Addition of *C*-phenyl-*N*-methyl nitrone to norbornene and norbornadiene

ROBERT R. FRASER AND Y. S. LIN
Department of Chemistry, University of Ottawa, Ottawa, Canada

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The reaction of *C*-phenyl-*N*-methyl nitrone with norbornene gave two 1:1 cycloadducts in a ratio of 9:1. Both adducts have been shown to possess an *exo-cis* isoxazolidine ring by nuclear magnetic resonance and to be diastereomeric at the benzylic carbon of the isoxazolidine ring by chemical degradation of both adducts to 3-*exo*-benzyl-2-*exo*-hydroxybicyclo[2·2·1] heptane. The reaction of the same nitrone with norbornadiene gave a 1:1 and a 2:1 adduct. The stereochemistry of the 1:1 adduct was shown to be the same as that of the major norbornene adduct which it gave on hydrogenation of the double bond. The structure of the 2:1 adduct was not investigated.

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The addition of a nitrone to a double bond to form an isoxazolidine ring is a reaction which belongs to the general category of 1,3-dipolar cycloadditions. Both the scope and the mechanistic aspects of these cycloadditions have been reviewed by Huisgen (1, 2). One of the many reactions studied by Huisgen and co-workers was the addition of *C*,*N*-diphenyl nitrone to norbornene which they reported gave two 1:1 adducts, "presumably epimeric at the atom bearing the phenyl substituent" (1). Details regarding the proof of structure of these adducts have not yet been published. Grashey, Huisgen, and Leitermann (3) have reported that *C*-phenyl-*N*-methyl nitrone adds to norbornene to give a 100% yield of product and adds to norbornadiene to give a 98% yield of product although no further data was given in this preliminary communication. We have independently studied the reaction of *C*-phenyl-*N*-methyl nitrone with norbornadiene and norbornene and wish to report the proof of structure and stereochemistry of the 1:1 cycloadducts obtained.

The reaction of *C*-phenyl-*N*-methyl nitrone with norbornene was carried out for 12 h in toluene at 110°. After removal of the solvent, a compound (**1**) was obtained in 79% yield by crystallization of the reaction mixture. A second compound (**2**) was isolated in 9% yield by chromatography of the mother liquors. When a solution of *C*-phenyl-*N*-methyl nitrone in norbornadiene was heated under reflux for 4 h, two products were produced. Compound **3** was isolated in 82% yield and compound (**4**) in 3% yield. Compound **3** absorbed one mole of hydrogen in the presence of platinum to give compound **1**. Elemental analysis of **1**, **2**, and **3** showed that they were all 1:1 adducts. Compound **4** had an elemental composition consistent with its being a 2:1 adduct. Its structure was not further investigated. The above findings are summarized in Scheme I.

We then subjected compounds **1** and **2** to a chemical degradation in order to establish their stereochemical interrelation. Compounds **1** and **2** were each methylated with methyl iodide, then reduced by zinc in acetic acid to produce two isomeric amino alcohols, **5** and **7** respectively. Repetition of methylation and reduction converted both **5** and **7** into the same compound, **6**. These reactions, which are shown in Scheme II, prove that **1** and **2** are indeed epimeric at the benzylic carbon of the isoxazolidine ring.

Both the gross structural features and the stereochemistry of the ring fusion in **3** and thus, in all the compounds related to it by the reactions in Schemes I and II, can be determined by an examination of the nuclear magnetic resonance (n.m.r.) spectrum of **3**. The spectrum of **3** is shown in Fig. 1 (*a*). The multiplet centered at τ 3.9 can only result from olefinic protons. Their presence immediately rules out the possibility of nortricyclene structure for **3**. The doublet at τ 5.63 (spacing 6.1 c.p.s.) is assigned to the proton on the carbon bearing the oxygen atom. The splitting of 6.1 c.p.s. is attributed to a vicinal interaction[1] with the adjacent *endo* hydrogen. Davis and Van Auken (4) reported a

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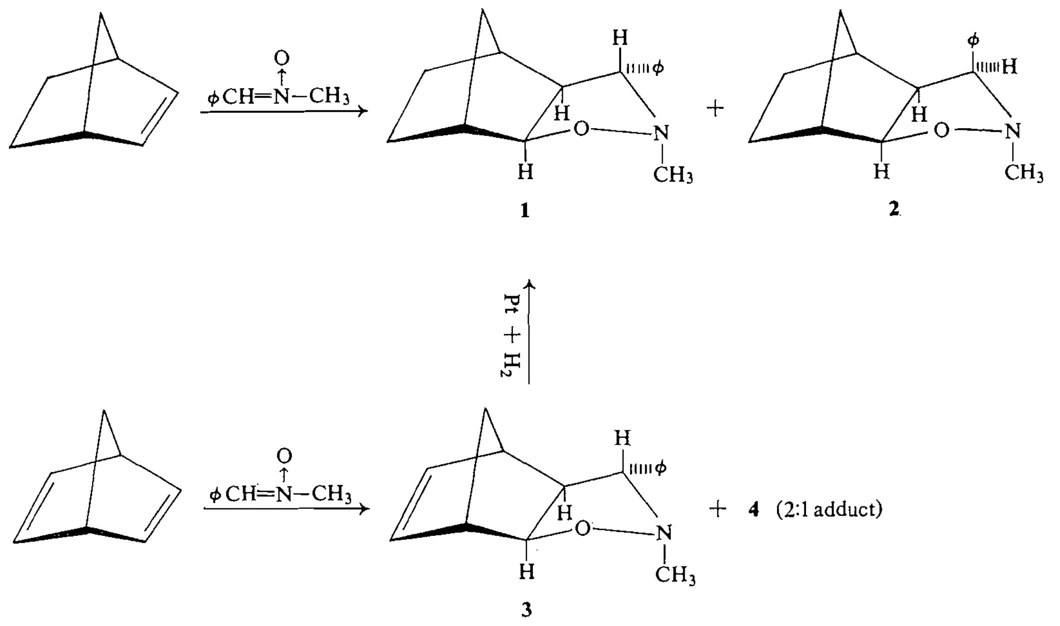
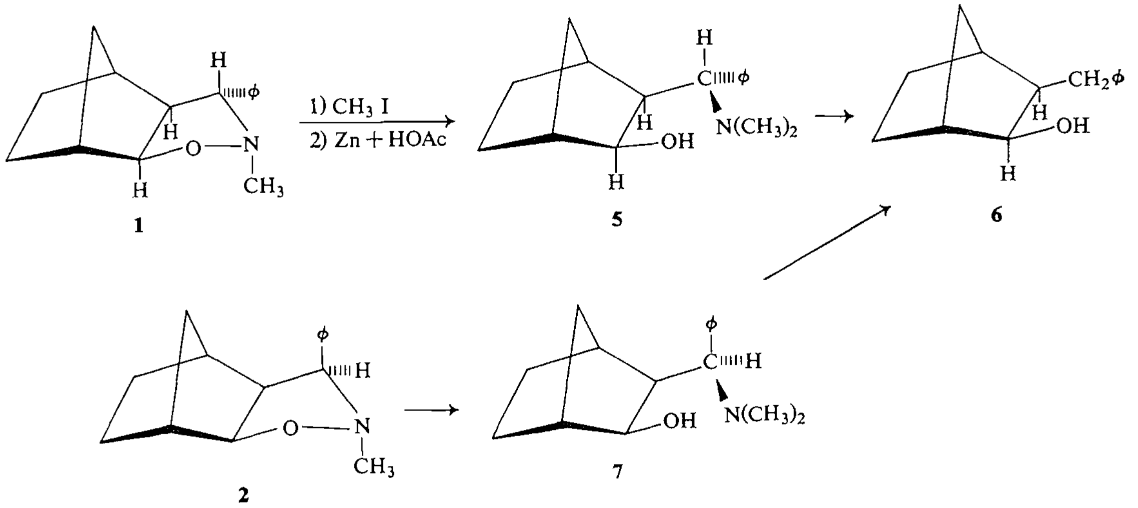
[1] We are purposefully avoiding the use of the word coupling constant in this instance as the spectra are not completely first order in character. Anet, Lee, and Sudmeier (5) have recently shown that some of the spacings reported by Davis and Van Auken as coupling constants for the compound 2-carbomethoxynorbornene are in error by more than 5 c.p.s. So the spacing of 6.1 c.p.s. in **3** does not necessarily represent the true coupling constant.



SCHEME I.



SCHEME II.

splitting of 5.6 c.p.s. for the *endo–endo* interaction in *exo*-2-hydroxynorbornene, 8.1 c.p.s. for the *exo–exo* splitting in the *endo* isomer and 3.0 c.p.s. for the *exo–endo* splitting. Thus the splitting of 6.1 c.p.s. indicates an *endo–endo* relation or possibly an *exo–exo* relation of the protons. That the proton in question is *endo* is conclusively established by the lack of any observable splitting with the adjacent bridgehead hydrogen. It has been established previously that the vicinal coupling constant J between a bridgehead proton and an *endo* proton is < 1 c.p.s., while J between a bridgehead and an *exo* proton is 3–5 c.p.s. (3, 4, and references therein). The lack of further observable splitting of the absorption at τ 5.63 establishes the orientation of the proton as *endo*. Thus the adducts **3**, **1**, and **2** are all *exo* adducts.

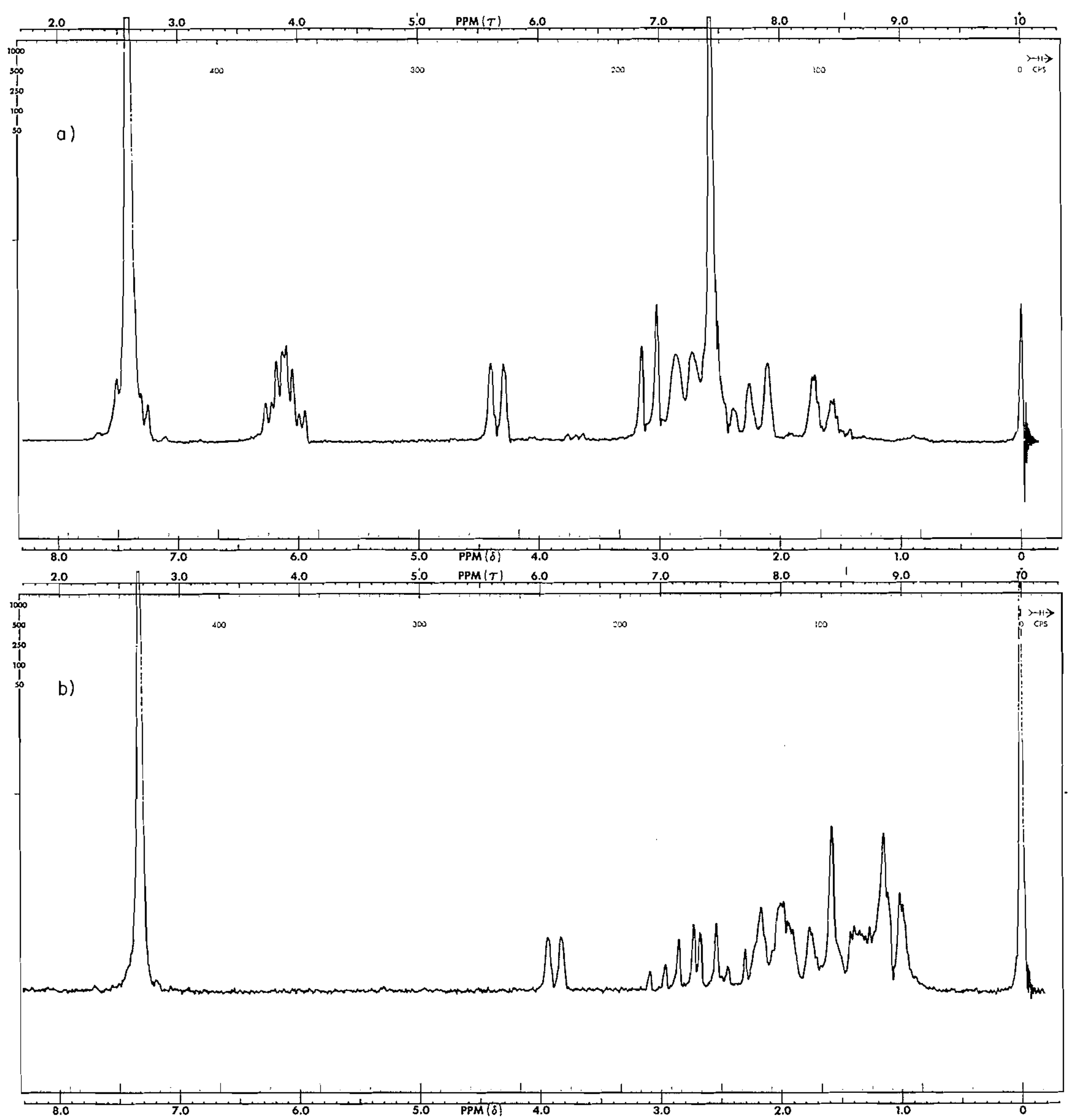


FIG. 1. (*a*) The 60 Mcycles spectrum of **3**, the 1:1 adduct of norbornadiene and *C*-phenyl-*N*-methyl nitrone in CCl_4. (*b*) The 60 Mcycles spectrum of **6**, 3-benzyl-2-hydroxybicyclo[2·2·1]heptane in CCl_4.

Similarly, the proton on carbon-2 of compounds **1**, **2**, **5**, **6**, and **7** always appeared as a doublet of spacing 6.1–6.5 c.p.s. which confirms the *exo* stereochemistry of these compounds. The spectrum of the final conversion product **6** serves to illustrate this behavior in Fig. 1*b*. Further support for the reliability of the above conclusions is provided by a recent paper of Huisgen and co-workers (6). They prepared the *endo* and *exo* adducts of diphenyl nitrile imine and norbornene. The n.m.r. spectra of these adducts provide model examples of the above correlation between *J* and the *exo–endo* relationship.

One final point of stereochemistry remains to be assigned, ie. the configuration at the benzylic carbon of adducts **1** and **2**. Unfortunately n.m.r. does not provide any definite evidence on this point; however, one fact does provide a clue.

Compound **1** is thermally stable whereas **2** is not. If **1** and **2** have the stereochemistry denoted in Schemes I and II this finding can be explained. An examination of molecular models of **1** and **2** reveals the presence of a serious non-bonded interaction between the phenyl substituent and the methylene bridge in **2** but not in **1**. This interaction would be expected to make **2** less stable than **1**. It is on this basis that the assignment of relative stereochemistry to the diastereoisomers **1** and **2** in Scheme I has been made.

In conclusion, we have established that *C*-phenyl-*N*-methyl nitrone adds to norbornene producing two *exo–cis* adducts. This nitrone also adds to norbornadiene to give an *exo–cis* adduct. Recently several papers have reported that the additions of diphenyl nitrile imine (6), thiobenzoyl isocyanate (7), and fulminic acid (8) all occur in the same *exo–cis* manner. In another paper, Huisgen and co-workers (9) discuss the mechanism of cycloaddition of diphenyl nitrile imine in considerable detail. Since our results provide no further evidence about this mechanism, they need not be discussed in this context.

Experimental

All melting points and boiling points are uncorrected. The nuclear magnetic resonance (n.m.r.) spectra were measured on a Varian V-4302 HA-60 spectrometer using tetramethylsilane as an internal standard. All infrared spectra were measured on a Beckman IR-8 spectrometer. Elemental analyses were performed by Alfred Bernhardt, Mülheim, W. Germany and H. Seguin, NRCC, Ottawa.

Reaction of C-Phenyl-N-methyl Nitrone with Norbornadiene

By following the procedure of Brady *et al.* (10), *C*-phenyl-*N*-methyl nitrone was prepared in 80% yield. A solution of *C*-phenyl-*N*-methyl nitrone (10.1 g, 0.075 mole) in norbornadiene (150 ml) was heated under reflux for 4 h. The excess of norbornadiene was removed by evaporation under reduced pressure. The residue was dissolved in ether (450 ml), and the ether solution was extracted with water (4 × 100 ml) to remove the unreacted nitrone. Concentration of the ether solution to dryness gave crude product (14 g, 82%). A solution of a portion of the crude product (4.5 g) in hexane (10 ml) was applied to a column of neutral grade alumina (200 g, Fisher reagent). The column was eluted with hexane (1000 ml), hexane–chloroform (2:1, v/v, 1200 ml), and hexane–chloroform (1:1, v/v, 1000 ml). Concentration of the hexane–chloroform (2:1, v/v) eluant under reduced pressure and recrystallization of the residue from hexane gave **3**,*N*-methyl-5-phenyl-3-oxa-4-azatricyclo-[5·2·1·0^{2,6}]dec-8-ene (4.1 g) as colorless crystals, m.p. 67–68°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.55; N, 6.16. Found: C, 79.47; H, 7.43; N, 6.10.

Concentration of the hexane–chloroform (1:1, v/v) eluant to dryness under reduced pressure and recrystallization of the residue from methanol gave the di-adduct **4**, possibly 4,10-dimethyl-5,11-diphenyl-3,9-dioxa-4,10-diazatetracyclo[5·5·1·0^{2,6},0^{8,12}]tridecane (0.15 g) as colorless crystals, m.p. 214–216° (decomp.).

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.42; H, 7.17; N, 7.59.

Catalytic Hydrogenation of N-Methyl-5-phenyl-3-oxa-4-azatricyclo[5·2·1·0^{2,6}]dec-8-ene (3)

A solution of **3** (0.22 g, 0.001 mole) in anhydrous methanol (25 ml) was shaken in a hydrogen atmosphere with prereduced Adam's catalyst at room temperature and atmospheric pressure. The hydrogen uptake corresponded to 0.001 mole. The reaction mixture was filtered and the filtrate was concentrated to dryness. Bulb-to-bulb sublimation of the residue under reduced pressure (0.02 mm) gave *N*-methyl-5-phenyl-3-oxa-4-azatricyclo[5·2·1·0^{2,6}]decane, isomer **1** (0.21 g, 96%), m.p. 64–65°.

Reaction of C-Phenyl-N-methyl Nitrone with Norbornene

A solution of *C*-phenyl-*N*-methyl nitrone (27.1 g, 0.2 mole) and norbornene (18.8 g, 0.2 mole) in toluene (250 ml) was heated under reflux for 12 h. After every 2 h of reflux a further portion of norbornene (4.7 g, 0.05 mole) was added. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in ether (700 ml). The ether solution was extracted with water (3 × 75 ml) to remove unreacted nitrone and was concentrated to dryness. Recrystallization of the residue from dioxane gave yellow *N*-methyl-5-phenyl-3-oxa-4-azatricyclo[5·2·1·0^{2,6}]decane, isomer **1** (36.2 g, 79%), which was purified further by bulb-to-bulb sublimation under reduced pressure. The sublimation gave a colorless needle-like crystalline compound, which melted at 65–66°. The mixture melting point with the material prepared in the previous experiment was 64–65°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.57; H, 8.35; N, 6.12. Found: C, 78.65; H, 8.28; N, 6.08.

The infrared and n.m.r. spectra of the present product were identical to those of the compound prepared in the previous experiment.

The mother liquors from the recrystallization described above were concentrated to dryness and the residue was dissolved in hexane (15 ml). The solution was poured onto a column of basic grade alumina (250 g, Shawinigan reagent). The column was eluted with hexane (1500 ml), hexane–chloroform (2:1, v/v, 1000 ml), and hexane–chloroform (1:1, v/v, 1000 ml). Concentration of the hexane eluant gave *N*-methyl-5-phenyl-3-oxa-4-azatricyclo[5·2·1·0^{2,6}]decane, isomer **2** (4.2 g, 9%) as colorless needle-like crystals, m.p. 62–64°. This compound slowly decomposed at room temperature. Its infrared and n.m.r. spectra were strikingly different from those of isomer **1**. For example, the proton on the benzylic carbon in **2** gives rise to an n.m.r. signal at τ 6.53 (doublet of spacing 7.6 c.p.s.) while that in **1** appears at τ 7.18 (doublet of spacing 8.0 c.p.s.). The instability of **2** prevented us from obtaining accurate combustion analyses.

3-(α-Dimethylaminobenzyl)-2-hydroxybicyclo[2·2·1]-heptane (5)

A mixture of isomer **1** (2.75 g, 0.012 mole) and methyl iodide (7 ml) was heated under reflux on an oil bath for 96 h. The reaction mixture was concentrated to dryness and the residue was used for the next step without further purification. Reductive cleavage of the isoxazolidine ring of the residue (3.7 g) with zinc dust (13 g), as described by Rayburn *et al.* (11), gave **5**, 3-(α-dimethylaminobenzyl)-2-hydroxybicyclo[2·2·1]heptane (2.45 g, 83%) as colorless crystals, m.p. 114–116 °C (recrystallization from hexane).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.91; H, 9.75; N, 5.64.

Methylation of 5 by Methyl Iodide and Reductive Cleavage of the Product by Zinc Dust

A mixture of **5** (0.73 g, 0.003 mole) and methyl iodide (10 ml) was heated under reflux on an oil bath for 96 h, after which the reaction mixture was concentrated to dryness. The residue (1.0 g) was used for the next step without further purification. Zinc dust (15 g) was added in small portions to a vigorously stirred solution of the above residue (0.97 g) in 20% acetic acid (100 ml). The reaction mixture was heated under reflux for 86 h on an oil bath and then was filtered. The filtrate was extracted with ether (5 × 50 ml). The ethereal extracts were washed with water (2 × 30 ml), with 10% hydrochloric acid solution (3 × 30 ml), with 10% sodium hydroxide solution (3 × 30 ml), and with water (3 × 30 ml) again. Concentration of the ethereal solution to dryness and bulb-to-bulb distillation of the residue under reduced pressure gave **7**, 3-benzyl-2-hydroxybicyclo-[2·2·1]heptane (0.6 g, 92%) as colorless crystals, m.p. 41–42°.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.21; H, 8.95.

The alcohol was converted to a crystalline phenyl urethane, m.p. 132–133°.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.32; H, 7.11; N, 4.52.

Degradation of Isomer 2 to 3-Benzyl-2-hydroxybicyclo-[2·2·1]heptane

Methylation of isomer **2** (4.1 g, 0.018 mole) with methyl iodide (10 ml) and reductive cleavage of isoxazolidine ring of the product with zinc dust (20 g), as described above for **1**, gave **7**, 3-(α-dimethylaminobenzyl)-2-hydroxybicyclo[2·2·1]heptane (3.9 g, 85%). The infrared and n.m.r. spectra of this product showed it to be slightly impure, yet different from **5**. For example the *N*-methyl singlet appeared at τ 7.87 in **5** and at τ 7.77 in **7**. Further methylation of **7** with methyl iodide (12 ml) then reductive cleavage of the carbon–nitrogen bond with zinc dust (15 g) gave **6**, 3-benzyl-2-hydroxybicyclo[2·2·1]-heptane (2.36 g, 64%). This sample of **6** was found to have a melting point of 40–41°. The melting point of this sample when mixed with that prepared from **1** was also 40–41°. The infrared and n.m.r. spectra of the product of the present experiment were indistinguishable from those of the compound prepared in the previous experiment.

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Reductive elimination of 1,2-dibromides with sodium borohydrides

J. F. King, A. D. Allbutt, and R. G. Pews
Department of Chemistry, University of Western Ontario, London, Ontario

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Sodium trimethoxyborohydride or a 1:3 mixture of sodium borohydride and sodium tetramethylborate reacts with a number of vicinal dibromides to form the corresponding olefin. Variable (sometimes good) yields were obtained when the bromine atoms were on secondary or tertiary carbons, but little or no olefin was detected when one bromine was primary.

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We have previously reported (1) on our study of the reductive elimination of 1,2-dibromides and related species with lithium aluminium hydride. In that account we mentioned that sodium trimethoxyborohydride reduced 2β,3α-dibromo-5α-cholestane to 5α-cholest-2-ene in good yield. In the hope of casting some light on the mechanism of reductive elimination we have further investigated the reaction of sodium borohydride and related reagents on some of the same compounds. We find that these reagents effect reductive elimination in fairly good yield with