H, s, COOH), 1.5-2.6 (13H, m, skeletal); ms: m/e 316 (M^+), 299 (M-17), 286 (M-30), 269 (M-47), 135, 134,133.

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.5; H, 6.37; N, 8.9. Found: C, 64.7; H, 6.57; N, 8.9.

The following compounds were prepared similarly:

2-(4-Chloro-2-nitroanilino)-1-adamantanecarboxylic Acid (**5b**).

Compound **5b** was obtained as above, m.p. 245-250° (chloroform-*n*-hexane); ir: 3500-2500, 1700, 1510, 1350, cm^{-1}; uv: λ max 244, 452 nm (log ε 4.33, 3.67); nmr (deuteriochloroform-DMSO-d_6): δ 4.18 (1H, d, singlet in deuterium oxide, H_2), 7.02 (1H, d, H_6'), 7.35 (1H, dd, H_5'),8.15 (1H, d, H_3'), 8.6 (1H, d, NH exchanged in deuterium oxide), 7.7 (1H, s, COOH), 1.5-2.5 (13H, m, skeletal).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_4$: C, 58.2; H, 5.45; N, 7.9; Cl, 10.1; O, 18.2. Found: C, 58.5; H, 5.49; N, 7.6; Cl, 10.4; O, 18.2.

2-(4-Fluoro-2-nitroanilino)-1-adamantanecarboxylic Acid (**5c**).

Compound **5c** was obtained as above, (yield 80%), m.p. 203-205° (methylene chloride-carbon tetrachloride); ir: 3500-2500, 1690, 1510, 1350 cm^{-1}; uv: λ max 234, 446 nm (log ε 4.34, 3.82); nmr: δ 4.09 (1H, broad d, singlet in deuterium oxide, H_2), 6.7-7.4 (2H, m, $H_5',_6'$), 7.80 (1H, dd, H_3'), 8.42 (1H, d, NH exchanged in deuterium oxide), 9.30 (1H, s, COOH), 1.4-2.3 (13H, m, skeletal).

Anal. Calcd. for $C_{17}H_{19}FN_2O_4$: C, 61.1; H, 5.72; N, 8.4; F, 5.7. Found: C, 61.1; H, 5.82; N, 8.4; F, 5.7.

2-Chloro-5,5a,12,13-tetrahydro-adamantano[2,1-*b*][1,5]benzodiazepin-12-one (**2b**).

A solution of 2-(4-chloro-2-nitroanilino)-1-adamantane carboxylic acid (**5b**) (0.2 g., 0.0006 mole) in ethyl acetate (50 ml.) was hydrogenated at atmospheric pressure in the presence of 10% Palladium-carbon (0.05 g.). After the uptake of hydrogen was complete, the catalyst was removed by filtration and the solution evaporated to dryness. The resulting amino acid, without further characterisation, was refluxed in xylene in the presence of Molecular Sieves (Type 3A) for 48 hours. The solution was filtered, washed with methanol and evaporated to a solid, which was crystallised from carbon tetrachloride to give **2b** (0.1 g., 58%), m.p. 250-255°; ir: 1643, 1505 cm^{-1}; uv: λ max 231, 268, 315 nm (log ε 4.61, 3.75, 3.67); nmr: δ 3.22 (1H, s, H5a), 6.6-7.0 (3H, m, Ph), 4.37 (1H, s, NH exchanged in deuterium oxide), 9.12 (1H, s, NHC=O), 1.3-2.5 (13H, m, skeletal); ms: m/e 302/304 (M^+) (little fragmentation).

Anal. Calcd. for $C_{17}H_{19}ClN_2O$: C, 67.4; H, 6.32; N, 9.3; Cl, 11.7; O, 5.3. Found: C, 67.4; H, 6.15; N, 9.4; Cl, 12.0; O, 5.4.

5,5a,12,13-Tetrahydroadamantano[2,1-*b*][1,5]benzodiazepin-12-one (**2a**).

Compound **2a** was obtained as above (yield 36%), m.p. 249-251° (carbon tetrachloride); ir: 1640, 1506, 744 cm^{-1}; uv: λ max 228, 266, 305 nm (log ε 4.54, 3.70, 3.67): nmr (deuteriochloroform-DMSO-d_6): δ 3.15 (1H, s, H5a), 6.5-7.1 (4H, m, Ph), 9.02 (1H, s, NHC=O), amine NH exchanged in DMSO, 1.6-2.6 (13H, m, skeletal); ms: m/e 268 (M^+), 253 (M-15), 240 (M-28), 197, 184, 149, 119.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.1; H, 7.51; N, 10.4; O, 6.0. Found: C, 76.1; H, 7.38; N, 10.4; O, 6.2.

2-Fluoro-5,5a,12,13-tetrahydroadamantano[2,1-*b*][1,5]benzodiazepin-12-one (**2c**).

2-(4-Fluoro-2-nitroanilino)-1-adamantanecarboxylic acid (5c) (6.0 g., 0.018 mole) in ethanol (150 ml.) was hydrogenated with 10% palladium-carbon (0.6 g.) at 60 psi. The catalyst was filtered off and the solution on evaporation gave a solid, which was stirred in dry tetrahydrofuran (150 ml.) with DCC (3.7 g.) overnight. The solution was filtered and the solid obtained after removal of the solvent was crystallised from chloroform-carbon tetrachloride to give **2c** (3.0 g., 58%); m.p. 258-260°; ir: 1645, 1520 cm^{-1}; uv: λ max 225, 260, 312 nm (log ε 4.51, 3.63, 3.70); nmr (deuteriochloroform-DMSO-d_6): δ 3.15 (H5a, obscured by solvent), 6.36-6.9 (3H, m, Ph), 4.15 (1H, s, NH), 9.23 (1H, s, NHC=O) 0.8-2.5 (13H, m, skeletal).

Anal. Calcd. for $C_{17}H_{19}FN_2O$: C, 71.3; H, 6.68; N, 9.8; F, 6.6. Found: C, 71.4; H, 6.57; N, 9.7; F, 6.9.

N-(2-Nitrophenyl)-2-oxo-1-adamantanecarboxamide (**7a**).

Thionylchloride (12 ml.) was added to 2-oxo-1-adamantanecarboxylic acid (**1**) (3.8 g., 0.02 mole) and the mixture was heated to reflux for 2 hours. Removal of the excess thionyl chloride under vacuum gave the crude 2-oxo-1-adamantanecarbonyl chloride (**6**); ir(neat): 1770 cm^{-1}. To a solution of 4-chloro-2-nitroaniline (2.8 g., 0.02 mole) in dry methylene chloride (100 ml.) was added triethylamine (2.2 ml.) followed by **6** in methylene chloride (10 ml.) dropwise with stirring. The solution was refluxed for 6 hours, washed with water, dilute sodium bicarbonate solution, dilute hydrochloric acid and water. The organic phase was dried and evaporated under reduced pressure at 40° to give a yellow solid, which was crystallised from ethanol to give **7a** (4.8 g., 78%) m.p. 111-113°; ir: 1710, 1690 cm^{-1}; uv: λ max 238, 348 nm (log ε 4.27, 3.49); nmr: δ 2.75 (1H, m, H_3), 8.18 (1H, dd, H6′), 8.70 (1H, dd, H3′), 7.20-7.65 (2H, m, H4′,5′), 11.27 (1H, NHC=O)-1.80-2.65 (12H, m, skeletal).

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.9; H, 5.78; N, 8.9. Found: C, 64.7; H, 5.73; N, 9.0.

N-(4-Chloro-2-nitrophenyl)-2-oxo-1-adamantanecarboxamide (**7b**).

Compound **7b** was obtained as above (yield 76%), m.p. 120-122° ethanol-methylene chloride); ir: 1710, 1690 cm^{-1}; uv: λ max 242 nm (log ε 4.35); nmr: δ 8.17 (1H, d, H3′), 7.58 (1H, dd, H5′), 8.68 (1H, d, H6′), 11.33 (1H, NHC=O), 1.60-2.80 (13H, m, skeletal).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_4$: C, 58.5; H, 4.91; N, 8.0. Found: C, 58.8; H, 5.05; N, 7.9.

N-(2-Aminophenyl)-2-oxo-1-adamantanecarboxamide (**8a**).

Reaction of **6** as above with 1,2-diaminobenzene gave **8a** (yield 50%), m.p. 195-197° (benzene-dichloromethane); ir: 3460-3350, 1690, 1650 cm^{-1}; uv: λ max 292 nm (log ε 3.44); nmr: δ 2.65 (1H, m, H_3), 6.5-7.3 (4H, m, Ph), 3.85 (2H, NH_2, exchanged in deuterium oxide), 8.97 (1H, NHC=O), 1.8-2.5 (12H, m, skeletal).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.8; H, 7.09; N, 9.8. Found: C, 71.6; H, 6.99; N, 9.7.

Compound **8a** also was obtained upon hydrogenation of the nitroamide (**7a**) in ethylacetate solution in the presence of 5% Palladium-carbon catalyst at 60 psi.

N-(2-Amino-4-chlorophenyl)-2-oxo-1-adamantanecarboxamide (**8b**).

Compound **8b** was obtained as above from **7b** in almost quantitative yield, m.p. 225-227°; ir: 1700, 1650 cm^{-1}; uv: λ max 245, 300 nm (log ε 3.94, 3.58); nmr: (deuteriochloroform-DMSO-d_6): δ 2.70 (1H, m, H_3); 6.80 (1H, d, H_3'), 7.11 (1H, d, H_6'), 6.64 (1H, dd, H_5'), 2.76 (2H, NH_2, exchanged in deuterium oxide), 9.0 (1H, NHC=O), 1.95-2.34 (12H, m, skeletal).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2$: C, 64.0; H, 6.00; N, 8.8; Cl, 11.1. Found: C, 63.8; H, 5.88; N, 8.7; Cl, 11.2.

N-(2-Amino-4-chlorophenyl)-2hydroxy-1-adamantanecarboxamide (**9b**).

A solution of **7b** (7 g., 0.02 mole) in ethyl acetate (250 ml.) was hydrogenated with Adam's catalyst (platinum oxide) (0.7 g.) at 60 psi. After the uptake of hydrogen was complete, the catalyst was removed by filtration and washed with hot ethanol. The solution on evaporation under reduced pressure at 40° left a solid, which was crystallised from ethanol to give **9b** (6.0 g., 93%) m.p. 225-227°; ir: 3540 cm^{-1}; uv: λ max 244, 300 nm (log ε 3.90, 3.56); nmr: (deuteriochloroform-DMSO-d_6): δ 4.03 (1H, b, H_2), 6.81 (1H, d, H3′), 7.13 (1H, d, H6′), 6.57 (1H, dd, H5′), 4.80 (2H, NH_2 exchanged in deuterium oxide), 5.10 (1H, OH exchanged in deuterium oxide), 8.80 (1H, NHC=O), 1.10-2.40 (13H, m, skeletal).

Anal. Calcd. for $C_{17}H_{21}ClN_2O_2$: C, 63.7; H, 6.59; N, 8.7; O, 10.0; Cl, 11.1. Found: C, 63.4; H, 6.42; N, 8.5; O, 10.2; Cl, 11.2.

N-(2-Aminophenyl)-2-hydroxy-1-adamantanecarboxamide (**9a**).

Compound **9a** was obtained as above, m.p. 210-212° (ethanol); ir: 3560, 3400-3280, 1660, 1620, 1510 cm^{-1}; uv: λ max 291 nm (log ε 3.48); nmr: (deuteriochloroform-DMSO-d_6): δ 4.05 (1H, b, H_2), 6.5-7.3 (4H, m, Ph), 5.06 (1H, b, OH), 3.15 (2H, NH_2 exchanged in deuterium oxide), 8.87 (1H, NHC=O), 1.2-2.5 (13H, m, skeletal); ms: m/e 286 (M^+), 240 (M-46), 197, 151, 135, 134.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.73; N, 9.8. Found: C, 71.6; H, 7.53; N, 9.6.

12,13-Dihydroadamantano[2,1-*b*][1,5]benzodiazepin-12-one (**11**).

A solution of *N*-(2-aminophenyl)-2-oxo-1-adamantanecarboxamide (**8a**) (1.0 g., 0.0035 mole) in absolute ethanol (60 ml.) was heated to reflux for 6 hours. Solvent was removed under reduced pressure at 50° to give a crystaline solid (1 g.); ir: 1660 cm^{-1}; ms: m/e 284 [M-46], 266 [M-(46+18)]; nmr: δ 0.79 (t), 3.32 (q); (hemiacetal) (**10**). The above solid was heated over phosphorus pentoxide at 130°/0.5 mm to give the cyclic imine (**11**); (0.5 g., 54%) m.p. 191-193°; ir: 3300-3000, 1660, 1590 cm^{-1}; uv: λ max 228, 265, 310 nm (log ε 4.53, 3.70, 3.67); ms: m/e 266 (M^+), 238 (M-28); nmr: δ 2.50 (1H, b, H6), 6.5-7.5 (4H, m, Ph), 7.95 (1H, NHC=O) 1.5-3.0 (12H, m, skeletal).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.81; N, 10.5. Found: C, 76.4; H, 6.65; N, 10.5.

2-(2-Chloroadamantan-1-yl)-6-chlorobenzimidazole (**12**).

To *N*-(2-amino-4-chlorophenyl)-2-hydroxy-1-adamantanecarboxamide (**9b**) (0.5 g., 0.0015 mole) cooled in an ice-salt bath, was added phosphoryl chloride (5 ml.) with stirring followed by

phosphorus pentachloride (2 g.) portionwise. The mixture was stirred at room temperature for 2 hours, poured onto ice water, and extracted with methylene chloride. The organic phase was washed with water, dried and evaporated under reduced pressure to give a solid (0.4 g., 80%), which was crystallised from benzene; m.p. 283-285°; ir: 2920, 2840, 1610 cm^{-1}; uv: λ max 250, 284, 292 nm (log ε 3.77, 3.92, 3.91); nmr: δ 4.89 (1H, b, H_2), 7.58 (1H, d, H7'), 7.15 (1H, dd, H5'), 7.61 (1H, d, H4'), 5.7 (1H, NH exchanged in deuterium oxide), 1.65-2.90 (13H, m, skeletal); ms: m/e 321 (M^+), 285.

Anal. Calcd. for $C_{17}H_{18}Cl_2N_2$: C, 63.6; H, 5.64; N, 8.7. Found: C, 63.3; H, 5.43; N, 8.5.

Reaction of Ethyl 2-Oxo-1-adamantanecarboxylate (**13**) with 1,2-Diaminobenzene.

A solution of ethyl 2-oxo-1-adamantanecarboxylate (**13**). [m.p. 79-81°; (8)] (0.67 g., 0.0034 mole) and 1,2-diaminobenzene (0.37 g., 0.0034 mole) in dry toluene (15 ml.) containing a trace of *p*-toluenesulphonic acid was refluxed for 48 hours with removal of water by means of a Dean and Stark apparatus. The solvent was removed under reduced pressure and the product chromatographed on silica gel eluting with ethyl acetate-methylene chloride (1:1) to give 2-(2-oxo-adamantan-1-yl)benzimidazole (**14**) (0.67 g.). The ^1H nmr spectra of the product at this stage showed a methyl triplet at 1.23 δ and a methylene quartet at 4.13 δ indicating that the ethanol formed in the reaction partially had been incorporated as the hemiacetal. Crystallisation from chloroform and drying at 110° *in vacuo* gave the pure ketone, m.p. 320-330° dec.; ir: 1720 cm^{-1}; uv: λ max 244, 275, 282 nm (log ε 3.79, 3.91, 3.98); ^1H nmr: (deuteriochloroform-DMSO-d_6): δ 7.0-7.3 (2H, m, H5',6'), 7.38-7.68 (2H, m, H4',7'), 1.2-2.75 (13H, m, skeletal); ^{13}C nmr (DMSO-d_6): δ 52.5 (s, Cl), 210.5 (s, C2), 46.4 (d, C3), 153.7 (s, C2'); ms: m/e 266 (M^+), 252, 238, 195.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.81; N, 10.5. Found: C, 76.4; H, 7.15; N, 10.4.

4-Oxo-5-protoadamantanecarboxylic Acid (**16**).

To methyllithium (60 ml., 2*M* in ether) in dry tetrahydrofuran (150 ml.) under nitrogen at -25° to -30° was added freshly distilled diisopropylamine (17.5 ml.). The solution was stirred until the gas evolution ceased, when a solution of protoadamantanone (11) (**17**) (14.1 g., 0.094 mole) in dry tetrahydrofuran was added keeping the temperature between 0° and -10°. The mixture was stirred for 30 minutes and then dry carbon dioxide gas was passed at 0° to 10° until the solution was saturated. Dilute hydrochloric acid was added dropwise, until the mixture was just acid followed by dilution with water and extraction with methylene chloride. The organic phase was washed with water, dried and the solvent evaporated to leave an oil which was dissolved in carbon tetrachloride and extracted with saturated sodium bicarbonate solution. The ketoacid was extracted back into methylene chloride after careful acidification with dilute hydrochloric acid. Evaporation of the solvent gave an oil which crystallised on trituration with diethyl ether-*n*-hexane, (7.81 g., 43%); m.p. 82-84° dec.; ir: (dichloromethane): 1754, 1675 cm^{-1}; nmr: δ 3.60 (1H, s, -*CH*CO_2H), 10.98 (1H, s, exchanged in deuterium oxide, CO_2H), 1.4-3.2 (12H, m, skeletal).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.27; O, 24.7. Found: C, 67.8; H, 7.54; O, 24.5.

The neutral organic solutions gave on evaporation 7.6 g. (54%) of starting ketone (**17**).

N-(2-Nitrophenyl)-4-oxo-5-protoadamantanecarboxamide (**18**).

Compound **16** (3.88 g., 0.02 mole) and 2-nitroaniline (3.0 g., 0.022 mole) was stirred with DCC (4.12 g., 0.02 mole) in tetrahydrofuran (50 ml.) overnight followed by reflux for 3 hours. The mixture was cooled in ice, the dicyclohexylurea (4.1 g.) was removed by filtration and the solution evaporated to leave an oil which was crystallised from 2-propanol-*n*-hexane, (4.3 g., 69%); m.p. 138-139°; ir: 3340, 1700 (broad), 1610, 1585, 1500 cm^{-1}; uv: λ max 234 nm (log ε 4.26); nmr: δ 3.6 (1H, broad s, H5), 7.19 (1H, t, H5'); 7.64 (1H, t, H4'), 8.18 (1H, dd, H6'), 8.65 (1H, dd, H3'), 11.7 (1H, b, NH), 1.6-3.2 (12H, m, skeletal).

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 65.0; H, 5.77; N, 8.9; O, 20.5. Found: C, 64.8; H, 5.71; N, 8.5; O, 20.6.

12,13-Dihydro-11*a*H-Protoadamantano[4,5-*b*][1,5]benzodiazepin-12-one (**15**).

A solution of **18** (4.0 g., 0.0127 mole) in ethanol (200 ml.) was hydrogenated with 10% palladium-carbon (0.6 g.) at 60 psi for 18 hours. The catalyst was removed by filtration and the solution evaporated and the residue chromatographed on silica gel eluting with ethyl acetate to give **15** (1.54 g., 46%) m.p. 196-198°; ir: 3200, 3070, 1675, 1645 cm^{-1}; uv: λ max 221 (log ε 4.54) with a bathochromic shift to 233 nm (log ε, 4.44) after addition of hydrochloric acid: ^1H nmr: δ 2.15-3.5 (5H, m, -CH), 7.05-7.45 (4H, m, Ph), 9.7 (1H, b, NH, exchanged in deuterium oxide), 1.4-2.05 (8H, m, -CH_2-); ^{13}C nmr (DMSO-d_6): δ 163.5 (s, C5a), 49.9 (d, C11a), in addition 107.9 (s) and 136.0 (s) assigned to C11a and C5a respectively in (**19**); ms: m/e 266 (M^+), 238 (m-28).

Anal. Calcd. for $C_{17}H_{18}N_2O.\frac{1}{2}H_2O$: C, 74.2; H, 6.96; N, 10.2. Found: C, 74.2; H, 6.88; N, 9.9.

A second component identified as **20** [5*a*-hydroxy-5,5*a*,12,13-tetrahydro-11*a*-protoadamantano[4,5-*b*][1,5]benzodiazepin-12-one] was isolated from the above chromatography (0.27 g., 8%); m.p. 205-208°; ir: 3360, 3180, 1660, 1400, 1345 cm^{-1}; uv: λ max 223, 255 (sh), 309 nm (log ε 4.54,3.71); ^1H nmr: δ 7.0-7.6 (4H, m, Ph), 2.05, 8.1, 8.3, (3H, exchangeable with deuterium oxide), 1.5-3.8 (13H, m, skeletal); ^{13}C nmr (DMSO-d_6): δ 76.0 (s, C5a), 46.5 (d, C11a); ms: m/e 284 (M^+), 282 (M-2), 254 (M-30), 226.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.8; H, 7.09; N, 9.8. Found: C, 72.1; H, 6.97; N, 9.6.

2,3-Dihydro-1-(protoadamant-4-en-4-yl)benzimidazole-2-one (**22**).

To a stirred mixture of **15** (0.27 g., 0.001 mole) and *N*-methylpiperazine (2.5 ml.) under nitrogen was added titanium tetrachloride (0.125 ml., 0.0011 mole) in toluene (1 ml.). The mixture was heated at reflux for 3 hours, cooled, poured onto ice and extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to an oil, which was chromatographed on silica gel eluting with methylene chloride to give **22** (0.1 g., 37%); m.p. 210-213°; ir: 1702 cm^{-1}; uv: λ max 211, 231 (sh), 283 nm (log ε 4.46, 3.78); ^1H nmr: δ 6.49 [1H, dd, H_5 J ≅ 1.8 Hz (allylic)], 7.05 (4H, s, Ph), 9.93 (1H, b, NH), 1.4-3.3 (12H, m, skeletal); ^{13}C nmr: δ 154.2 (s, C2'), 142.4 (s, C4), 133.3 (d, C5); ms: m/e 266 (M^+), 249 (M-17), 244.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.81; N, 10.5; O, 6.0. Found: C, 76.4; H, 6.89; N, 10.3; O, 6.1.

Reaction of Ethyl-4-oxo-5-protoadamantanecarboxylic Acid (**21**) with 1,2-Diaminobenzene.

A mixture of **21** (1.1 g., 0.005 mole) and 1,2-diaminobenzene (0.55 g., 0.0051 mole) was refluxed in xylene in a Dean and Stark apparatus for 48 hours. The solution was evaporated and the residue chromatographed on Florisil eluting with methylene chloride-ethylacetate (9:1). The product was crystallised from ethylacetate-*n*-hexane to give **22** (0.55 g., 42%).

13-(3-Dimethylaminopropyl)-2-fluoro-5,5*a*,12,13-tetrahydro adamantano[2,1-*b*][1,5]benzodiazepin-12-one (**23**).

A solution of **2c** (2.9 g., 0.01 mole) in dry dimethylformamide (50 ml.) was added to sodium hydride (50% dispersion in mineral oil) (1.5 g., 0.03 mole) in dimethylformamide (50 ml). The mixture was stirred at 60° for 30 minutes, and *N*,*N*-dimethyl-3-chloropropylamine hydrochloride (1.6 g., 0.01 mole) in dimethylformamide (50 ml.) was added. The mixture was stirred at 80° overnight, poured onto water and extracted with diethyl ether. The organic phase was washed with water and extracted with dilute hydrochloric acid. The acidic solution was basified, and extracted with diethyl ether to give the base (2.1 g., 57%), which was converted into the maleate (1.9 g.), m.p. 184-186° (ethanol-diethyl ether); ir: 3500-2000, 1660 cm^{-1}; uv: λ max 317 nm (log ε 3.66); nmr (DMSO-d_6): δ 2.72 (6H, s, $N(CH_3)_2$), 5.2 (1H, s, NH), 6.0 (2H, s, -CH=CH-) 6.7-7.25 (3H, m, Ph), 1.0-4.0 (remaining aliphatics).

Anal. Calcd. for $C_{20}H_{30}FN_3O \cdot C_4H_4O_4$: C, 64.1; H, 7.02; N, 8.6; F, 3.9. Found: C, 64.3; H, 6.91; N, 8.7; F, 3.8.

12-[3-(4-Methylpiperazino)]propylamino-2-fluoro-5,5*a*-dihydro-adamantano[2,1-*b*][1,5]benzodiazepine (**25**).

The amide (**2c**) was converted to the corresponding thioamide (**24**) by refluxing with phosphorus pentasulfide in dry pyridine, m.p. 191-195° (ethanol); uv: λ max 276, 308, 358 nm (log ε 3.91, 3.75 4.07); nmr (deuteriochloroform-DMSO-d_6): δ 3.22 (1H, s, H5a), 6.4-7.2 (3H, m, Ph), 5.21 (1H, s, NH), 11.5 (1H, s, NHC=S), 0.9-2.1 (13H, m, skeletal).

Anal. Calcd. for $C_{17}H_{19}FN_2S$: C, 67.6; H, 6.33; N, 9.3; F, 6.3; S, 10.6. Found: C, 67.8; H, 6.14; N, 9.1; F, 6.6; S, 10.5.

A mixture of **24** (1.6 g., 0.0052 mole) and 3-(4-methylpiperazino)propylamine (1.6 g., 0.0104 mole) in triethylamine (20 ml.) was heated at 90° for 90 hours. Most of the triethylamine was distilled off and the residue partitioned between aqueous maleic acid and ethylacetate. The aqueous solution was basified with ammonia and the resulting base was filtered and dried under vacuum at 60°; (1.9 g., 86%); nmr (deuteriochloroform-DMSO-d_6): δ 3.2-3.6 (3H, m, H_{5a}, NH-CH_2-), 2.26 (3H, s, $N-CH_3$), 6.3-7.0 (3H, m, Ph), 6.15 (1H, NH), 2.3-2.7 (11H, m, $[N(C_2H_4)2N]$, NCH_2, NH (exchanged in deuterium oxide), 1.5-2.16 (15H, m, $C-CH_2-C$, rest skeletal); trimaleate: m.p. 184-86° (ethanol).

Anal. Calcd. for $C_{25}H_{36}FN_5 \cdot C_{12}H_{12}O_{12}$: C, 57.4; H, 6.25; N, 9.1; F, 2.5. Found: C, 57.4; H, 6.24; N, 8.9; F, 2.7.

6-Fluoro-9,9*a*-dihydro-3-methyladamantano[2,1-*b*][1,2,4]triazolo-[4,3-*d*][1,5]benzodiazepine (**26**).

A solution of **24** (1.7 g., 0.006 mole) and acethydrazide (5 g.) in a mixture of 1-butanol (25 ml.) and acetic acid (25 ml.) was refluxed for 36 hours. The solvent was removed under reduced pressure and the crude product partitioned between 2*N* sodium hydroxide and ethyl acetate. The organic layer was washed with water and extracted with dilute hydrochloric acid. The acidic solution was basified with ammonia and extracted into ethylacetate to give the base (1.3 g., 71%), which was converted into its hydrochloride salt; m.p. 225-28° (ethanol-diethyl ether); ir: 3270 cm^{-1} (NH), 2700-2400 cm^{-1} ($\equiv NH^+$); uv: λ max 257, 322 nm (log ε 3.78, 3.46); nmr (deuteriochloroform-DMSO-d_6): δ 2.77 (3H, s, CH_3), 3.8 (1H, s, H9a), 6.35-7.45 (3H, m, Ph), 1.2-2.4 (13H, m, skeletal).

Anal. Calcd. for $C_{19}H_{21}FN_4 \cdot HCl$: C, 63.2; H, 6.14; N, 15.5; Cl, 9.8; F, 5.3. Found: C, 63.1; H, 6.11, N, 15.5; Cl, 9.6; F, 5.4.

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