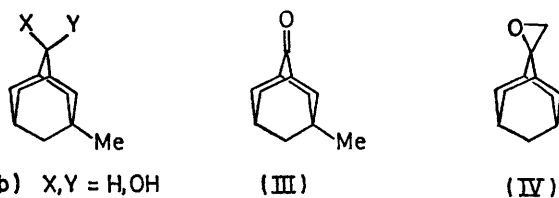


Preparation of the 5-Methyladamantan-2-ols and the 2,5-Dimethyladamantan-2-ols

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The oxidation of 1-methyladamantane, 3-methyladamantan-1-ol, or 2-methyladamantan-2-ol, with sulphuric acid is a more complex process than has previously been realised, but it gives 5-methyladamantanone as the major product. Reduction of the ketone affords the corresponding secondary alcohols, and a variety of methods provide the related methyl-carbinols. None of these reactions is usefully stereospecific, and the separation of the mixtures obtained, although successfully accomplished, is exceptionally difficult.

FOR stereochemical studies of substitution reactions we needed the two 5-methyladamantan-2-ols (I) and the corresponding tertiary alcohols (II). These were synthesised from 5-methyladamantanone (III), which at the outset of this work had not been reported, but which has recently been described.¹ Oxidative rearrangements of



(Ia, b) X, Y = H, OH

(IIa, b) X, Y = Me, OH

(III)

(IV)

3-methyladamantan-1-ol and 2-methyladamantan-2-ol gave ketonic products in yields of 30 and 10%, respectively; oxidations of the 98.5 : 1.5 equilibrium mixture of 1-methyladamantane and 2-methyladamantane obtained from tricyclo[6.2.1.0^{2,7}]undecane, or of 1-methyladamantane derived *via* the alcohol and bromide from adamantane-1-carboxylic acid, gave a 20% yield directly. All these ketonic products had similar compositions, comprising typically 80% of 5-methyladamantanone, 10% of 1-methyladamantanone, 7% of adamantanone itself, 2.5% of at least two other methyladamantanones (from the identification of parent ions after g.l.c.; presumably they were two or all of the three isomers having secondary methyl groups), and 0.5% of a compound which, from its short relative retention time on Carbowax, and mass spectral molecular ion, must be one (or more) of the dimethyladamantanones having tertiary methyl groups,² probably the 5,7-isomer. Very careful purification of 1-methyladamantane did not eliminate the small yield of C₁₂ and the more appreciable yield of C₁₀ compounds, whose origin is unknown.

The preparative separation of the 5-methyl- and the 1-methyladamantanones by chromatography on alumina was difficult; moreover, the complexity of the ketonic mixture was not at first realised,³ and early specimens of the 5-methyl compound contained some unrecognised adamantanone (*ca.* 1–2%) and (secondary methyl) adamantanones (*ca.* 3%). McKervery and his co-workers^{1b} have reported a 10% yield of 5-methyladam-

antanone only from the oxidation of 2-methyladamantan-2-ol by sulphuric acid at 65°.

The 1-methyl- and 5-methyladamantanones were distinguished by their 100 MHz n.m.r. spectra; both have singlet methyl resonances indicating tertiary methyl groups, but the 5-methyl isomer shows signals for two protons at low field (HC·CO) whereas the 1-methyl isomer has only one. The mixture of secondary alcohols (I) (*ca.* 1 : 1 with all reducing agents) obtained on reduction of 5-methyladamantanone, proved to be extraordinarily difficult to separate. Systematic chromatography at high (1000 : 1) alumina-substrate ratios ultimately gave a 97 : 3 mixture and a 16 : 84 mixture of isomers [(Ia) : (Ib)]. This work has been described briefly;³ subsequently it has been discovered that (*a*) the configurations tentatively assigned should be interchanged, and (*b*) small quantities (2–3%) of adamantan-2-ol were present in the 16 : 84 mixture. The epimeric alcohols (I) and all derivatives investigated formed continuous series of solid solutions, and both in adsorption chromatography and in g.l.c. they showed very similar retention indices. Mixtures were best analysed by chromatography of the trifluoroacetates on Apiezon L; 2-adamantyl derivatives proved to have the same retention index as the derivatives from (Ia), which was eluted before (Ib) on alumina.

The preparation of 2-methyladamantan-2-ol from adamantanone was used as a model for the synthesis of the tertiary alcohols (II). Methods used were the Grignard reaction, reduction of adamantane-2-spirooxiran (IV) formed by various routes from adamantanone, and oxymercuration-demercuration of 2-methyleneadamantane. These standard synthetic procedures worked well in all cases, but the stereoselectivity for which we had hoped, for example in the epoxidation of the 2-methyleneadamantane and in methylene transfer to the corresponding ketone, did not eventuate to a useful degree. The mixture of alcohols (IIa,b), however, unexpectedly proved much easier to separate than their secondary counterparts. Systematic chromatography at a 1000 : 1 alumina-substrate ratio gave both isomers in greater than 99% isomeric purity. Mixtures were best analysed by chromatography of the trimethylsilyl ethers on Apiezon L; 2-methyl-2-adamantyl derivatives co-chromatographed on alumina and Apiezon L with

¹ (*a*) H. W. Geluk and J. L. M. A. Schlatmann, *Rec. Trav. chim.*, 1969, **88**, 13; (*b*) M. A. McKervery, J. R. Alford, J. F. McGarrrity, and E. J. F. Rea, *Tetrahedron Letters*, 1968, 5165.

² Also found by H. W. Geluk, personal communication.

³ J. A. Bone and M. C. Whiting, *Chem. Comm.*, 1970, 115.

those of (IIb), which was found to contain 0.3% of 2-methyladamantan-2-ol.

The assignment of *cis*- and *trans*-configurations to the two pairs of epimers (Ia,b; IIa,b) proved difficult, and is discussed in the following paper.

EXPERIMENTAL

Solvents.—Ether was dried by distillation from calcium hydride; ether for chromatography was dried over calcium chloride overnight and filtered. Petroleum, unless otherwise stated, refers to light petroleum (b.p. 30–40°) purified by passage through a column of chromatographic silica gel, followed by distillation. Tetrahydrofuran was dried by distillation from lithium aluminium hydride, and dimethyl sulphoxide by distillation under reduced pressure from calcium hydride.

Organic solutions were dried over anhydrous magnesium sulphate; alumina used was B.D.H. chromatographic, activity II.

M.p.s of adamantane derivatives were determined for samples in sealed capillary tubes in an Electrothermal apparatus.

I.r. spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer, n.m.r. spectra on a Varian HA-100 instrument (tetramethylsilane as internal standard), and mass spectra on a Varian CH-7 spectrometer linked to a Varian 1200 gas chromatograph. G.l.c. involved Perkin-Elmer F11 gas chromatographs with S.C.O.T. 50 ft columns; conditions are quoted as (column type, column temperature in °C, nitrogen flow-rate in ml min⁻¹).

Tricyclo[6,2,1,0^{2,7}]undecane was prepared by two methods, (i) from cyclopentadiene and benzoquinone *via* zinc reduction, hydrogenation, and Wolff-Kishner reduction,⁴ or (ii) by Diels-Alder reaction between bicyclo[2,2,1]heptene and butadiene, followed by hydrogenation.⁵ Although differing stereochemically, the two saturated hydrocarbon mixtures behaved indistinguishably during isomerisation. The two synthetic methods were comparably satisfactory, relative convenience depending upon the availability of the bicycloheptene and the high-pressure equipment needed for its use.

Methyladamantanes.—The isomerisation of tricyclo[6,2,1,0^{2,7}]undecane mixtures by the method of Schleyer and Nicholas⁶ was difficult to reproduce and was best monitored by g.l.c. (Carbowax 1540, 110, 4); initially the 1-methyladamantane-2-methyladamantane ratio was *ca.* 2:1, and the time taken to reach equilibrium (98.5:1.5) varied (typically 48 h at 70°). The separation of the isomers was impracticable.

1-Bromomethyladamantane.—This was obtained from 1-hydroxymethyladamantane (prepared by reduction with lithium aluminium hydride of commercially available adamantane-1-carboxylic acid⁷) in 70% yield by the procedure of Stepanov and Baklan,⁸ m.p. (sublimed) 42–43° (lit.,⁸ 43.5°). We found that 18% of 1-acetoxymethyladamantane was also formed (comparison of the i.r. spectrum with that of an authentic sample; reduction

with lithium aluminium hydride gave 1-hydroxymethyladamantane). This was separated from the bromide by chromatography on alumina (30:1); elution with petroleum gave bromide, with 10% ether in petroleum gave acetate, and with ether gave unchanged alcohol.

1-Methyladamantane.—This was prepared from 1-bromomethyladamantane as described previously,⁸ and was found to be free from adamantane and 2-methyladamantane ($\leq 0.05\%$) as shown by g.l.c. analysis (Apiezon L, 110, 4).

Methyladamantanones.—(i) 1-Methyladamantane [prepared from adamantane-1-carboxylic acid (10 g)] was mixed with 96% sulphuric acid (160 ml), and the mixture was stirred vigorously at 75° in a loosely stoppered flask (to allow escape of sulphur dioxide) with occasional shaking to redissolve sublimed material. Samples were quenched periodically; the products were extracted with ether and the dried ethereal solution was analysed by g.l.c. (Carbowax 20M, 140, 6). After 5 h the principal product was 5-methyladamantanone; the mixture was then poured on ice (1000 g) and steam distilled; the ethereal extract of the distillate was dried and evaporated to 4.6 g of solid. Chromatography on alumina (30:1) separated 1-methyladamantane (0.4 g) and a ketone fraction (2.1 g, 20%) (elution with petroleum) and an alcohol fraction (1.5 g) (elution with ether).

(ii) 3-Methyladamantan-1-ol⁷ (9.2 g) dissolved in 96% sulphuric acid (72 ml) was stirred vigorously at 75° for 4.5 h in a loosely stoppered flask with occasional shaking, the reaction being monitored as in (i). Work up as (i) gave 1-methyladamantane (0.4 g), ketones (2.8 g, 30%), and alcohols (0.4 g).

(iii) 2-Methyladamantan-2-ol⁹ (100 mg) dissolved in 96% sulphuric acid (0.8 ml) was stirred vigorously at 75°. After 5 h the principal product was 5-methyladamantanone, but isolation of the ketones as described in (i) showed an overall yield of less than 10%.

The addition of tetrahydrothiophen dioxide to increase homogeneity in the reaction with 1-methyladamantane necessitated higher temperatures, this increased the polymerisation rate and did not improve the ketone yield.

The action of hot 96% sulphuric acid on 1-bromomethyladamantane did not give a high ketone yield with or without tetrahydrothiophen dioxide.

Analysis of Ketone and Alcohol Fractions.—Fractions were analysed by g.l.c. (Carbowax 20M, 140, 6). The typical

G.l.c. analysis (Carbowax 20M, 140, 6) of the ketone fraction from the oxidation of 1-methyladamantane with sulphuric acid

t_R /min	Peak area (%)	M^+
9	0.5	178
10	10.0	164
11	80.0	164
12.5	7.0	150
15	1.0	164
17	1.5	164

composition of the ketone fraction and the mass spectral molecular ions are given in the Table. From collected data for adamantane compounds on Carbowax 20M¹⁰ it was

⁴ C. Swithenbank and M. C. Whiting, *J. Chem. Soc.*, 1963, 4573.

⁵ K. Alder, J. Mönch, and H. Wirtz, *Annalen*, 1959, 627, 47.

⁶ P. von R. Schleyer and R. D. Nicholas, *Tetrahedron Letters*, 1961, 305.

⁷ C. A. Grob, W. Schwarz, and H. P. Fischer, *Helv. Chim. Acta*, 1964, 47, 1385.

⁸ F. N. Stepanov and V. F. Baklan, *J. Gen. Chem. (U.S.S.R.)*, 1964, 34, 580.

⁹ P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, 1961, 83, 182.

¹⁰ J. Burkhard, J. Vais, L. Vodicka, and S. Landa, *J. Chromatog.*, 1969, 42, 207.

assumed that the 10 and 80% peaks were the methyladamantanones with tertiary methyl groups, the component in larger amount probably being the less hindered 5-methyladamantanone. At least one of the dimethyladamantanones (0.5%) was also formed,² with two and perhaps all three of the methyladamantanones with secondary methyl groups (2.5%), and a compound thought to be adamantanone (7%),^{1a} which ran concurrently with an authentic sample on both a polar and a non-polar column. This assignment was checked by reduction with lithium aluminium hydride of a sample containing 25% of suspected adamantanone (from later alumina chromatography); coinjection of adamantan-2-ol on a polar column gave an increase in size of the corresponding 25% alcohol peak.

The alcohol fraction of the oxidation was typically composed largely of 3-methyladamantan-1-ol (90%), with at least six other alcohols, among them being one or more of the dimethyladamantanols (1%). This material had a characteristically shorter retention time than 3-methyladamantan-1-ol, and a molecular ion of *m/e* 180. The alcohol fractions were combined and used for further sulphuric acid oxidation experiments.

Separation of the Ketones.—The ketone fraction (5.7 g) was chromatographed on alumina (2 kg), with 20% ether in petroleum as eluant (100 ml fractions). The methyl ketones did not completely separate; the 10% component was eluted first and the mixed fractions were combined and rechromatographed to give only a small number of mixed fractions, containing little of the major component. The 100 MHz n.m.r. spectra (CCl₄) of the ketones determined their identity; first-eluted ketone, τ 7.58(1H), 7.9—8.3(14H), and 9.11(3H, s); second-eluted ketone, 7.63(2H), 8.0—8.4(13H), and 9.13(3H, s). The complexity of the mixture was not at first realised;³ the 5-methyladamantanone was assumed pure, m.p. (from petroleum at -78°) 125—126° (lit.,^{1b} 126—127°) (Found: C, 80.4; H, 9.55. Calc. for C₁₁H₁₆O: C, 80.5; H, 9.75%). 1-Methyladamantanone, recrystallised from petroleum at -78° , had m.p. 105—107° (lit.,¹¹ 106.5—108.5°).

5-Methyladamantanone was eluted only slightly ahead of adamantanone, and fractions were combined according to their adamantanone content. Those containing as much as or more adamantanone than the original mixture were rechromatographed to give more 5-methyladamantanone containing only a little adamantanone. Finally, the combined 5-methyladamantanone (2 g, 2.3% adamantanone) was chromatographed again to give material containing 0.8% adamantanone (1 g) and material containing 3.7% adamantanone (1 g). The final specimen of 5-methyladamantanone also contained secondary methyl ketones (3.5%) and 1-methyladamantanone (0.5%).

5-Methyladamantan-2-ols.—Reduction of 5-methyladamantanone with lithium aluminium hydride and with aluminium isopropoxide in propan-2-ol both gave 1:1 mixtures of the epimeric alcohols, m.p. 125—135°; other possibly stereospecific syntheses were not considered worthwhile. Use of lithium aluminium hydride gave the higher yield (95%).

The alcohols were not resolved by g.l.c. on any column, but mixtures could be analysed as the trifluoroacetates on Apiezon L. Typically the alcohols (4 mg) were dissolved in

dry pyridine (0.2 ml) and trifluoroacetic anhydride (0.05 ml) was added. After 5 min, the solution was extracted with petroleum (5 ml) and the extracts were washed with dilute acid, then with water. The dried solution was used directly for g.l.c. analysis (Apiezon L. 120, 4).

Separation of the Alcohols.—The alcohols (2.5 g) were chromatographed on alumina (2.5 kg), with dry ether as eluant (100 ml fractions); typically some 30—40 alcohol-containing fractions were obtained. Selected fractions were analysed as the trifluoroacetates, and the band was divided into batches of limited composition range [10—30% (Ib), etc.]. Persistent rechromatography of the less separated batches eventually gave substantial amounts of the material of the limiting isomer ratios. In no run was any fraction found to contain a pure isomer at either the leading or trailing edge of the band and the composition of the extreme fractions converged to a constant isomer ratio which was independent of the alcohol mixture applied to the column. The first-eluted isomer (Ia) was not enriched beyond 97%, but 20 recrystallisations from petroleum at -78° purified it to 99.7%; m.p. 150—152° (Found: C, 79.2; H, 10.8. C₁₁H₁₆O requires C, 79.5; H, 10.85%). The second-eluted isomer (Ib) was not enriched beyond 84%; m.p. 123—127°. Thermal analysis of specimens of intermediate composition led to a diagram typical for a range of solid solutions.

It was not realised at the time of our earlier communication³ that the 84:16 mixture of 5-methyladamantan-2-ols also contained ca. 2% adamantan-2-ol, and that compound (Ia), before the repeated crystallisation purifications, also contained ca. 3% of an alcohol having a secondary methyl group. 2-Adamantyl acetate, trifluoroacetate, and trimethylsilyl ether have practically the same retention index on Apiezon L at 120° as the corresponding derivatives of (Ia); on raising the column temperature, the 2-adamantyl derivatives have a relatively lower index, and the mixture can be analysed at 16,000 plates (100 ft S.C.O.T. column) at 200°.

Routes to 2-Methyladamantan-2-ol.—(a) *By use of methylmagnesium iodide.* As previously described.⁹

(b) *From adamantane-2-spiro-oxiran* (IV). (i) Adamantanone (1.5 g, 10 mmol) dissolved in the minimum of warm dimethyl sulphoxide was added to a solution of dimethylsulphoxonium methylide¹² (12 mmol) in dimethyl sulphoxide (15 ml). The solution was stirred at 50° for 12 h, water (40 ml) was added, and the solution was extracted with ether (2 × 30 ml, 2 × 15 ml). The combined extracts were washed with 1:1 water-dimethyl sulphoxide (20 ml), then with 50% saturated salt solution (20 ml). The solution was dried and the ether removed to give a white solid which was sublimed to give the epoxide (1.15 g, 70%), m.p. (from petroleum at -78°) 176—178° (lit.,¹³ 178—181°) (Found: C, 80.9; H, 9.75. Calc. for C₁₁H₁₆O: C, 80.5; H, 9.75%).

(ii) Adamantanone (0.8 g, 5.3 mmol) dissolved in dry tetrahydrofuran (10 ml) was added quickly to a solution of dimethylsulphonium methylide¹² (6.6 mmol) in dry dimethyl sulphoxide-tetrahydrofuran (2:1; 12 ml) at -10° . The solution was stirred at 0° for 20 min then at room temperature for 2 h, and diluted with water (50 ml). Work-up as in (i) gave the epoxide (0.6 g, 70%), m.p. (petroleum -78°) 175—177° (Found: C, 80.6; H, 9.75. Calc. for C₁₁H₁₆O: C, 80.5; H, 9.75%).

¹¹ D. Lenoir, R. Glaser, P. Mison, and P. von R. Schleyer, *J. Org. Chem.*, 1971, **36**, 1821.

¹² E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.

¹³ C. A. DeBock and J. L. M. A. Schlattmann, Ger. Pat. 1,910,560 (*Chem. Abs.*, 1970, **72**, 21,403).

(iii) A 0.9M-solution of monoperphthalic acid in ether (16 ml; prepared by the method of Royals and Harrell¹⁴) was added to 2-methyleneadamantane (1 g, 7 mmol), and the solution was stirred at room temperature for 4 h. The precipitate of phthalic acid was filtered off and washed with ether; the filtrate was washed with ice-cold 5% sodium hydrogen carbonate solution until addition of a sample to 20% potassium iodide solution produced no iodine. Pyridine-water (3:7; 1 ml) was then added; the solution was stirred for 2 h at room temperature and then washed with 5% sodium hydrogen carbonate solution, 0.2M-sulphuric acid (2 × 20 ml), and water, and dried. Removal of the ether gave a solid which was sublimed to give the epoxide (0.56 g, 50%), m.p. (petroleum -78°) 174–176° (Found: C, 80.3; H, 9.65. Calc. for C₁₁H₁₆O: C, 80.5; H, 9.75%). The samples prepared by all three routes had identical i.r. spectra, including a characteristic C-H stretching band at 3020 cm⁻¹.

Treatment of the epoxide with excess of lithium aluminium hydride in ether for 3 h gave 2-methyladamantan-2-ol only (g.l.c.), in 80% yield.

(c) *Oxymercuration-Demercuration of 2-methyleneadamantane*. The procedure is that of Brown and Geoghegan.¹⁵ Mercury(II) acetate (640 mg, 2 mmol) was dissolved in water (2 ml), and tetrahydrofuran (4 ml) was added giving a yellow precipitate. 2-Methyleneadamantane (296 mg, 2 mmol) was added and the mixture was stirred at room temperature for 20 min (the yellow colour disappeared after 2 min). Sodium hydroxide solution (3M; 2 ml) was added, giving a cream precipitate, followed by a 0.5M-solution of sodium borohydride in a 3M-solution of sodium hydroxide (2 ml), giving an immediate grey-black precipitate of mercury; this was allowed to settle, the water layer was saturated with salt, and the upper tetrahydrofuran layer was separated. Removal of the tetrahydrofuran gave a grey solid which was purified on an alumina column to give 2-methyladamantan-2-ol (235 mg, 70%), m.p. (sublimed) 205–208° (lit.,⁹ 208–209°).

2,5-Dimethyladamantan-2-ols.—The five methods described for the preparation of 2-methyladamantan-2-ol from adamantanone were applied to the synthesis of the 2,5-dimethyladamantan-2-ols from 5-methyladamantanone.

Mixtures were analysed as the trimethylsilyl ethers (Apiezon L 100 ft, 180, 4); typically¹⁶ alcohol mixture (2 mg), dimethyl sulphoxide (30 μl), and hexamethyldisilazane (20 μl) were sealed into an ampoule which was placed in a boiling bath overnight. The upper layer of trimethylsilyl ethers was used directly for g.l.c. analysis; 2-methyl-2-adamantyl trimethylsilyl ether had the same retention time as the longer retention time isomer, and the composition of the mixture was corrected for this. Compositions found were (method, % in order of retention time): a 42:58; b(i), 53:47; b(ii), 49:51; b(iii), 51:49; c, 59:41. The method chosen for large-scale product of alcohol was the most direct one, a.

5-Methyl-2-methyleneadamantane and the 5-methyladamantan-2-spiro-oxirans were observed as liquid intermediates in methods b and c by g.l.c. and their characteristic i.r. spectra; they were not otherwise characterised.

Separation of the Alcohols.—The alcohol mixture (42:58) from the Grignard reaction (1.2 g), was chromatographed on alumina (1.2 kg), with dry ether as eluant (100 ml fractions). Even the first chromatogram gave an early fraction containing pure epimer (IIa) and a late one containing 97% pure (IIb), with a series of mixed fractions between. Mixed fractions were rechromatographed to give an accumulation of fractions containing more than 90% of each epimer, and a small amount of pure (IIa). These fractions were then rechromatographed and finally gave epimerically pure [$<0.1\%$ (IIb)] (IIa) (250 mg), and 99.4% epimerically pure (IIb) (400 mg). G.l.c. analysis (Carbowax 20M, 140, 6) showed that (IIa) contained 2.4% of alcohol formed from the long retention time (secondary methyl) ketone, and that (IIb) contained 0.3% 2-methyladamantan-2-ol. *Compound* (IIa) was recrystallised from petroleum at -78° (but still contained 2.1% impurity); m.p. 52.5–54.0° (Found: C, 79.8; H, 11.2. C₁₂H₂₀O requires C, 80.0; H, 11.1%). *Compound* (IIb) was recrystallised from petroleum at -78° and improved to 99.9% isomeric purity (0.2% 2-methyladamantan-2-ol), m.p. 97.0–97.5° (Found: C, 80.2; H, 10.75%).

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¹⁴ E. E. Royal and L. L. Harrell, *J. Amer. Chem. Soc.*, 1955, **77**, 3405.

¹⁵ H. C. Brown and P. J. Geoghegan, *J. Org. Chem.*, 1970, **35**, 1844.

¹⁶ S. Friedman and M. L. Kaufman, *Analyt. Chem.*, 1966, **38**, 144.