

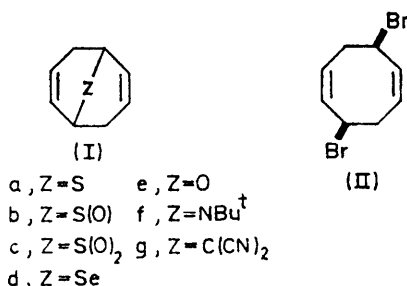
## Flexible Two-step Synthesis of the Bicyclo[3.3.1]nona-2,6-diene Skeleton and its 9-Hetera-analogues from (*Z,Z*)-Cyclo-octa-1,5-diene

By Eric Cuthbertson and David D. MacNicol,\* Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

A new method for the preparation of the 9-heterabicyclo[3.3.1]nona-2,6-dienes (Ia and d–f), and of 9,9-dicyano-bicyclo[3.3.1]nona-2,6-diene (Ig) from (*Z,Z*)-*cis*-3,7-dibromocyclo-octa-1,5-diene (II) is described.

In view of the current interest<sup>1–3</sup> in compounds possessing the general structure (I), where Z denotes either a single carbon bridge or a hetero-atom, we sought a general route to compounds of this type.

The crystalline dibromide (II), which can be easily prepared (see Experimental section) from (*Z,Z*)-cyclo-octa-1,5-diene, appeared to be an especially appropriate precursor owing to the *cis*-arrangement of its allylic bromine atoms.<sup>4</sup> Accordingly, we found that treat-



ment of (II) with anhydrous sodium sulphide in dimethylformamide (DMF) gave, in 22% yield, a crystalline<sup>†</sup> compound, C<sub>8</sub>H<sub>10</sub>S, m.p. 41–41.5 °C. The structure (Ia), consistent with simple nucleophilic displacement by sulphide ion, was assigned on the basis of its reduction with di-imide to the known 9-thiabicyclo[3.3.1]non-2-ene, formation of a single sulphoxide (Ib), m.p. 120–122 °C [ $\nu_{\max}$  (KBr) 1049 vs cm<sup>-1</sup> (S=O)], and the analysis of its <sup>1</sup>H n.m.r. spectrum.<sup>‡</sup> Unlike<sup>6</sup> its isomer 9-thiabicyclo[4.2.1]nona-2,4-diene, (Ia) possesses high thermal stability showing no decomposition (n.m.r. monitoring) after being heated in [<sup>2</sup>H<sub>8</sub>]toluene in a sealed tube at 200 °C for 16 h. The corresponding selenide (Id) (m.p. 54–55 °C) was similarly prepared in 13% yield by the action of Na<sub>2</sub>Se on (II) and has a <sup>1</sup>H n.m.r. spectrum very closely resembling that of (Ia).

The discovery that oxygen-bridging could be brought about was made while studying the hydrolysis of (II). The dibromide (II) proved to be very resistant to the hydrolysis conditions normally employed for allylic bromides: refluxing (II) with NaHCO<sub>3</sub> for 3 days in aqueous tetrahydrofuran (THF) brought about no significant hydrolysis.<sup>7</sup> However, refluxing overnight

<sup>†</sup> This compound was not previously obtained in crystalline form.<sup>5</sup>

<sup>‡</sup> The conformational implications of this detailed computer analysis will be described elsewhere.

§ Bridgehead equivalence is also observed for (Ia and c–f).

<sup>1</sup> N. S. Zefirov and S. V. Rogozine, *Russ. Chem. Rev.*, 1973, **42**, 190.

<sup>2</sup> G. L. Buchanan, *Topics Carbocyclic Chem.*, 1969, **1**, 199.

<sup>3</sup> C. Ganter *Chimia*, 1973, **27**, 18.

with an excess of NaHCO<sub>3</sub> in aqueous acetonitrile caused disappearance of (II) with the formation of (Ie) (14% isolated yield) as shown by comparison of <sup>1</sup>H n.m.r. and mass spectra with those from an authentic sample<sup>8</sup> of (Ie). The formation of this compound is readily rationalised on the basis of an S<sub>N</sub>2 displacement of one bromine by hydroxide ion, followed by base-catalysed transannular cyclisation of the intermediate *trans*-bromo-alcohol.

Direct introduction of a nitrogen bridge results from treatment of (II) with *t*-butylamine, refluxing overnight in acetonitrile in the presence of CaCO<sub>3</sub> giving, after basic work-up, a compound C<sub>12</sub>H<sub>19</sub>N (45%) assigned structure (If) by consideration of its <sup>1</sup>H n.m.r., i.r., and mass spectra. The proton spectrum of (If) at room temperature is consistent with rapid (on the n.m.r. time scale) nitrogen inversion and rapid rotation around the N–Bu<sup>t</sup> bond. Not unexpectedly, the effective C<sub>2</sub> symmetry axis of the free amine is lost on protonation; the proton spectrum of the hydrochloride in CDCl<sub>3</sub> is more complex, corresponding to slow inversion about protonated nitrogen.

Reaction of (II) in dimethyl sulphoxide (DMSO) with malononitrile in the presence of sodium hydride<sup>9</sup> gave a 58% yield of a crystalline compound, m.p. 118–119 °C, C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>, whose structure (Ig) followed from its high resolution mass spectrum, its i.r. absorption  $\nu_{\max}$  (KBr) 2240 cm<sup>-1</sup> (C≡N), and its <sup>1</sup>H n.m.r. spectrum which, despite large solvent shifts between CDCl<sub>3</sub> and C<sub>6</sub>D<sub>6</sub>, maintains the equivalence of the two bridgehead protons.<sup>§</sup>

Preliminary attempts to effect direct introduction of a two-atom bridge across (II) have not been promising. For example, reaction of (II) with Na<sub>2</sub>S<sub>2</sub> did not lead to the isolation of the expected bicyclo[3.3.2]heterocycle, though, interestingly, an appreciable amount of the monobridged sulphide (Ia), detected by n.m.r., was formed.

### EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were measured on Perkin-Elmer 225 or 257 instruments. <sup>1</sup>H n.m.r. spectra were recorded on a Varian

<sup>4</sup> R. K. Mackenzie, D. D. MacNicol, H. H. Mills, R. A. Raphael, F. B. Wilson, and J. A. Zabkiewicz, *J.C.S. Perkin II*, 1972, 1632.

<sup>5</sup> F. Lautenschlaeger, *J. Org. Chem.*, 1968, **33**, 2627.

<sup>6</sup> P. H. McCabe and C. M. Livingston, *Tetrahedron Letters*, 1973, 3029.

<sup>7</sup> A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, 1961, **83**, 198.

<sup>8</sup> H. Stetter and K. Heckel, *Chem. Ber.*, 1973, **106**, 339.

<sup>9</sup> J. J. Bloomfield, *J. Org. Chem.*, 1961, **26**, 4112.

HA-100 instrument with tetramethylsilane as internal lock signal. Mass spectra were obtained on an A.E.I.-G.E.C. MS12 spectrometer and high-resolution mass measurements made on an A.E.I.-G.E.C. MS902 spectrometer. In most cases, no attempt has been made to optimise the yields.

(*Z,Z*)-cis-3,7-Dibromocyclo-octa-1,5-diene (II).—(Improved method of preparation.) To a stirred suspension of dry *N*-bromosuccinimide (712 g, 4.0 mol) and  $\alpha$ -azoisobutyronitrile (7.5 g) in dry carbon tetrachloride (2.5 l) was added (*Z,Z*)-cyclo-octa-1,5-diene (216 g, 2.0 mol) and the mixture heated to boiling with efficient stirring. When the initially vigorous reaction had moderated, the mixture was refluxed gently with stirring for a further 1.5 h. After cooling in ice, the precipitated succinimide was filtered off and washed with carbon tetrachloride (2  $\times$  40 ml). The filtrate was concentrated under reduced pressure, and the residual yellow oil dissolved in 95% ethanol (1.4 l). Some crystals separated immediately, and the bulk of the required dibromide crystallised out on cooling overnight at  $-30^\circ$ . The crystals were filtered off cold, and washed with methanol and then methanol-ether (2:1). Concentration of the mother liquors and cooling for several weeks at  $-30^\circ$  gave more (II) (total yield 39.5 g). The material obtained in this way is sufficiently pure for further use, but may be re-crystallised from ethanol, giving long needles, m.p. 122–123°.

9-Thiabicyclo[3.3.1]nona-2,6-diene (Ia).—A solution of (II) (1.33 g, 5.0 mmol) in dry DMF (15 ml) was added to a stirred suspension of anhydrous sodium sulphide (4.55 g, 5.84 mmol) in dry DMF (25 ml). The mixture became intensely yellow, and, after stirring for 3 h at room temperature, was poured into saturated brine (50 ml), extracted with *n*-pentane (3  $\times$  20 ml), and the combined extracts were washed in turn with water (10 ml) and brine (25 ml). The pentane solution was dried ( $\text{Na}_2\text{SO}_4$ ) and the pentane removed at room temperature under reduced pressure. The residual pale yellow oil (0.53 g) was chromatographed on silicic acid [Mallinckrodt; 25%  $\text{CH}_2\text{Cl}_2$ -petroleum (b.p. 40–50°) as eluant], giving the crystalline, highly volatile (Ia) (150 mg, 22%), which was further purified by low-temperature sublimation. The pure compound crystallised in prisms, m.p. 41–41.5° (Found: C, 69.55; H, 7.35.  $\text{C}_8\text{H}_{10}\text{S}$  requires C, 69.5; H, 7.3%), *m/e* 138;  $\nu_{\text{max}}$  (KBr) 3017m ( $\text{:C-H}$  str.) and 1644mw (C=C str.)  $\text{cm}^{-1}$ ,  $\tau$  ( $\text{CDCl}_3$ ) 3.7–4.5 (4H, m), 6.4–6.7 (2H, m), and 7.2–8.1 (4H, m).

Di-imide Reduction of (Ia).—The method was based on that of Hamersma and Snyder,<sup>10</sup> using potassium azodicarboxylate as di-imide generator. With anhydrous pyridine as solvent, the potassium azodicarboxylate was not noticeably decomposed by an excess of acetic acid, and (Ia) was recovered unchanged after 3 days. Dioxan was then used as solvent. Glacial acetic acid (0.16 ml) was added with stirring to a mixture of (Ia) (113.5 mg, 0.823 mmol) and potassium azodicarboxylate (640 mg, 3.3 mmol) in pure, dry dioxan (6 ml). An immediate brisk effervescence ensued, and the yellow colour had been discharged within 30 min. The mixture was stirred for a further 30 min, and left overnight at room temperature. It was then poured into water (15 ml) and extracted with methylene chloride (3  $\times$  5 ml), and the combined extracts were washed with water (10 ml) and brine (2  $\times$  10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated, giving a waxy solid (113 mg) which was sublimed at 80° at 760 mmHg, m.p. 126–131°; the i.r.

spectrum<sup>11</sup> indicated that the material was a mixture of 9-thiabicyclo[3.3.1]non-2-ene and a minor amount of 9-thiabicyclo[3.3.1]nonane. Use of a 15-fold excess of potassium azodicarboxylate increased the relative proportion of the saturated compound.

Effect of Heat on (Ia).—A solution of (Ia) in [ $^2\text{H}_8$ ]toluene was heated at 200° in a sealed n.m.r. tube, and the  $^1\text{H}$  spectrum monitored periodically. After 16 h, the spectrum showed no significant alteration,  $\tau$  3.9–4.7 (4H, m), 6.75–7.05 (2H, m), and 7.3–8.5 (4H, m).

9-Thiabicyclo[3.3.1]nona-2,6-diene 9-Oxide (Ib).—To a stirred solution of (Ia) (84.3 mg, 0.610 mmol) in methylene chloride (2 ml) at  $-10^\circ$  was added dropwise a solution of 85% *m*-chloroperbenzoic acid (113 mg, 0.56 mmol) in methylene chloride (2 ml), and the mixture was allowed to warm to room temperature during 1 h. The solution was washed with saturated sodium carbonate solution (5 ml) and saturated brine (2  $\times$  5 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent and excess of (Ia) were evaporated off under reduced pressure. The crystalline sulphoxide (Ib) (88 mg) obtained was sublimed at 95° at 0.1 mmHg, m.p. 120–122° (Found: C, 62.55; H, 6.5.  $\text{C}_8\text{H}_{10}\text{OS}$  requires C, 62.35; H, 6.55%), *m/e* 154,  $\nu_{\text{max}}$  (KBr) 3021mw ( $\text{:C-H}$  str.), 1644w (C=C str.), and 1049vs ( $\text{S=O}$  str.)  $\text{cm}^{-1}$ ,  $\tau$  ( $\text{CDCl}_3$ ) 3.8–4.5 (4H, m), 6.15–6.55 (2H, m), and 6.95–8.1 (4H, m).

9-Thiabicyclo[3.3.1]nona-2,6-diene 9,9-Dioxide (Ic).—To a stirred solution of (Ia) (82.9 mg, 0.60 mmol) in methylene chloride (2 ml) was added 85% *m*-chloroperbenzoic acid (245 mg, 1.21 mmol) in methylene chloride (5 ml) and the mixture left 1 h at room temperature. Work-up as for (Ib) gave the sulphone (102 mg), containing a small amount of sulphoxide. Sublimation at 110° (0.1 mmHg) gave crystals, m.p. 165–167° (Found: C, 56.75; H, 5.9.  $\text{C}_8\text{H}_{10}\text{O}_2\text{S}$  requires C, 56.45; H, 5.9%), *m/e* 170,  $\nu_{\text{max}}$  (KBr) 3059w and 3029w ( $\text{:C-H}$  str.), 1641w (C=C str.), 1300vs ( $\text{SO}_2$  asym. str.), and 1119vs ( $\text{SO}_2$  sym. str.)  $\text{cm}^{-1}$ ,  $\tau$  ( $\text{CDCl}_3$ ) 4.0–4.5 (4H, m), 6.35–6.65 (2H, m), and 6.75–7.65 (4H, m).

9-Selenabicyclo[3.3.1]nona-2,6-diene (Id).—Anhydrous sodium selenide (2.04 g, 16.3 mmol) was added in portions in an atmosphere of nitrogen to a stirred solution of (II) (2.77 g, 10.4 mmol) in dry, nitrogen-purged DMF (60 ml). The mixture became warm and darkened, and after stirring for 3 h at room temperature, was worked up as for (Ia), giving an orange oil (0.322 g). This was passed through a short column of silicic acid [Mallinckrodt; 25%  $\text{CH}_2\text{Cl}_2$ -petroleum (b.p. 40–50°) as eluant] to give a yellow oil (0.252 g, 1.36 mmol, 13%) which crystallised on slight cooling. Sublimation at 45° and 0.1 mmHg gave the colourless, highly volatile product (Id), m.p. 54–55° (Found:  $M^+$ , 185.9944.  $\text{C}_8\text{H}_{10}^{80}\text{Se}$  requires  $M$ , 185.9947),  $\nu_{\text{max}}$  ( $\text{CCl}_4$ ) 3016ms ( $\text{:C-H}$  str.) and 1644m (C=C str.)  $\text{cm}^{-1}$ ,  $\tau$  ( $\text{CDCl}_3$ ) 3.7–4.4 (4H, m), 6.2–6.5 (2H, m), and 7.1–8.0 (4H, m).

Hydrolysis of (II).—(a) A solution of (II) (50 mg) in acetone (5 ml) containing water (0.1 ml) was left at room temperature. After 4 days, (II) was recovered unchanged.

(b) To a solution of (II) (0.532 g, 2 mmol) in THF (5 ml) was added a solution of sodium hydrogen carbonate (0.50 g) in water (1 ml) and the mixture was (i) stirred at room temperature for 1 day, or (ii) stirred and refluxed for 3 days. In both cases, only unchanged (II) could be detected by n.m.r.

<sup>10</sup> J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, 1965, **30**, 3985.

<sup>11</sup> E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, 1966, **31**, 1669.

(c) A mixture of (II) (2.00 g, 7.52 mmol) and sodium hydrogen carbonate (5.0 g) in acetonitrile (60 ml) and water (ca. 3 ml) was stirred and refluxed under nitrogen for 16 h. The brown mixture was poured into water (100 ml) and extracted with pentane (4 × 40 ml), and the combined extracts were washed with brine (3 × 25 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and the pentane was carefully evaporated at room temperature under reduced pressure. The orange residue (ca. 400 mg), which was by <sup>1</sup>H n.m.r. mainly 9-oxabicyclo[3.3.1]nona-2,6-diene (Ie) was given two short-path distillations at 10 mmHg and (Ie) (ca. 130 mg, 14%) was obtained, *m/e* 122, 93, 81, 79, 78, 77, 68, and 66,  $\tau$  (CDCl<sub>3</sub>) 4.0–4.4 (4H, m), 5.35–5.65 (2H, m), and 7.2–8.35 (4H, m), identical with authentic (Ie), independently synthesised.<sup>8</sup>

9-*t*-Butyl-9-azabicyclo[3.3.1]nona-2,6-diene (If).—A mixture of (II) (0.744 g, 2.80 mmol), *t*-butylamine (0.4 ml), and powdered calcium carbonate (1 g) in dry acetonitrile (25 ml) was stirred and refluxed for 16 h in a static nitrogen atmosphere. The dark solution was filtered, and the filtrate evaporated under reduced pressure. The residue was dissolved in methanol (10 ml), basified with 5M-aqueous sodium hydroxide solution, and the resulting solution extracted with 1:1 ether-petroleum (b.p. 40–60°) (3 × 7 ml). The combined extracts were washed with brine (3 × 10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure to give crude amine (0.486 g). Chromatography on alumina (Woelm basic, grade II), eluting with 10% chloroform-petroleum (b.p. 40–60°) gave (If) (223 mg, 1.26 mmol, 45% overall yield) as an almost colourless liquid, *m/e* 177,  $\nu_{\max}$  (CCl<sub>4</sub>) 3020m (:C–H str.) and 1650w (C=C str.) cm<sup>-1</sup>,  $\tau$  (CDCl<sub>3</sub>) 4.0–4.4 (4H, m), 6.15–6.45 (2H, m), 7.50–8.40 (4H, m), and 8.86 (9H, s).

A solution of (If) (100 mg) in anhydrous ether (5 ml) was treated with dry hydrogen chloride, precipitating quantitatively the *hydrochloride* as a white solid. This was filtered off and washed with anhydrous ether. Recrystallisation (× 3) from di-isopropyl ether-ethanol (4:1) gave an analytical sample (Found: C, 67.35; H, 9.75; N, 7.1. C<sub>12</sub>H<sub>20</sub>ClN requires C, 67.45; H, 9.45; N, 6.6%),  $\nu_{\max}$  (KBr) 3040w and 3020mw (:C–H str.), 2735m,br and 2530s,br (N–H str), and 1655w (C=C str) cm<sup>-1</sup>,  $\tau$  (CDCl<sub>3</sub>) 3.9–4.4

<sup>12</sup> E. Rosén and R. Tegman, *Acta Chem. Scand.*, 1971, **25**, 3329.

(4H, m), 5.5–6.0br (2H, d), 6.50–8.10 (4H, m), and 8.38 (9H, s).

9,9-Dicyanobicyclo[3.3.1]nona-2,6-diene (Ig).—The method is based on that of Bloomfield.<sup>9</sup> To a stirred suspension of powdered sodium hydride (1.00 g, 25 mmol; 60% benzene dispersion) in dry DMSO (30 ml) was added malononitrile (0.715 g, 11 mmol) in dry DMSO (15 ml). After evolution of hydrogen had ceased, a solution of (II) (2.66 g, 10 mmol) in benzene (20 ml) and DMSO (20 ml) was added with stirring during 10 min, and stirring was continued for 3 h. The mixture was then poured into saturated brine (250 ml) and extracted with ether (4 × 50 ml), and the combined extracts were washed with water (25 ml) and brine (3 × 50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the ether under reduced pressure gave a light brown oil (1.33 g) which crystallised on cooling. Sublimation (70° at 0.01 mmHg) followed by recrystallisation from aqueous ethanol gave *needles* of (Ig) (0.99 g, 58%) (Found: *M*<sup>+</sup>, 170.0839. C<sub>11</sub>H<sub>10</sub>N<sub>2</sub> requires *M*, 170.0849),  $\nu_{\max}$  (KBr) 3045m (:C–H str.), 2245mw and 2240mw (C≡N str.), and 1649mw (C=C str.) cm<sup>-1</sup>,  $\tau$  (CDCl<sub>3</sub>) 3.95–4.40 (4H, m), 6.75–7.00 (2H, m), and 7.10–8.00 (4H, m),  $\tau$  (C<sub>6</sub>D<sub>6</sub>) 4.50–5.05 (4H, m), 7.60–7.85 (2H, m), and 7.60–8.80 (4H, m).

*Reaction of (II) with Na<sub>2</sub>S<sub>2</sub>*.—Sodium disulphide (0.357 g, 3.24 mmol), prepared by heating anhydrous sodium sulphide with sulphur,<sup>12</sup> was dissolved in water (2 ml). To this was added with stirring a solution of (II) (0.532 g, 2.00 mmol) in acetonitrile (15 ml) and the mixture stirred for 16 h at room temperature. Addition of water (50 ml) and extraction with methylene chloride gave a viscous, pale yellow material (0.235 g) which, after chromatography on silicic acid (Mallinckrodt), eluting with 30% methylene chloride-petroleum (b.p. 40–50°), gave a small amount of a poorly crystalline solid (ca. 25 mg, 9%) whose <sup>1</sup>H n.m.r. spectrum corresponds to that of (Ia). The other amorphous products appeared to be polymeric.

We thank Mrs. F. Lawrie for i.r. spectra, Miss F. Cowan for microanalytical services, Mr. J. Gall for <sup>1</sup>H n.m.r. spectra, and Mr. A. Ritchie for mass spectral determinations. We also thank Professor R. A. Raphael for helpful discussions.

[4/523 Received, 18th March, 1974]