Chemistry of 2-substituted adamantanes. II. Preparation of 2-adamantanethiol and some of its derivatives.[1] Aromatic solvent-induced shifts in their n.m.r. spectra

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Reduction ($NaBH_4$) of adamantanethione gives high yields of pure 2-adamantanethiol, from which several derivatives including the methyl sulfide, sulfoxide, and sulfone were prepared. The sulfenyl chloride was prepared and used *in situ*. From the n.m.r. spectra the aromatic solvent-induced shifts $\Delta = \tau(\text{benzene}) - \tau(CCl_4 \text{ or } CDCl_3)$ were determined, where possible.

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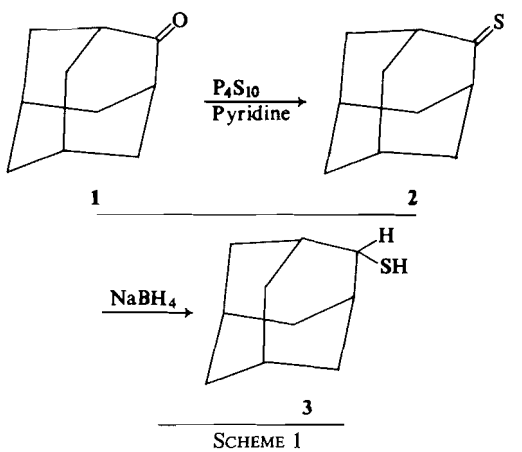
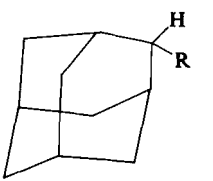
Recently we reported the details for the preparation of adamantanethione (**2**), which can be obtained in a 90% yield from adamantanone (**1**) by treatment with phosphorus pentasulfide in pyridine (2) (Scheme 1). Reduction of **2** seemed an attractive method to prepare 2-adamantanethiol (**3**) which had not yet been reported. Its



SCHEME 1

isomer, 1-adamantanethiol, has been prepared from the readily available 1-bromoadamantane via the isothiouronium salt (3). Ionic substitution reactions in adamantane derivatives occur much less readily at the secondary carbon than at the bridgehead positions (4). But even if it would be possible to prepare the 2-thiol from the 2-bromo compound in a good yield, then the starting material would still have to be prepared from the ketone: adamantanone → 2-adamantanol → 2-bromoadamantane.[2] For economic and practical reasons it seemed to us therefore unlikely that a more satisfactory method than the sequence **1** → **2** → **3** would become available for the preparation of 2-adamantanethiol, if a good reduction method could be found. As sodium borohydride reacts very readily with the thiocarbonyl group (7) and had been used successfully by others in a few cases (8), it was our first choice.

We now report the details for the preparation and purification of the thiol (**3**) and a number of derivatives (**4**–**10**).



4 R = S—CH_3
5 R = SO—CH_3
6 R = SO_2—CH_3
7 R = 2-adamantyldithio
8 R = S-3,5-dinitrobenzoyl
9 R = S—Cl
10 R = S—phthalimido

Adamantanethione (**2**) was reduced with excess sodium borohydride in 1,2-dimethoxyethane at approximately 45°. We have used impure starting material (**2**) containing up to 30% of adamantanone (**1**) and found that the crude thiol, which on occasion contained large quantities of 2-adamantanol, can be easily and effectively purified via its yellow lead salt. In the experimental section the conversion of **2**, containing about 1% of ketone, into pure thiol is described (yield 85%). 2-Adamantanethiol sublimes readily (90°, 15 Torr), like so many adamantane derivatives.

The new thiol was converted into *S*-(2-adamantyl) 3,5-dinitrobenzoate (**8**), and by methylation (yield 83%) into 2-methylthioadamantane (**4**). The latter, a liquid, was oxidized with 1-chloro-

[1]Part of this work has been reported in a preliminary communication (1).

[2]Practical syntheses of 2-bromoadamantane from the secondary alcohol have been reported, using either phosphorus pentabromide (65% yield (5)) or thionylbromide (88% yield (6)).

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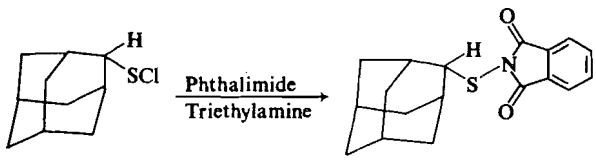

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SCHEME 2

benzotriazole (9) to 2-methylsulfinyladamantane (**5**), or with hydrogen peroxide in acetic acid to the corresponding sulfone (**6**). Oxidation of **3** with iodine gave di-(2-adamantyl) disulfide (**7**).

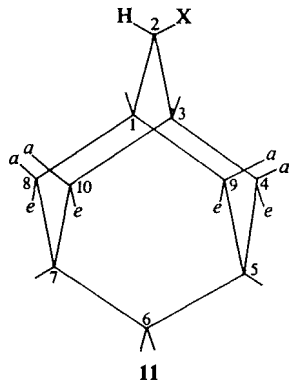
As 2-adamantanesulfenyl chloride (**9**) seemed a compound of considerable potential in the synthesis of a variety of 2-adamantylthio-compounds, a reaction with the sulfenyl chloride, prepared by the general method of Emde (10), was carried out.

When *N*-chlorosuccinimide was added to 2-adamantanethiol (**3**) in benzene, a yellow–orange solution of **9** was obtained in less than 15 min. After filtration the solution was used for the reaction with phthalimide, giving *N*-(2-adamantylthio)-phthalimide (**10**) (Scheme 2), yield 72%.

The Nuclear Magnetic Resonance Spectra of Compounds 3–7

The n.m.r. spectra showed in general the typical pattern for a 2-monosubstituted adamantane (**11**), as reported by van Deursen and Korver (11). In Table 1 the observed chemical shifts (or calculated origin positions in the case of the AB systems) are presented for all protons where this was possible in compounds **3–7**, as well as for 2-adamantanol. Carbon tetrachloride or deuteriochloroform, and benzene were used as solvents.[3]

In most cases, a.s.i.s. values could be determined for the five protons H-2, H-4,9(*e*), and H-4,9(*a*) on the adamantane skeleton **11**, in addition to shift values for some other protons. Unfortunately it was impossible to get a.s.i.s. values



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for the two other proton pairs H-8,10 (*a* and *e*) in any of the compounds, including 2-adamantanol.[4]

Our data show that the methyl protons in the sulfide **4**, sulfoxide **5** and sulfone **6** are becoming more deshielded in the order given in all solvents, but the aromatic solvent-induced shift $\Delta = \tau(\text{benzene}) - \tau(CCl_4 \text{ or } CDCl_3)$ increases from 0.21 p.p.m. for the sulfide to 0.69 p.p.m. for the sulfone, *i.e.* in the order of their expected dipole moments.[5]

In all cases where complete data could be collected, the a.s.i.s. values show that the equatorial (with respect to the substituent X) proton pair H-4,9(*e*), and H-2 (except in compound **7**) are shielded, while the axial pair H-4,9(*a*) is deshielded by the aromatic solvent.

The thiol proton in 2-adamantanethiol (**3**) shows virtually no solvent-induced shift in our experiments. It is interesting to note that in 1-adamantanethiol the thiol proton shows a downfield solvent shift of 0.13 p.p.m. for the same solvent pair (unpublished observations of the author). This fact shows clearly how much caution is required in the interpretation of aromatic solvent shift data.

The lack of data for the sulfoxide **5** in Table 1 is the result of the complexity of its n.m.r. spectrum, especially in the region where H-2, H-1,3, and H-4,9(*a*) were expected to have their

[3]As carbon tetrachloride and benzene are for various reasons an ideal pair (12) for the study of aromatic solvent-induced shifts (a.s.i.s.), deuteriochloroform was used only when solubility problems were met. Solvent shifts for the pair $CDCl_3$ and CCl_4 have been determined for a number of substituted cyclohexanones and in most cases were found to be small, although there were some striking exceptions (13). The shifts for the two solvent pairs as reported in this work are therefore not strictly comparable in all cases, but our mixed data fit well together and no trends, if noticeable, seem disturbed by the change of solvent.

[4]This compound was the only one for which the origin positions for the H-8,10 (*a* and *e*) protons could be determined by van Deursen and Korver (11) in $CDCl_3$ solution. In CCl_4 or benzene this was not possible, we found.

[5]The following dipole moments μ have been reported in benzene solution: dimethyl sulfide, 1.45 D (14); dimethyl sulfoxide, 3.9 D (15); dimethyl sulfone, 4.25 D (16).

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TABLE 1

Chemical shift (τ units) of protons in compounds 3–7,* and in 2-adamantanol, and their aromatic solvent-induced shift Δ†

	3			4			5			6			7			2-adamantanol		
Protons‡	CCl_4	Benzene	Δ	CCl_4	Benzene	Δ	$CDCl_3$	Benzene	Δ	$CDCl_3$	Benzene	Δ	CCl_4	Benzene	Δ	CCl_4	Benzene	Δ
H-1,3					8.06					7.43	7.68	+0.25	7.90	7.79	−0.11			
H-2	6.68§	6.90§	+0.22	7.11	7.20	+0.09				6.88	7.31	+0.43	6.87	6.73	−0.14	6.23	6.40	+0.16
H-4,9(*e*)‖	8.49	8.62	+0.13	8.49	8.54	+0.05				8.38			8.47	8.54	+0.07	8.55	8.59	+0.04
H-4,9(*a*)‖	7.81	7.79	−0.02	7.82	7.68	−0.14				7.52	7.32¶	−0.20	7.86	7.72	−0.14	7.89	7.83	−0.06
H-8,10(*e*)‖					8.37					8.24								
H-8,10(*a*)‖					8.22					8.00								
—XH(X=O or S)	8.54§	8.53§	−0.01													8.60	8.96	+0.36
Methyl-H				7.96	8.17	+0.21	7.45	8.02	+0.57	7.13	7.82	+0.69						

*Solutions were 5–10% (w/w).
†Δ = τ(benzene) − τ(CCl_4 or $CDCl_3$). A positive value of the solvent shift indicates a shift to higher field, *i.e.* more shielding, in the aromatic solvent.
‡Designation as in text.
§Doublet, J = 7 Hz.
‖Representing one half of an AB quartet, J = 12 Hz.
¶Approximately; signal for H-4,9(*e*) could not be observed.

signals. We found it impossible to make the necessary assignments and seek the explanation for the far more complicated spectrum in the fact that the two bridgehead protons H-1,3 are not equivalent any more as a result of the adjacent sulfoxide group.

General conclusions regarding the shifts induced by aromatic solvents cannot be drawn from the data in Table 1. They are presented as a contribution to the gradually increasing body of information on these shifts which ultimately may make it possible to arrive at a more quantitative understanding of the phenomenon. At present the qualitative aspects are on many occasions not clear.

Experimental

Melting points were determined on a Büchi melting point apparatus in sealed capillary tubes, and are uncorrected. The i.r. spectra were recorded on a Perkin–Elmer spectrophotometer, Model 337. The mass spectra were determined on a Varian-Mat CH-15 instrument at an ionization energy of 70 eV. The n.m.r. spectra were recorded at 60 or 100 MHz on Varian A-60 and HA-100 spectrometers, in the solvent indicated, at concentrations 5–10% (w/w). Tetramethylsilane ($\tau = 10$) was used as internal standard. Microanalyses were carried out by Dr. C. Daesslé, Organic Microanalysis, Montreal, Quebec, and by Mrs. S. Swaddle of this Department.

2-Adamantanethiol (3)

To a stirred solution of 22.5 g (135 mmoles) of adamantanethione (**2**) (containing approximately 1% adamantanone) in 170 ml of 1,2-dimethoxyethane was added 3.0 g (80 mmoles) of sodium borohydride in small portions in 3 min. When the temperature of the reaction mixture had risen to about 45°, external cooling was started to keep the temperature from rising more. The orange color of the thione faded and after 10 min some colorless precipitate was present. To decompose excess borohydride, 10 ml of water was added dropwise, and then very slowly concentrated hydrochloric acid till p*H* 2 was reached. The reaction mixture was extracted four times with carbon tetrachloride. The extract was washed twice with water, dried ($MgSO_4$), and concentrated *in vacuo* giving 22.4 g of solid crude 2-adamantanethiol. It was dissolved in a mixture of 150 ml of 1,2-dimethoxyethane and 100 ml of ethanol. This solution was added to a stirred solution of 25.8 g (68 mmoles) of lead acetate in 250 ml of 70% ethanol. A bright yellow lead thiolate precipitated. After filtration, the lead salt was twice washed with water, then twice with acetone. After drying, 36.1 g of the fine yellow powder was obtained. This was suspended in 150 ml of water and 250 ml of petroleum ether (boiling range 30–60°) was added. Hydrogen sulfide was bubbled through the aqueous layer for 1 h and lead sulfide was removed by filtration. The aqueous and organic layers were separated, the petroleum ether was washed three times with water, dried ($MgSO_4$), and concentrated to dryness, giving 19.2 g of 2-adamantanethiol (**3**) (yield 85% from the thione), m.p. 153–155°.

An analytical sample of the thiol was obtained by sublimation at 90° and 15 Torr, m.p. 160–161°.

Anal. Calcd. for $C_{10}H_{16}S$: C, 71.37; H, 9.58; S, 19.05. Found: C, 71.42; H, 9.79; S, 18.81.

Mass spectrum: *m/e* 168 (M^+). The i.r. spectrum ν_{max}(KBr): 2560 cm^{-1} (weak, SH); for the n.m.r. spectrum, see Table 1 and text.

S-(2-Adamantyl) 3,5-Dinitrothiobenzoate (8)

Reaction of 2-adamantanethiol with 3,5-dinitrobenzoylchloride in the presence of pyridine afforded *S*-(2-adamantyl) 3,5-dinitrothiobenzoate (**8**), m.p. 171–172° after two recrystallizations from chloroform – petroleum ether.

Anal. Calcd. for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.04; H, 4.95; N, 7.52.

The i.r. spectrum ν_{max}(KBr): 1660 (C=O), 1545 and 1350 cm^{-1} (C—NO_2), all very strong; n.m.r. spectrum $\tau(CDCl_3)$: between 0.75 and 1.00 (multiplet, 3H, aromatic protons), 5.71 (singlet, 1H, proton at C-2), between 7.67 and 8.50 (unresolved multiplet, 14H).

2-Methylthioadamantane (4)

To a solution of 8.40 g (50 mmoles) of **3** in 25 ml of methanol and 50 ml of 1,2-dimethoxyethane was added a solution of 2.6 g (65 mmoles) of sodium hydroxide in 20 ml of water. While this mixture was well stirred in a N_2-atmosphere, 7.56 g (60 mmoles) of dimethyl sulfate was added dropwise in 5 min and the reaction mixture was stirred for another 2 h. It contained a lower layer of the sulfide and after 200 ml of water had been added the reaction mixture was extracted three times with petroleum ether. After washing (H_2O), drying ($MgSO_4$), and concentration of the extract, 8.42 g of oil was obtained which was distilled at 95–97° and 4 Torr giving 7.50 g of 2-methylthioadamantane (yield 83%), n_D^{25} 1.5460.

Anal. Calcd. for $C_{11}H_{18}S$: C, 72.46; H, 9.95; S, 17.59. Found: C, 72.31; H, 9.94; S, 17.42.

Mass spectrum: *m/e* 182 (M^+). For the n.m.r. spectrum see Table 1 and text.

2-Methylsulfinyladamantane (5)

With 1-chlorobenzotriazole 1.46 g (8 mmoles) of **4** in methanol – methylene chloride (2:1) at −78° was converted into the corresponding sulfoxide using a recently reported method (9). 2-Methylsulfinyladamantane (**5**) was obtained in a 77% yield, m.p. 120°. After recrystallization from *n*-hexane (containing 5% benzene) shiny plates were obtained, m.p. 122–123°.

Anal. Calcd. for $C_{11}H_{18}OS$: C, 66.61; H, 9.15; S, 16.16. Found: C, 66.79; H, 8.99; S, 15.89.

Mass spectrum: *m/e* 198 (M^+). The i.r. spectrum ν_{max}(KBr): 1041 and 1030 cm^{-1} (very strong, SO stretching in sulfoxide); for the n.m.r. spectrum see Table 1 and text.

2-Methylsulfonyladamantane (6)

Oxidation of 0.88 g (4.8 mmoles) of **4** with hydrogen peroxide in glacial acetic acid gave a 60% yield of 2-methylsulfonyladamantane, m.p. 114.5–115.5°.

Anal. Calcd. for $C_{11}H_{18}O_2S$: C, 61.64; H, 8.47; S, 14.96. Found: C, 61.47; H, 8.41; S, 14.66.

Mass spectrum: *m/e* 214 (M^+). The i.r. spectrum ν_{max}(KBr): 1130 and 1275 cm^{-1} (very strong, SO_2); for the n.m.r. spectrum see Table 1 and text.

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Di(2-adamantyl) Disulfide (7)

A solution of 1.27 g (5 mmoles) of iodine in 25 ml of ethanol was added dropwise to a stirred solution of 1.68 g (10 mmoles) of 2-adamantanethiol and 0.54 g (10 mmoles) of sodium methoxide in 50 ml of a 1:1 mixture of ethanol and 1,2-dimethoxyethane. The disulfide precipitated and was isolated by filtration (weight 1.61 g). It was very well soluble in carbon tetrachloride, benzene, ethylacetate, and petroleum ether, only slightly in hot acetonitrile or hot ethanol. It was twice recrystallized from benzene – acetonitrile (1:2) giving 1.32 g of di(2-adamantyl) disulfide (yield 79%), m.p. 275°.

Anal. Calcd. for $C_{20}H_{30}S_2$: C, 71.80; H, 9.04; S, 19.16. Found: C, 71.44; H, 8.95; S, 19.14.

Mass spectrum: *m/e* 334 (M^+). For the n.m.r. spectrum see Table 1 and text.

*N-(2-Adamantylthio)-phthalimide (**10**)*

A solution of 2-adamantanesulfenyl chloride (**9**) was prepared as follows (10): to a stirred suspension of 2.72 g (20.4 mmoles) of *N*-chlorosuccinimide in 30 ml of benzene was added a solution of 3.36 g (20 mmoles) of 2-adamantanethiol in 10 ml of benzene. The vigorously stirred reaction mixture turned yellow–orange and was filtered after 15 min.

The clear filtrate, containing the sulfenylchloride was added to 2.94 g (20 mmoles) of phthalimide in 20 ml of *N,N*-dimethylformamide containing 2.7 g (27 mmoles) of triethylamine. After 20 min of stirring at 25°, the reaction mixture was left standing for 40 h. After filtration to remove the formed triethylammonium chloride the filtrate was poured into 200 ml of water. After extraction with carbon tetrachloride (three times) the extract was washed with water, dried ($MgSO_4$), and concentrated till almost dry. Addition of 100 ml of petroleum ether, filtration, and drying of the product gave 4.5 g of almost colorless *N*-(2-adamantylthio)-phthalimide (72%), which could be recrystallized from ethanol; m.p. 166–167°.

Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47; S, 10.23. Found: C, 69.20; H, 6.16; N, 4.28; S, 10.46.

Mass spectrum: *m/e* 313 (M^+). The i.r. spectrum ν_{max}(KBr): 1755 cm^{-1} (very strong, C=O); n.m.r. τ (CCl_4): 2.19 (multiplet, 4H, aromatic protons), 6.52 (singlet, 1H, proton at C-2), τ 6.4–8.7 (unresolved multiplet, 14H).

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Identification of 1-(4-methoxyphenyl)-1-methoxy-2-aminopropane diastereoisomers

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A method for the assignment of *erythro* and *threo* configurations to the diastereoisomeric 1-(4-methoxyphenyl)-1-methoxy-2-aminopropanes and related compounds based on p.m.r. data is presented and discussed.

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The physiological activities of the (+) and (−) forms of the *erythro* and *threo* isomers of derivatives of phenylpropanolamine, $C_6H_5CH(OH)CH(CH_3)NH_2$ may be expected to differ, and a positive identification of the forms is essential in analysis and for investigations of structure–activity relationships (1). Synthetic compounds of the type $ArCH(OR^1)CHR^2NH_2$ (2, 3) are a case in point, and the difficulties in assigning configurations to the potentially hypo-

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