Reduction by Dissolving Metals. Part XVIII.[1] Metal–Ammonia Reductions of Some Bicyclo[2,2,2]octene Derivatives: Structural Effects on Double Bond Reduction and Nitrile Cleavage

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The reduction of the double bond in some bicyclo[2,2,2]octene derivatives by lithium in liquid ammonia is assisted by a methoxy- or a substituted amino-group at the bridgehead, and by an *endo*-carbinol group. Reductive removal of a cyano-group from the 2-position of bicyclo[2,2,2]octene or octane derivatives is similarly assisted by bridgehead methoxy- or amino-groups.

Double Bond Reductions.—Metal–ammonia reduction of carbon–carbon double bonds that are not in conjugation with other unsaturated centres is usually difficult to accomplish, because of the usual unfavourable position of the electron addition equilibrium.[2] Among other possibilities which exist for assisting reduction are: (i) the adjacency of an appropriate group which may stabilise the intermediate anion-radical by means other than conjugation and thus increase its concentration; and (ii) the cyclic donation of a proton enabling the conversion of a low equilibrium proportion of the anion-radical into reduction products.

The reduction of some bicyclo[2,2,2]oct-2-ene derivatives has been examined, since the rigid nature of the ring system enables groups to be placed in appropriate positions relative to the double bond such that the extent to which these factors influence the reactions can be examined.

Substrates were prepared by Diels–Alder reactions of dienophiles (acrylonitrile or but-3-en-2-one) with cyclohexadienes, mostly prepared by metal–ammonia reduction of anisole or of derivatives of *N*-phenylmorpholine.[3,4] The adducts were usually mixtures of *endo*- and *exo*-epimers relative to the double bond, with the former predominant.[4,5]

In order to determine whether an *endo*-alcohol function assists in reduction of the double bond, the mixture of epimers [1; $R^1 = OMe$, $R^2 = CH(OH)Me$] was used since the bridgehead methoxy-protons of the epimers resonate at different positions in the ^1H n.m.r. spectrum.[4] The mixture was prepared from the mixture of ketones (1; $R^1 = OMe$, $R^2 = Ac$) by reduction with sodium borohydride in methanol; the ^1H n.m.r. spectrum (solution in [$^2H_6$]acetone) and g.l.c. revealed the presence of three of the four possible diastereoisomers, as previously reported.[4] The upfield methoxy-resonance at δ 3·36 p.p.m. was assigned to an *endo*-alcohol in a proportion of 40% and that at 3·39 to *exo*-isomers.[4] The mixture was reduced because reductions in ammonia are subject to a number of irreproducible catalytic influences and it was thought better to examine both types under exactly the same conditions.

Treatment of the mixed alcohols [1; $R^1 = OMe$, $R^2 = CH(OH)Me$] with lithium–ammonia resulted in 70% reduction to dihydro-derivatives [2; $R^1 = OMe$, $R^2 = CH(OH)Me$], as shown by ^1H n.m.r. spectrum and g.l.c.; the unchanged material was an *exo*-isomer of [1; $R^1 = OMe$, $R^2 = CH(OH)Me$] as shown by the OMe resonance at δ 3·39 p.p.m. The presence of the bridgehead OMe facilitates reduction of the double bond, as indicated by reduction under the same conditions of compound (3; $R = H$) in 15% yield to (4; $R = H$) with lithium and t-butyl alcohol in ammonia; consequently both *endo*- and *exo*-isomers of [1; $R^1 = OMe$, $R^2 = CH(OH)Me$] should be reducible to some extent, irrespective of the presence of the carbinol group. However the much greater extent of reduction of the *endo*-carbinol supports the assumption of cyclic donation of a proton from this group.

Nitrile Cleavages.—There have been few instances until recently[4,6,7] of the reductive cleavage of nitriles by metal–ammonia solutions, although the cleavage of tertiary nitriles under these conditions has been used as an analytical procedure.[8] An attempted reduction of the isolated double bond in some bicyclo[2,2,2]oct-5-ene-2-carbonitriles resulted under some conditions in reductive cleavage of the nitrile as the major process.

Reduction of both 4-methyl- and 5-methyl-1-morpholinobicyclo[2,2,2]oct-5-ene-*endo*-2-carbonitrile [(5; $R^1 = Me$, $R^2 = H$, $R^3 = CN$) and (5; $R^1 = H$, $R^2 = Me$, $R^3 = CN$)] with lithium in ammonia, in the absence of a proton source, gave, in high yield after a short reaction time, the decyano-products, 4-methyl- and 3-methyl-1-morpholinobicyclo[2,2,2]oct-2-ene [(5; $R^1 = Me$, $R^2 = R^3 = H$) and (5; $R^1 = R^3 = H$, $R^2 = Me$)]. No reduction of the double bond was detected under the experimental conditions. In order to determine whether the double bond or the bridgehead amino-group was facilitating the cleavage, possibly through the stabilisation of an intermediate radical, the corresponding saturated nitrile, 5-methyl-1-morpholinobicyclo[2,2,2]octane-*endo*-2-carbonitrile (6; $R = CN$) was treated

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[1] Part XVII, A. J. Birch, E. G. Hutchinson, and G. Subba Rao, *J. Chem. Soc.* (*C*), 1971, 2049.

[2] A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, 1972, **6**, 1.

[3] A. J. Birch, E. G. Hutchinson, and G. Subba Rao, *J. Chem. Soc.* (*C*), 1971, 637.

[4] L. Alfaro, W. Ashton, L. D. McManus, R. C. Newstead, K. L. Rabone, N. A. J. Rogers, and W. Kernick, *Tetrahedron*, 1970, **26**, 201.

[5] A. J. Birch and J. S. Hill, *J. Chem. Soc.* (*C*), 1966, 419.

[6] P. G. Arapakos, M. K. Scott, and F. E. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 2059.

[7] J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, 1971, **36**, 877.

[8] P. G. Arapakos and M. K. Scott, *Tetrahedron Letters*, 1968, 1975.

similarly. The sole product was once again the decyano-derivative, 3-methyl-1-morpholinobicyclo[2,2,2]octane (6; R = H).

An adduct containing a bridgehead methoxy-group was then examined, with a similar result: reduction of 1-methoxybicyclo[2,2,2]oct-5-ene-*endo*-2-carbonitrile (3; R = CN) in the absence of a proton source gave 1-methoxybicyclo[2,2,2]oct-2-ene (3; R = H). In the presence of methanol, the major product was reported [4] to be the corresponding primary amine (7; R = OMe), with only a small proportion of (3; R = H) present. However, in our hands these conditions led to a high proportion of polymeric material, together with the epimeric primary amine (7; R = OMe) and the ether (3; R = H). Experimental conditions are thus critical in determining which product is formed, and absence of a proton source favours the uncomplicated cleavage reaction.

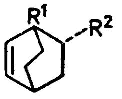
The possibility of double-bond participation in the foregoing example was again ruled out by treating the saturated nitrile, 1-methoxybicyclo[2,2,2]octane-*endo*-2-carbonitrile (4; R = CN) to form the decyano-product only: 1-methoxybicyclo[2,2,2]octane (4; R = H). That an electron-donating group at the bridgehead seems necessary for efficient cleavage was shown by examination of the reduction of the mixture [9] of epimeric bicyclo[2,2,2]oct-5-ene-2-carbonitriles (1; R^1 = H, R^2 = CN). In the absence of a proton source, three products were isolated from the reduction, none of them the decyano-material. The only readily distillable product was a mixture of epimeric bicyclo[2,2,2]oct-5-en-2-ylmethylamines (7; R = H), from saturation of the nitrile. Chromatography gave two further products; a small proportion of epimeric bicyclo[2,2,2]oct-5-ene-2-carbaldehydes (3; R = CHO) (presumably formed from the imine), and bisbicyclo[2,2,2]oct-5-en-2-ylmethylamine (8), which was characterised by spectra. I.r. absorptions at 3360, 3040, and 1620 cm^{-1} indicated the presence of both amine and unsaturated centres. The ^{1}H n.m.r. spectrum exhibited a signal at δ 1·00 p.p.m. (NH_2) which was readily removed by deuterium oxide and a broad multiplet due to the allylic protons and the proton geminal to the amino-group at δ 2·2—2·7 p.p.m.; the vinyl protons resonated as a multiplet (δ 6·1—6·4). The molecular ion in the mass spectrum had *m/e* 243 ($C_{17}H_{25}N$) and the base peak at *m/e* 136 ($C_9H_{14}N$) confirmed the symmetrical nature of the amine, since cleavage of either ring system under electron impact with charge retention on the nitrogen atom would give the same ion.

The unexpected production of compound (8) is possibly explicable in terms of reaction of an enolate salt of the nitrile, formed under the basic conditions, with imine resulting from partial reduction, and final cleavage of the tertiary nitrile.

The epimeric aldehydes (3; R = CHO) were not detected when the reaction was carried out in the presence of an alcohol; presumably reduction past the imine stage proceeded readily. An example of imine formation in reduction of a nitrile in the absence of a proton source was that of benzonitrile,[10] which gave benzaldehyde upon hydrolysis of the product. With only a few examples, generalisation is unwarranted, but it appears at present that a substituent at the bridgehead which can stabilise an intermediate radical by electron donation [*e.g.* (9)] may be required in order to allow the cleavage to occur in high yield.

Initial addition of one electron to the nitrile group will give an anion radical which may lose cyanide ion to leave a stabilised radical of type (9), which is then further reduced. In the absence of stabilisation of type (9) the anion radical may exist long enough to add another electron, and the products then represent reduction of the nitrile.

Removal of the cyano-group in this way constitutes in some instances a useful synthetic procedure equivalent to a Diels–Alder addition of an olefin to the initial diene.



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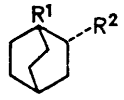

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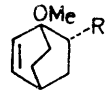

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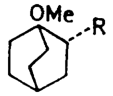

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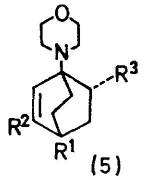

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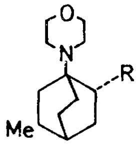

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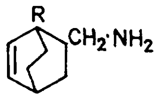

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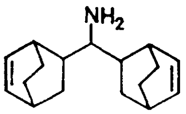

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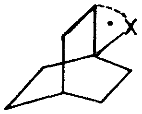

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EXPERIMENTAL

Reduction of 1-(1-*Methoxybicyclo*[2,2,2]*oct*-5-*en*-endo- *and* exo-2-*yl*)*ethanol* [1; R^1 = OMe, R^2 = CH(OH)Me].—The epimeric mixture of 1-methoxybicyclo[2,2,2]oct-5-en-2-yl methyl ketones [11] from Diels–Alder addition of but-3-en-2-one to methoxycyclohexadiene was treated with sodium borohydride to produce the isomeric alcohols, t_R 4·4, 5·3, and 5·5 min (5% QF1 at 150°), ν_{max} 3460, 3040, 1611, and 697 cm^{-1}; δ 1·03 and 1·16 (2d, *J* 7 Hz, CH*Me*), 1·2—1·9 (7H, m, CH_2 and CHR), 2·14br (0·4H, d, *J* 4 Hz, *endo*-OH, removed by D_2O), 2·44 (m, C=C·CH), 3·36 (1·2H, s, *endo*-OMe), 3·39 (1·8H, s, *exo*-OMe), 3·4—4·1 [1H, m, CH·C*H*(OH)Me], 5·06 (0·6H, s, *exo*-OH, removed by D_2O), and 6·1—6·4 p.p.m. (2H, m, =CH); δ [$(CD_3)_2CO$] 0·91, 0·97, and 1·06 (3d, *J* 7 Hz, CH*Me*), 1·2—2·0 (7H, m, CH_2 and CHR), 2·23 (0·4H, d, *J* 5 Hz, *endo*-OH), 2·43 (m, C=C·CH), 3·30 (1·2H, s, *endo*-OMe), 3·36 (1·8H, s, *exo*-OMe), 3·5—4·1 [m, CH·C*H*(OH)Me], 4·53 and 4·62 (0·6H, 2s, *exo*-OH), and

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[9] K. Alder, H. Kreiger, and H. Weiss, *Chem. Ber.*, 1955, **88**, 144.

[10] A. J. Birch and J. Cymerman-Craig, unpublished results.

[11] A. J. Birch, P. L. Macdonald, and V. H. Powell, *J. Chem. Soc.* (*C*), 1970, 1474.

6·1—6·4 p.p.m. (m, =CH) (Found: C, 72·8; H, 9·8. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%).

Hydrogenation of the alcohols (10% Pd–C) gave diastereoisomeric 1-(1-*methoxybicyclo*[2,2,2]*octan-2-yl*)*ethanols*, t_R 4·3 (35%) and 6·9 min (65%) (5% QF1 at 150°), δ 1·16 and 1·21 (2d, *J* 7 Hz, CH*Me*), 1·3—2·0 (12H, m, CH_2 and CHR), 1·74br (0·35H, s, OH, removed by D_2O), 3·16 and 3·19 (3H, 2s, OMe, ratio 3·5 : 6·5), 3·7—4·0 [m, CH·C*H*(OH)Me], and 5·16 p.p.m. (0·65H, s, OH, removed by D_2O), *m/e* 184 (M^+) (Found: C, 71·2; H, 10·8. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%).

Reduction of the mixture of isomeric unsaturated alcohols (ratio 2 : 3) (500 mg) with lithium (95 mg) and t-butyl alcohol (1·5 ml) in ammonia (50 ml) gave an oil, t_R 4·3 (33%), 5·2 (37%), and 6·9 min (30%) (5% QF1 at 150°). The peaks at 4·3 and 6·9 min were identical in t_R with those of the foregoing saturated carbinols. The ^1H n.m.r. spectrum (OMe resonances) showed the ratio of saturated to unsaturated alcohols to be 7 : 3. Interpretation of the spectrum permitted its separation into peaks due to the saturated and unsaturated alcohols: δ (saturated) 1·16—1·21 (2d, *J* 7 Hz, CH*Me*), 1·3—1·9 (11H, m, CH_2 and CH), 1·94br (0·5H, s, OH, removed by D_2O), 3·16 and 3·19 (2s, OMe), 3·6—3·9 (1H, m, CHR), and 5·12 (0·5H, s, OH, removed by D_2O); δ (unsaturated) 1·14 (d, *J* 7 Hz, CH*Me*), 1·3—1·9 (6H, m, CH_2), 2·24 (m, C=C·CH), 3·39 (s, OMe), 3·4—4·0 (m, CHR), 5·06 (s, OH, removed by D_2O), and 6·1—6·4 p.p.m. (m, =CH), identical with authentic spectra.

Reduction of 1-*Methoxybicyclo*[2,2,2]*oct*-2-*ene*.—The unsaturated ether (500 mg, 3·6 mmol) (see later) was treated with lithium (0·13 g, 18 mmol) in t-butyl alcohol (3 ml) and ammonia (60 ml). The resulting oil, on g.l.c. (5% QF1 100°) showed two peaks: t_R 2·8 (85%), identical with starting material, and 3·8 min (15%), identical with an authentic specimen of 1-methoxybicyclo[2,2,2]octane obtained by catalytic hydrogenation of the starting material.

Reduction of 5-*Methyl- and* 4-*Methyl*-1-*morpholinobicyclo*[2,2,2]*oct*-5-endo-2-*carbonitrile* (5; R^1 = H *or* Me, R^2 = Me *or* H, R^3 = CN).—Lithium (35 mg, 5 mmol) was added to a stirred solution of the 4-methyl nitrile (232 mg, 1 mmol) in tetrahydrofuran (10 ml) and ammonia (40 ml). After 1 h methanol was added and work-up gave 4-*methyl*-1-*morpholinobicyclo*[2,2,2]*oct*-2-*ene* (200 mg), m.p. 71—72°, $\nu_{max.}$ ($CHCl_3$) 1612 cm^{-1}; δ 1·12 (3H, s, CMe), 1·25—1·7 (8H, m, CH_2), 2·68 (4H, m, CH_2·N·CH_2), 3·74 (4H, m, CH_2·O·CH_2), 5·95 (1H, d, *J* 9 Hz, 1H, C*H*·CNR_2), and 6·20 p.p.m. (1H, d, *J* 9 Hz, C*H*·CMe) (Found: C, 75·0; H, 10·0. $C_{13}H_{21}NO$ requires C, 75·3; H, 10·2%).

A similar reduction of the 5-methyl isomer gave 3-*methyl*-1-*morpholinobicyclo*[2,2,2]*oct*-2-*ene* as an oil, $\nu_{max.}$ 3035, 1650, 1122, and 876 cm^{-1}; δ 1·2—1·7 (8H, m, CH_2), 1·79 (d, *J* 2 Hz, =CMe), 2·24br (s, C=C·CH), 2·68 (m, CH_2·N·CH_2), 3·75 (m, CH_2·O·CH_2), and 5·80br p.p.m. (d, *J* 2 Hz, =CH), *m/e* 207 (38%, M^+) (Found: C, 74·8; H, 10·6; N, 7·1%; *m/e* 207·1624. $C_{13}H_{21}NO$ requires C, 75·3; H, 10·2; N, 6·8%; *M*, 207·1623).

Reduction of 5-*Methyl*-1-*morpholinobicyclo*[2,2,2]*octane*-endo-2-*carbonitrile* (6; R = CN).—5-Methyl-1-morpholinobicyclo[2,2,2]-oct-5-ene-*endo*-2-carbonitrile was hydrogenated (Adams catalyst). Crystallisation from ether–light petroleum gave 5-*methyl*-1-*morpholinobicyclo*[2,2,2]*octane*-endo-2-*carbonitrile*, m.p. 84—85°, $\nu_{max.}$ 2245 cm^{-1}; δ 1·00 (d, *J* 6 Hz, CH*Me*), 1·2—2·2 (10H, m, CH_2 and CHR), 2·56 (m, CH_2·N·CH_2), 2·90 (m, bridgehead H), and 3·68 p.p.m. (m, CH_2·O·CH_2), *m/e* 234 (M^+) (Found: C, 71·7; H, 9·3. $C_{14}H_{22}N_2O$ requires C, 71·8; H, 9·5%). Reduction with lithium was carried out as before to give 3-*methyl*-1-*morpholinobicyclo*[2,2,2]*octane* as an oil, $\nu_{max.}$ 1450 and 1122 cm^{-1}; δ 0·98 (d, *J* 6 Hz, CH*Me*), 1·2—2·2 (12H, m, CH_2 and CH), 2·52 (m, CH_2·N·CH_2), and 3·68 p.p.m. (m, CH_2·O·CH_2) (Found: *m/e*, 209·1779. $C_{13}H_{23}NO$ requires *M*, 259·1780).

Reduction of 1-*Methoxybicyclo*[2,2,2]*oct*-5-*ene*-endo- *and* exo-2-*carbonitriles* (3; R = CN).—The mixture of nitriles[11] (15 g, 90 mmol) was reduced with lithium (1·9 g, 270 mmol) to give 1-methoxybicyclo[2,2,2]oct-2-ene (3·0 g), b.p. 68—70° at 18 mmHg, $\nu_{max.}$ 3040, 1611, and 694 cm^{-1}, δ 1·2—1·9 (m, 4 CH_2), 2·46br (s, bridgehead H), 3·36 (s, OMe), and 6·20—6·35 p.p.m. (m, 2 =CH) (Found: C, 77·9; H, 10·2. $C_9H_{14}O$ requires C, 78·2; H, 10·2%), together with the epimeric 1-*methoxybicyclo*[2,2,2]*oct*-5-*en*-2-*ylmethylamines* (2·8 g), b.p. 60—61° at 0·2 mmHg, $\nu_{max.}$ 3370, 3300, 3040, 1640, 1610, and 695 cm^{-1}, δ 1·29 (s, NH_2, removed by D_2O), 1·1—3·2 (9H, m, CH_2 and CH), 2·44 (m, =C·CH), 3·12 and 3·14 (2s, OMe), 6·16 (0·8H, m, =CH *exo*), and 6·11 and 6·41 p.p.m. (1·2H, 2d, *J* 9 Hz, =CH *endo*) (Found: C, 71·8; H, 9·8; N, 8·2. $C_{10}H_{17}NO$ requires C, 71·8; H, 10·2; N, 8·4%).

The title nitrile was hydrogenated (Pd–C) to 1-methoxybicyclo[2,2,2]octane-2-carbonitrile, and this compound (0·7 g) on reduction with lithium (0·15 g) gave 1-methoxybicyclo[2,2,2]octane (0·5 g), $\nu_{max.}$ 1455 and 1107 cm^{-1}; δ 1·4—1·9 (13H, m, CH_2 and CH) and 3·15 p.p.m. (s, OMe) (Found: *m/e*, 140·1199. $C_9H_{16}O$ requires *M*, 140·1201).

Reduction of Bicyclo[2,2,2]*oct*-5-*ene*-endo- *and* -exo-2-*carbonitriles*.—To a stirred solution of the isomeric compounds (4·5 g, 34 mmol) in tetrahydrofuran (20 ml) and ammonia (80 ml) was added lithium (1·2 g, 170 mmol). After 1 h methanol was added and the product (3·6 g) was isolated as usual. Distillation gave the epimeric *bicyclo*[2,2,2]*oct*-5-*en*-2-*ylmethylamines* (1·0 g), b.p. 44° at 0·6 mmHg, $\nu_{max.}$ 3360, 3280, 1610, 815, and 710 cm^{-1}; δ 1·1—1·9 (7H, m, CH_2 and CH), 1·17 (s, NH_2, removed by D_2O), 2·3—2·8 (2H, m, bridgehead H), and 6·0—6·4 p.p.m. (m, 2 =CH), *m/e* 137 (M^+) (Found: C, 78·5; H, 10·8; N, 10·2. $C_9H_{15}N$ requires C, 78·8; H, 11·0; N, 10·2%). Preparative t.l.c. of the distillation residue gave a small proportion of a mixture of epimeric *bicyclo*[2,2,2]*oct*-5-*ene*-2-*carbaldehydes*, $\nu_{max.}$ 3040, 2705, 1718, and 710 cm^{-1}; δ 1·1—2·1 (m, 3 CH_2), 2·5—3·0 (3H, m, C*H*·CHO and C=C·CH), 6·0—6·4 (m, 2 =CH), 9·47 (0·8H, d, *J* 2 Hz, *endo*-CHO), and 9·79 p.p.m. (0·2H, d, *J* 2 Hz, *exo*-CHO), *m/e* 136 (M^+) (Found: *m/e*, 136·0888. $C_9H_{12}O$ requires *M*, 136·0888), and *bisbicyclo*[2,2,2]*oct*-5-*en*-2-*ylmethylamine* (1 g), $\nu_{max.}$ 3360, 3040, 1620, and 710 cm^{-1}; δ 1·00br (s, NH_2, removed by D_2O), 1·1—2·0 (14H, m, CH_2 and CH), 2·2—2·7 (3H, m, C=C·CH and C*H*·NH_2), and 6·1—6·4 p.p.m. (m, 4 =CH) (Found: *m/e*, 243·1994, 136·1125. $C_{17}H_{25}N$, $C_9H_{14}N$ require *M*, 243·1987, 136·1126).

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