Synthesis and Reactions of 2-Methyl-3-methylamino-2-azabicyclo[3.2.1]-oct-6-ene and its Valence Isomer

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2-Methyl-3-methylamino-2-azabicyclo[3.2.1]oct-6-ene (4) has been prepared and shown to coexist with *N*-methyl-4-(2-methyliminoethyl)cyclopent-2-enylamine (3). This material behaves as the *gem*-diamine (4) on catalytic reduction and as the imine (3) on reduction with metal hydrides. A useful method of synthesising *cis*-3,5-disubstituted cyclopentenes is reported.

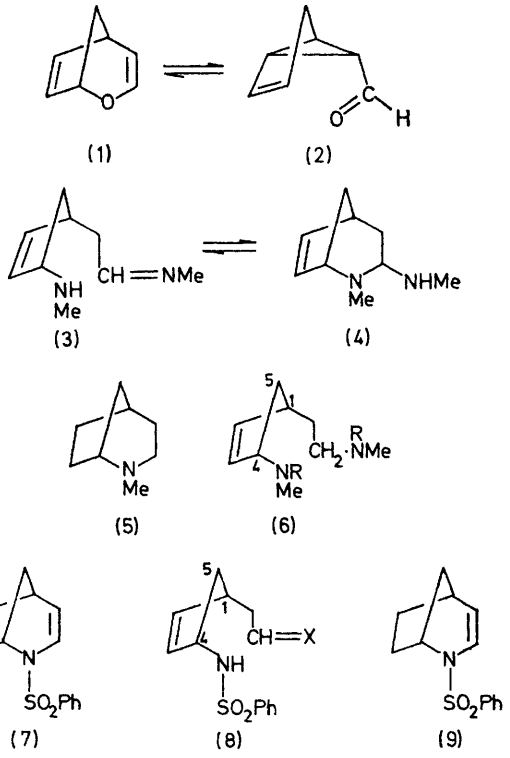
2-Oxabicyclo[3.2.1]octa-3,6-diene (1) exists in equilibrium with *endo*-6-formylbicyclo[3.1.0]hex-2-ene (2) through a degenerate Cope rearrangement.[1] When this equilibrium mixture was treated with an excess of methylamine an adduct was obtained which had an n.m.r. spectrum † interpretable in terms of an equilibrium mixture of the imine (3) and the *gem*-diamine (4).

On catalytic reduction the product reacted as though it were the *gem*-diamine (4), giving a good yield of 2-methyl-2-azabicyclo[3.2.1]octane (5), identical with an authentic specimen.[2] Reduction of the mixture with lithium aluminium hydride, on the other hand, yielded a product whose spectra were compatible with the structure (6; R = H) and which was readily transformed into the sulphonamide (6; R = $PhSO_2$), whose structure was confirmed by decoupling experiments.

Independent synthesis of the sulphonamide (6; R = $PhSO_2$) was facilitated by an accidental finding. During a study of the possibility of Cope rearrangement of the sulphonamide (7) to the corresponding bicyclo-[3.1.0]hexene derivative by variable temperature n.m.r. spectroscopy with [$^2H_6$]dimethyl sulphoxide as solvent, we noted a slow irreversible reaction at 110 °C which was facilitated by addition of water. The reaction was evidently a hydrolysis and could be performed cleanly on a preparative scale. Spectra suggested that the compound was the aldehyde (8; X = O), and reduction with lithium aluminium hydride gave the corresponding alcohol, the n.m.r. spectrum of which, with extensive decoupling, verified our structural assignment. The aldehyde (8; X = O) could be oxidised with silver oxide to the corresponding acid, and, on dehydration with toluene-*p*-sulphonic acid in benzene, reverted to the original sulphonamide (7). In view of the ready availability of the sulphonamide (7),[3] this very ready and high-yielding hydrolysis allows synthesis of a variety of *cis*-3,5-disubstituted cyclopentenes. The hydrolytic conditions are critical and when we attempted to apply them to the dihydro-derivative (9) [3] we were unable to achieve reaction. It therefore seems that the additional ring strain in the diene (7) must be a requirement for hydrolysis.

The aldehyde (8; X = O) was converted into a mixture of the *syn*- and *anti*-oximes (8; X = NOH), which was reduced to the corresponding amine. The amine was readily converted into the bis-sulphonamide (8; X = H,$NHSO_2Ph$), and methylation yielded compound (6; R = $PhSO_2$), identical with the sample obtained from the imine (3).

We have therefore shown that treatment of the equilibrium mixture (1) ⇌ (2) with an excess of methylamine yields the equilibrium mixture (3) ⇌ (4), and

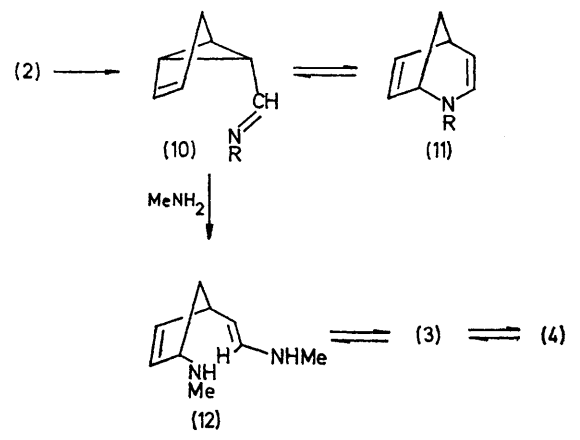


that this behaves as the *gem*-diamine (4) on catalytic reduction and as the imine (3) on reduction with lithium aluminium hydride. Since we have shown [4,5] that the reaction of the equilibrium mixture (1) ⇌ (2) with controlled amounts of primary amines yields 2-alkyl-2-azabicyclo[3.2.1]octa-3,6-dienes (11), presumably *via* the imines (10), it is reasonable to assume that reaction with an excess of methylamine occurs as outlined in the Scheme. 1,6-Addition of methylamine to (10; R = Me)

† All spectral data and n.m.r. decoupling experiments are reported in the Experimental section.

[1] M. Rey and A. S. Dreiding, *Helv. Chim. Acta*, 1965, **48**, 1985.
[2] A. G. Anastassiou, *J. Org. Chem.*, 1966, **31**, 1131.
[3] A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.*, 1965, **30**, 4205.
[4] P. Barraclough, D.Phil. Thesis, University of Sussex, 1972.
[5] P. Barraclough, S. Bilgic, and D. W. Young, unpublished observations.

would yield the enamine (12) and hence the imine (3) ⇌ *gem*-diamine (4) mixture.



SCHEME

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 237 instrument and u.v. spectra with a Unicam SP 800 spectrophotometer. N.m.r. spectra were taken (by Mr. P. Dew) with a Varian HA100 spectrometer and mass spectra (by Mr. A. Greenway) with Hitachi RMU-6 and A.E.I. MS9 instruments. G.l.c. was performed by Mr. C. Simpson and his staff using a Pye-Unicam 104/64 instrument. T.l.c. was performed with silica gel G (0.25 mm plates for analytical work and 0.5 mm plates for preparative work). We thank Mr. and Mrs. A. G. Olney for microanalyses.

Reaction of Bicyclo[3.1.0]*hex-2-ene*-endo-6-*carbaldehyde* (2) *with an Excess of Methylamine*.—A solution of methylamine (1.4 g) in dry benzene (50 ml) was added over 10 min to a stirred suspension containing anhydrous magnesium sulphate (2.0 g) and the aldehyde (2)[1] (2.0 g) in dry benzene (15 ml). The mixture was stirred for a further 2 h and filtered. The solvent was removed *in vacuo* at room temperature to yield a yellow oil (2.3 g), which slowly decomposed at room temperature but could be stored unchanged at −78 °C. The product was distilled at −10 °C and 0.005 mmHg to yield an oil, $\nu_{max.}$ (film) 3 280 (NH), 1 675, and 1 645 cm^{-1} (C=N), *m/e* 122 (M^+ − MeNH) and 121 (M^+ − $MeNH_2$), τ ($CDCl_3$) 2.40 (s, CH=N) and 6.78 (s, C=NMe) [for the imine (3)] and 6.30 (t, *J* 7 Hz, N–C*H*–N) [for the *gem*-diamine (4)], 4.25 (olefinic), and 7.60 and 7.72 (NMe). Integration indicated that the isomers were present in the ratio *ca.* 1 : 1.

Catalytic Reduction of the Product [(3) ⇌ (4)].—The product (600 mg) was dissolved in methanol (25 ml). 10% Palladium–charcoal (80 mg) was added and the mixture was shaken under hydrogen at room temperature and pressure until no further uptake was observed. The catalyst was filtered off and the solvent removed *in vacuo* to yield a yellow oil (500 mg) which on g.l.c. (5 ft column of APL–2% KOH at 90 °C) showed two components, t_R 5 (86%) and 6.1 min (13%). The retention time of the major component was identical with that of authentic 2-methyl-2-azabicyclo-[3.2.1]octane.[2] Since the contaminant exhibited NH i.r. absorption, the product was purified (400 mg) by addition of 2N-sodium hydroxide (3 ml) and benzenesulphonyl chloride (150 mg). The mixture was stirred at room temperature for 3 h, acidified with dilute hydrochloric acid, and extracted with ether. The aqueous layer was made alkaline with dilute aqueous potassium hydroxide and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield a liquid which was distilled at 78 °C and 40 mmHg. The product (280 mg) had spectra identical with those of authentic [2] 2-methyl-2-azabicyclo[3.2.1]octane.

Reduction of the Product [(3) ⇌ (4)] *with Lithium Aluminium Hydride*.—A solution of the crude mixture [(3) ⇌ (4)] (500 mg) in dry diethyl ether (15 ml) was added over 10 min to a stirred suspension of lithium aluminium hydride (250 mg) in dry diethyl ether (15 ml). The mixture was stirred at room temperature for 6 h and the excess of hydride was destroyed by careful addition of methanol followed by water. The inorganic salts were filtered off and the filtrate was concentrated *in vacuo*, diluted with water, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to yield a dark yellow oil with an amine-like smell (350 mg). This compound decomposed at room temperature but could be stored satisfactorily at −78 °C. The product (6; R = H) was adjudged pure by t.l.c. and n.m.r. spectroscopy; *m/e* 124 (M^+ − NHMe) and 123 (M^+ − $MeNH_2$), $\nu_{max.}$ (film) 3 243 cm^{-1} (NH), τ ($CDCl_3$) 4.2 (2 H, s, olefinic), 6.29 (1 H, t, *J* 7 Hz, H–4), 7.55 (6 H, s, NMe), 7.0—7.9 (4 H, m), and 8.2—9.0 (3 H, m).

N-*Methyl*-2-[4-(N-*methylphenylsulphonylamino*)*cyclopent*-2-*enyl*]-N-*phenylsulphonylethylamine* (6; R = SO_2Ph).—The amine (6; R = H) (200 mg) was suspended in 2N-sodium hydroxide (10 ml) and redistilled benzenesulphonyl chloride (650 mg) was added over 5 min. The mixture was stirred for 5 h and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield a semi-solid (420 mg) which was purified by preparative t.l.c. (chloroform as eluant) to yield a *solid*, m.p. 108—109° (Found: C, 57.75; H, 5.9; N, 6.7. $C_{21}H_{26}N_2O_4S_2$ requires C, 58.05; H, 6.05; N, 6.45%), *m/e* 434, τ ($CDCl_3$) 2.2—2.42 (10 H, m, aromatic), 4.17 (1 H, dt, *J* 6 and 2 Hz, H-3), 4.69 (1 H, dt, *J* 6 and 2 Hz, H-2), 4.86br (1 H, t, *J* 6 Hz, H-4), 7.0 (2 H, t, *J* 7 Hz, CH_2·N), 7.30 (3 H, s, NMe), 7.36 (3 H, s, NMe), 7.70 (1 H, m, H-1), and 7.6—9.15 (4 H, m, H-5 and 1-CH_2). Support for both structure and n.m.r. assignments was obtained by decoupling experiments. Irradiation at τ 8.48 (1-CH_2) caused the τ 7.0 triplet to collapse to a singlet, and irradiation at τ 7.0 simplified the τ 8.5 region considerably. Irradiation at τ 7.70 (H-1) simplified the H-2 resonance.

2-(4-*Phenylsulphonylaminocyclopent*-2-*enyl*)*acetaldehyde* (8; X = O).—The sulphonamide (7)[3] (18 g) was dissolved in dimethyl sulphoxide (433 ml) and water (217 ml) and heated at 110 °C under nitrogen for 12 h. The solution was concentrated *in vacuo*, and the residue dissolved in chloroform. This solution was washed with water, dried (Na_2SO_4), and evaporated and the residue was chromatographed on silica gel G (650 g). Elution with ether gave a fairly pure semi-solid (14 g, 73%), which could be further purified by preparative t.l.c. (chloroform as eluant); $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1} (aldehyde), *m/e* 247 (M^+ − H_2O), τ ($CDCl_3$) τ 0.36 (1 H, s, CHO), 2.15 and 2.49 (5 H, 2 m, aromatic), 4.29 (1 H, dt, *J* 5 and 2 Hz, olefinic), 4.58 (1 H, dt, *J* 5 and 2 Hz, olefinic), 4.77 (1 H, d, *J* 9 Hz, NH, exchangeable with D_2O), 5.64 (1 H, m, H-4), 7.02 (1 H, m, H-1), 7.47 (3 H, m), and 8.80 (1 H, sext) (H-5 and 1-CH_2).

2-(4-*Phenylsulphonylaminocyclopent*-2-*enyl*)*acetic Acid*.—

The aldehyde (8; X = O) and silver nitrate (1 g) were added to water (3 ml) and ethanol (2 ml), and aqueous 10% sodium hydroxide (5 ml) was added over 30 min. The mixture was stirred for 4 h and filtered. The filtrate was washed with diethyl ether, acidified with 5N-hydrochloric acid, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to yield the acid (270 mg), which could be purified by preparative t.l.c. ($CHCl_3$ as eluant); $\nu_{max.}$ ($CHCl_3$) 3 340 and 3 240 (NH, OH), and 1 712 cm^{-1} (C=O), *m/e* 281, τ ($CDCl_3$) 2.08 and 2.41 (5 H, 2 m, aromatic), 4.21 (1 H, d t, *J* 6 and 2 Hz, olefinic), 4.62 (1 H, d t, *J* 6 and 2 Hz, olefinic), 5.64 (1 H, m, H-4), 7.08 (1 H, m, H-1), 7.54 (3 H, m), and 8.74 (1 H, sextuplet) [absorptions at τ 3.63 and 4.50 (NH and OH) were exchanged in D_2O].

2-(4-*Phenylsulphonylaminocyclopent-2-enyl*)*ethanol* (8; X = H,OH).—A solution of the aldehyde (8; X = O) (500 mg) in dry diethyl ether (10 ml) was added over 10 min at room temperature to a stirred suspension of lithium aluminium hydride (300 mg) in dry diethyl ether (10 ml). Stirring was continued for 3 h and the excess of hydride was destroyed by careful addition of methanol and then water. Inorganic salts were filtered off and the filtrate was concentrated *in vacuo*, diluted with water, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to yield a semi-solid (250 mg), which was purified by preparative t.l.c. (methanol as eluant); $\nu_{max.}$ ($CHCl_3$) 3 443 and 3 244 cm^{-1} (NH,OH), *m/e* 267 (M^+), τ ($CDCl_3$) 2.14 and 2.48 (5 H, 2 m, aromatic), 4.23 (1 H dt, *J* 5 and 2 Hz, olefinic), 4.60 (1 H, dt, *J* 5 and 2 Hz, olefinic), 4.71 (1 H, d, *J* 7 Hz, NH, exchangeable in D_2O), 5.70 (1 H, m, H-4), 6.40 (2 H, t, *J* 6 Hz, CH_2·OH), 7.40 (1 H, m, H-1), 7.68 (1 H, dt), 8.40 (2 H, m), and 8.74 (1 H, dt). Support for structure and peak assignment was obtained by decoupling experiments. Irradiation of the H-4 signal simplified both olefinic proton signals to broad doublets and simplified the τ 8.74 (dt) absorption, implying that this latter peak was due to one of the 5-protons. This was confirmed by irradiation at τ 8.74, which simplified the H-4 signal to a triplet. Irradiation at τ 8.40 caused the triplet at τ 6.40 to collapse to a singlet and so the absorbance at τ 8.40 must correspond to the diastereotopic 1-CH_2 protons.

Conversion of the Aldehyde (8; X = O) *into the Sulphonamide* (7).—The aldehyde (8; X = O) (100 mg) was dissolved with toluene-*p*-sulphonic acid (10 mg) in benzene (35 ml) and refluxed for 2 days under a Soxhlet thimble containing calcium hydride. The mixture was cooled and filtered and washed with 2N-sodium hydroxide. The benzene layer was dried (Na_2SO_4) and evaporated to yield a solid (85 mg), which was purified by preparative t.l.c. (chloroform as eluant) to yield the sulphonamide (7), identical with an authentic sample.[3]

2-(4-*Phenylsulphonylaminocyclopent-2-enyl*)*acetaldehyde Oxime* (8; X = NOH).—Potassium carbonate (3 g) was added to a solution of the aldehyde (8; X = O) (5 g) in 1 : 1 water–methanol (70 ml). Hydroxylamine hydrochloride (4 g) was added in small portions over 15 min and the solution was stirred at room temperature for 5 h and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to yield a semi-solid which was chromatographed on silica gel (200 g) (elution with chloroform). The resulting *semi-solid* (3.7 g) exhibited two spots, for *syn*- and *anti*-oximes, on t.l.c. (Found: *m/e* 280.088 21, $C_{13}H_{16}N_2O_3S$ requires *M*, 280.088 17), τ ($CDCl_3$) 2.15 and 2.48 (6 H, 2 m, aromatic, and CH=N), 4.28 (1 H, m, olefinic), 4.56 (1 H, m, olefinic), 5.66 (1 H, m, H-4), and 7.36—9.0 (5 H, other protons).

2-(4-*Phenylsulphonylaminocyclopent-2-enyl*)*ethylamine* (8; X = H,NH_2).—The oxime (8; X = NOH) (3 g) was dissolved in dry diethyl ether (30 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (700 mg) in dry diethyl ether (40 ml) over 30 min. The mixture was stirred at room temperature for 14 h and the excess of hydride was destroyed by careful addition of methanol followed by water. The inorganic salts were filtered off and the filtrate was concentrated *in vacuo*, diluted with water, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to yield a dark yellow liquid (1.8 g), *m/e* 266, $\nu_{max.}$ ($CHCl_3$) 3 350 and 3 250 cm^{-1} (NH), τ ($CDCl_3$) 2.10 and 2.45 (5 H, 2 m, aromatic), 4.30 (1 H, m, olefinic), 4.61 (1 H, m, olefinic), 5.71 (1 H, m, H-4), and 7.2—9.0 (7 H, m).

N-*Phenylsulphonyl*-2-(4-*phenylsulphonylaminocyclopent-2-enyl*)*ethylamine* (8; X = H,$PhSO_2NH$).—Benzenesulphonyl chloride (1.4 g) was added over 10 min to a stirred suspension of the foregoing crude amine (1.5 g) in 2N-sodium hydroxide (25 ml). The mixture was stirred for 6 h at room temperature and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and evaporated to yield a yellow semi-solid which was chromatographed on silica gel (100 g). Elution with diethyl ether–chloroform (1 : 1) yielded a *solid* (1.85 g) which was further purified by preparative t.l.c. [elution with MeOH–$CHCl_3$ (2 : 98)]; m.p. 48 °C (Found: C, 55.8; H, 5.65; N, 7.1. $C_{19}H_{22}N_2O_4S_2$ requires C, 56.15; H, 5.45; N, 6.9%), *m/e* 406 $(M)^+$, $\nu_{max.}$ ($CHCl_3$) 3 340 and 3 250 cm^{-1} (NH), τ ($CDCl_3$; D_2O added) 2.13 and 2.50 (10 H, 2 m, aromatic), 4.38 (1 H, m, olefinic), 4.67 (1 H, m, olefinic), 5.76 (1 H, m, H-4), 7.16br (2 H, t, CH_2·N), 7.4—8.0 (2 H, m, H-1 and one H-5), 8.53 (2 H, septet, 1-CH_2), and 8.95 (1 H, sext, H-5).

The Bis-sulphonamide (6; R = SO_2Ph).—Methyl iodide (10 ml) was added to a solution of the sulphonamide (8; X = H,$PhSO_2NH$) (1.5 g) in 1 : 1 water–methanol (25 ml) containing sodium hydroxide (1.0 g). The mixture was stirred at room temperature for 24 h, diluted with water, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to yield a semi-solid (980 mg), a sample of which was purified by preparative t.l.c. (chloroform as eluant). This product, m.p. 108—109°, was identical with the sample obtained from the imine (3).

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