Annelation of Cyclic Dienes to Amino- and Azabicyclic Diols by Iterated Cycloadditions of Nitrones

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Bimolecular cycloadditions of nitrones to cyclic dienes, followed by MCPBA N-oxidations of the resulting unsaturated isoxazolidines, intramolecular cycloadditions of the derived nitrones, and hydrogenolyses of the corresponding tricyclic isoxazolidines, annelated the dienes to amino- and azabicyclic diols. Cycloocta-1,5-diene and *N*-methylnitrone gave 3-azabicyclo[4.3.2]undecane-6,9-diol (**1**), 3-isopropyl-3-azabicyclo[3.3.3]undecane-6,9-diol (**2**), and 9-methylaminobicyclo[4.2.1]nonane-2,5-diol (**4**). *N*-Phenylnitrone changed 1,5-cyclooctadiene to 9-(cyclohexylamino)bicyclo[4.2.1]nonane-2,5-diol (**5**). *N*-Methylnitrone annelated 1,4- and 1,3-cyclohexadienes to 3-azabicyclo[3.3.1]nonane-6,8- and -6,9-diols (**6** and **7**, respectively). ^1H and ^{13}C NMR spectroscopy established the regio- and stereoisomeric structures of the diols **1–6** and **20–21**. Dynamic ^{13}C NMR experiments showed that **2** and **3** took part in degenerate conformational equilibria like manxane. At about 65 °C proton-decoupled ^{13}C NMR spectra of **2** and **3** showed eight and ten resonances, respectively. The number of resonances increased to 13 and 15 at −32 and −43 °C.

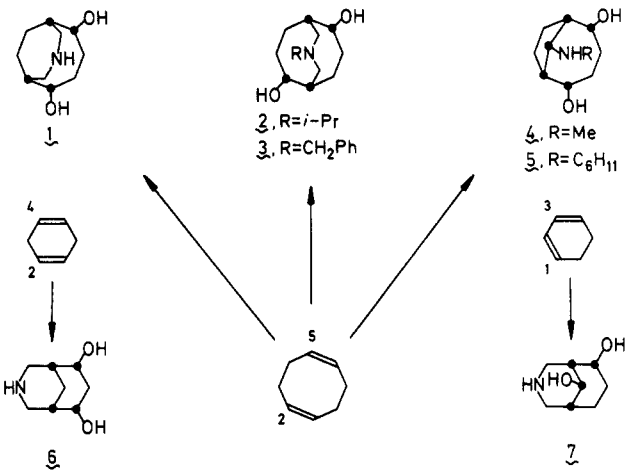
Isoxazolidines are unique among the adducts of 1,3-dipoles and dipolarophiles. Cycloadditions of nitrones to olefins close the rings of isoxazolidines,[1-8] while N-oxidations open the rings of saturated isoxazolidines to nitrones or *N*-hydroxyoxazines.[9-14] The nitrones resulting from N-oxidations of isoxazolidines add predictably to olefins,[10-12] and Tufariello and his co-workers used this fact deftly in a synthesis of *dl*-cocaine.[10,11]

Results

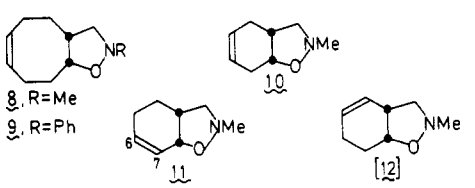
Bimolecular cycloadditions of simple nitrones to cyclic 1,5-, 1,4-, and 1,3-dienes, N-oxidations, and intramolecular cycloadditions formed tricyclic isoxazolidines **16–18**, **25**, and **29**. Hydrogenolyses of the tricycloadducts yielded the desired amino- and azabicyclic diols. *N*-Methylnitrone changed 1,5-cyclooctadiene to three kinds of products, **1**, **2–3**, and **4**. *N*-Phenylnitrone and 1,5-cyclooctadiene gave diol **5** after catalytic reduction. Reactions of *N*-methylnitrone with 1,4- and 1,3-cyclohexadienes gave diols **6** and **7**, respectively. Scheme I illustrates the six annelations.

We used ^{13}C NMR spectroscopy to learn both the regio- and stereoisomeric structures of diols **1–6** and **20**. Diols **1–6**, **20**, and **21** had effective C_s or C_2 symmetry, so the numbers of resonances in proton-decoupled ^{13}C NMR spectra of **1–6**, **20**, and **21** were smaller than the numbers of carbons each compound contained. ^{13}C DNMR experiments showed that the 3-azabicyclo[3.3.3]undecanediols **2** and **3** changed their symmetry groups from C_1 at relatively low temperature to C_2 at high temperature. Diols **2** and **3** took part in degenerate conformational equilibria like the related compounds manxane,[15] manxine,[16] and 1,5-diazabicyclo[3.3.3]undecane.[17]

Scheme I. Annelation of Cyclic Dienes by Iterated Cycloadditions of Nitrones



Starting Materials. We chose three cyclic dienes for their variety and two unsubstituted nitrones for their simplicity. Each diene was taken in excess, each nitrone was used in situ, and each cycloaddition gave a single, bimolecular adduct (TLC and ^1H NMR and mass spectra). *N*-Methyl- and *N*-phenylnitrones added to 1,5-cyclooctadiene to give the unsaturated isoxazolidines **8** and **9**. *N*-Methylnitrone was allowed to react with 1,4- and 1,3-cyclohexadiene and gave **10** and **11**.



Regiochemistry of Cycloadduct 11. ^1H NMR decoupling experiments and ^{13}C NMR spectroscopy showed

(1) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495.
(2) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403.
(3) Gatrone, R. C.; Tufariello, J. J. *Tetrahedron Lett.* **1978**, 2753–2756.
(4) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–632.
(5) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633–645.
(6) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123–180.
(7) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10–23.
(8) Furusaki, F.; Takeuchi, Y. *Adv. Heterocycl. Chem.* **1977**, *21*, 207–250.
(9) Le Bel, N. A. *Trans. N. Y. Acad. Sci.* **1965**, *27*, 858–867.
(10) Mullen, G. B.; Tufariello, J. J. *J. Am. Chem. Soc.* **1978**, *100*, 3638–3639.
(11) Ali, S. A.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Tufariello, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 2435–2442.
(12) Hwang, D.; Post, M. E.; Le Bel, N. A. *J. Org. Chem.* **1979**, *44*, 1819–1823.
(13) Brambilla, R.; Friary, R.; Ganguly, A.; McPhail, A. T.; Onan, K.; Puar, M. S.; Sunday, B. R.; Wright, J. *Tetrahedron*, **1981**, *37*, 3615–3625.
(14) Formally, the oxidation of isoxazolidines to nitrones might find an iterative, convergent series of reactions like the Mannich reaction. In the limit of the simplest series, *N*-methylnitrone and ethylene would in principle yield $[(HOCH_2CH_2)_3C]_2NH$ after six cycles comprising cycloaddition and oxidation and ending with hydrogenolysis.
(15) Doyle, M.; Gunn, D. A.; Macniol, D. D.; Martin, J.; Parker, W. *Tetrahedron Lett.* **1970**, 3619–3622.
(16) Coll, J. C. Crist, D. R.; Barrio, M. d. C. G.; Leonard, N. J. *J. Am. Chem. Soc.* **1972**, *94*, 7092–7098.
(17) Alder, R. W.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1972**, 747–748.

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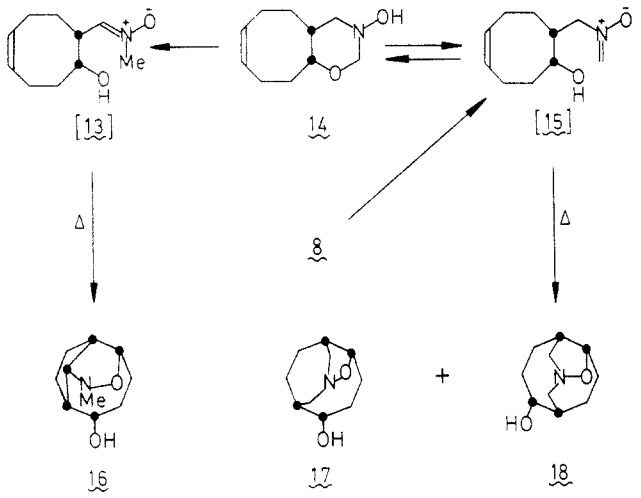
Scheme II



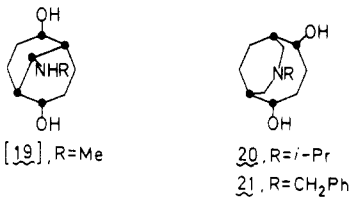
that the adduct of 1,3-cyclohexadiene and *N*-methylnitrone had the expected[2,3] regioisomeric structure **11**. Irradiation of the signal of H_7 in the ^1H NMR spectrum of **11** collapsed the broad[18] signal of the vicinal, angular H_{7a} proton to a doublet.[19] The coupling constants J_{7-7a} and J_{6-7a} in the ^1H NMR spectrum of **11** were 3 and 2 Hz, respectively. The differential chemical shifts of the olefinic proton and carbon resonances of **11** were 1.5 and 7 ppm, respectively. These facts implied we had made **11**, not the other regioisomer [**12**].

The H_7-decoupled signal of the angular H_{7a} proton in [**12**] would have had a multiplicity greater than that of the observed doublet. The signal of H_{7a} in [**12**] would have shown vicinal couplings to $H_{7\alpha}$ and $H_{7\beta}$. Any observable five-bond coupling of H_5 to H_{7a} in a spectrum of [**12**] would have been smaller than either J_{7-7a} or J_{6-7a} in the ^1H NMR spectrum of **11**. The olefinic proton and carbon $\Delta\delta$ values in ^1H and ^{13}C NMR spectra of [**12**] would have been smaller than those observed in the spectra of **11**.

Intramolecular Cycloadditions. Regio- and Stereochemistry of the Tricycloadducts and Bicyclic Diols. We kept a solution of *N*-hydroxyoxazine **14** in CD_3OD at 25 °C for 21 h, after which **14** had formed a small amount of nitrone [**15**]. A ^1H NMR spectrum showed a new, low-field AB quartet assigned to the terminal vinylic protons of [**15**]. Although the relative intensity of the quartet decreased with time, the quartet persisted for more than 8 months. If any intramolecular cycloaddition occurred, it was incomplete at 25 °C in CD_3OD.

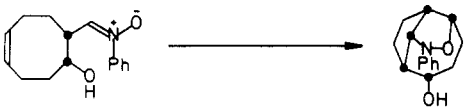
Heating **14** completed the cycloadditions (Scheme II). Compound **14** formed both nitrone [**13**] and [**15**] in an unknown ratio. Nitrone [**13**] cyclized to tricycloadduct **16**, but [**15**] gave both possible adducts, **17** and **18**. The cycloadditions yielded 65% (from **14**) of the three products **16**–**18** which we isolated by chromatography in a ratio of 2:3:1. The distinction between **16** and **17**–**18** followed from the ^1H NMR spectrum of **16**. The spectrum had an *N*-methyl resonance.

We inferred the regioisomeric structure of **16** from the ^{13}C NMR spectrum of aminobicyclic diol **4**, which resulted from catalytic hydrogenolysis of **16**. The spectrum of **4** had only six proton-decoupled ^{13}C NMR resonances because of the effective C_s symmetry of **4**. A ^{13}C NMR spectrum of the dissymmetric regioisomer [**19**] would have shown ten lines. Fortuitous coincidences of ^{13}C NMR chemical shifts in relatively small molecules are unlikely.[20]



To distinguish **17** from **18**, we used the difference between enantiotopism and diastereotopism.[21,22] N-Isopropylation of both **17** and **18** followed by reduction of the resulting quaternary salts gave the azabicyclic diols **20** and **2**, respectively. ^{13}C NMR spectra of **20** and **2** gave subtle but arresting proof of the regioisomeric structures of the two compounds. The ^{13}C NMR spectrum of **20** had seven resonances because of the enantiotopic methyl carbons and effective C_s symmetry of **20**. A spectrum of **2** had eight lines because of the diastereotopic methyl carbons and effective C_2 symmetry of **2**. The differential chemical shift of the methyl carbons of **2** was 3.1 ppm. Like the methyl carbons of **20** and **2**, the methyl protons of **20** and **2** were enantiotopic and diastereotopic, respectively. The methyl protons of **20** resonated as a doublet, but the methyl protons of **2** resonated as a pair of doublets. The differential chemical shift of the methyl protons of **2** was 0.03 ppm. The ^1H NMR spectra of the N-benzylated compounds **21** and **3** also showed the regioisomeric difference between **17** and **18** from which we prepared **21** and **3**. The enantiotopic benzylmethylene protons of **21** resonated as a singlet, but the diastereotopic benzylmethylene protons of **3** resonated as an AB quartet ($\Delta\delta$ = 0.20 ppm). Counting the number of resonances in ^{13}C NMR spectra of **21** and **3** did not distinguish the two regioisomers. Each spectrum showed ten lines despite the differing symmetry groups in each compound.

Intramolecular cycloaddition of nitrone [**22**] gave adduct **23** in a yield of 27% from **9**. ^1H NMR spectra of **16** and **23** were similar and suggested the expected structural relation between the two compounds. Hydrogenation accompanied catalytic hydrogenolysis of **23** and gave **5**. The ^{13}C NMR spectrum of **5** showed nine lines because compound **5** had effective C_s symmetry. The number of resonances in the spectrum of **5** established the regioisomeric structures of **5** and **23**.



Boiling a solution of **24** in 2-Me-2-BuOH or in toluene gave the single tricycloadduct **25** in a yield of 54% from **10** (Scheme III). Adduct **25** was the only product we could isolate by chromatography or detect by TLC. Reduction of **25** gave the 3-azabicyclo[3.3.1]nonanediol **6**. We deduced the regiochemical structures of **25** and **6** from ^1H NMR spectra of the two compounds and from the ^{13}C NMR spectrum of **6**. ^1H NMR spectra of **25** and **6** lacked *N*-methyl resonances. If the regioisomer 7-(methyl-

(18) At $h/2$ the width of the signal of H_{7a} of **11** was 25 Hz at ambient temperature (ca. 35 °C) but was only 13 Hz at 75 °C. Heating the sample also sharpened other resonances. Line broadening was also apparent in the ^{13}C NMR spectrum of **11**.

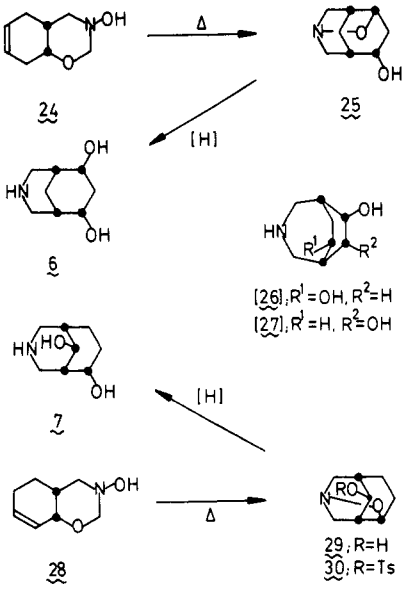
(19) By contrast, irradiation of the signal of H_7 of **11** at ambient temperature had only a slight effect on the appearance and half-width of the signal of H_{7a}.

(20) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra", Heyden & Son Ltd.: Philadelphia, 1978; p 155.

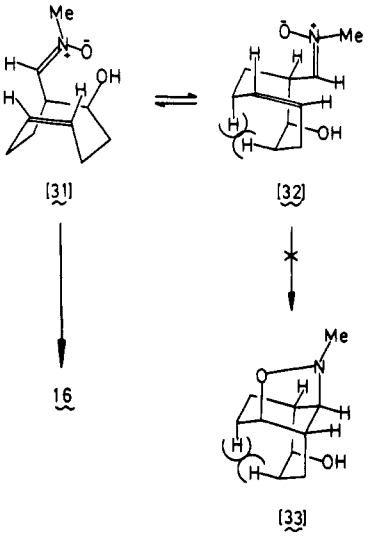
(21) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1–38.

(22) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307–322.

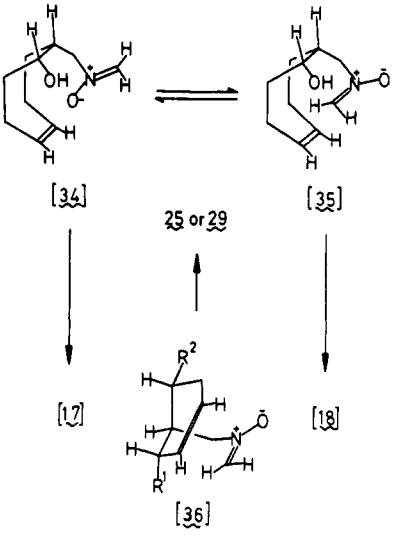
Scheme III



Scheme IV



Scheme V



amino)bicyclo[2.2.1]heptane-2,5-diol had been obtained instead of **6**, the ^{1}H NMR spectrum of the product would have shown an *N*-methyl resonance. Formation of the bicyclo[2.2.1]heptane regioisomer was unlikely, however.[23] The ^{13}C NMR spectrum of **6** showed five lines because **6** had effective C_s symmetry. The observed number of resonances implied that **6** had the illustrated regioisomeric structure. A ^{13}C NMR spectrum of regioisomer [**26**] would have shown four lines because of effective C_2 symmetry under time-averaging conditions or eight lines if [**26**] had had the trivial C_1 axis of symmetry.

Intramolecular cyclization of **28** gave adduct **29** in a yield of 49% from **11** (Scheme III). Hydrogenolysis of **29** gave the azabicyclo[3.3.1]nonanediol **7**. We tosylated **29** to **30** to learn the regioisomeric structures of **29**, **7**, and **30** from ^{1}H NMR spectroscopy. ^{1}H NMR spectra of tricycloadduct **29**, diol **7**, and tosylate **30** lacked *N*-methyl resonances. Consequently, none of the three compounds had the (methylamino)bicyclo[2.2.1]heptane structural unit. ^{1}H NMR decoupling experiments with tosylate **30** established the illustrated regioisomeric structures of **29**, **7**, and **30**.[24] One methine proton of **30** was coupled identically to both of the methine protons of the oxygenated carbons of **30**. These identical couplings would have been absent from a spectrum of the regioisomeric isoxazolidine tosylate corresponding to [**27**].

We could not tell the regioisomeric structure of **7** from the eight resonances in the ^{13}C NMR spectrum of **7**. The carbons of [**27**] are potentially diastereotopic, so a spectrum of [**27**] might also have shown eight lines. A spectrum of [**27**] might have shown four lines because of effective C_s symmetry. Although the appearance of four lines would have distinguished [**27**] from **7**, we lacked [**27**].

The intramolecularity of the cycloadditions and the numbers of resonances in proton-decoupled ^{13}C NMR spectra of diols **1–6**, **20**, and **21** implied the assignments of stereochemistry we made. The numbers of resonances in spectra of **1–6**, **20**, and **21** were smaller than the numbers of carbon atoms in each diol. As a consequence, only symmetrical stereoisomers accounted for the reduced numbers of resonances.[25]

Regioselectivity of the Intramolecular Cycloadditions. Intramolecular cycloadditions of nitrones to olefins are controlled kinetically at relatively low temperatures.[6,7,27] Steric interactions within the cyclic transition states may determine the regioisomeric structures of the resulting isoxazolidines.[6,7,27] We presume the intramolecular cycloadditions yielding adducts **16–18**, **25**, and **29** were kinetically controlled.

If the cycloaddition of nitrone [**13**] was kinetically controlled, then the regioisomeric structure of the product **16** was unsurprising. In stereomodels the transition from nitrone conformer [**31**] to adduct [**33**] (Scheme IV) was

(23) Le Bel, N. A.; Slusarczuk, G. M. J.; Spurlock, L. A. *J. Am. Chem. Soc.* **1962**, *84*, 4360–4361.

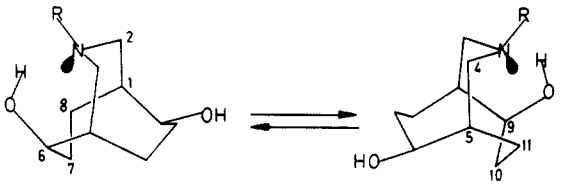
(24) These experiments incidentally confirmed the assignment of regioisomeric structure to **11**. They showed that the CHOTs proton of **30** had no large vicinal coupling. The (axial) CHOTs proton of the corresponding azaoxatricyclodecane derived from [**12**] would have had a larger vicinal coupling constant than that observed (5 Hz).

(25) C_2 or C_s symmetric stereoisomers other than **1–6**, **20**, and **21** would also account for the observed numbers of ^{13}C NMR resonances in our spectra. Other symmetric stereoisomers would have resulted if two epimerizations attended any of the sequences of intermolecular cycloaddition, N-oxidation, cis-stereospecific intramolecular cycloaddition, and hydrogenolysis. Coincidence of two epimerizations is improbable but possible.

(26) Bicyclo[3.3.3]undecane and 1-azabicyclo[3.3.3]undecane are called manxane[18] and manxine,[19] after the three-legged arms of the Isle of Man. To distinguish the three possible 1-, 2-, and 3-azabicyclo[3.3.3]undecanes in this trivial nomenclature, we propose they be termed [1]-, [2]-, and [3]manxines, respectively.

(27) Le Bel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759–3767.

Scheme VI. Degenerate Conformational Equilibria of [3]Manxine-6,9-diols



2, R=CH(CH$_3$)$_2$ 3, R=CH$_2$Ph

hindered by a severe 1,5-transannelar interaction of two of the methylene groups of [32]. Similar interactions account for the formations of five- rather than six-membered carbocycles in two related intramolecular nitrone–olefin cycloadditions.[28,29] The six-membered carbocyclic product from one of these cycloadditions was shown to be the thermodynamic product.[28]

Inspection of stereomodels showed that [34] and [35] were the least crowded of all conformers of nitrone [15] having the dipoles and dipolarophiles in parallel planes.[30] No nonbonded interactions distinguished [34] from [35], however. Preferential formation of 17 (Scheme V) may be due to entropic discrimination between the seven-membered cyclic transition state leading to 17 and the eight-membered cyclic transition state leading to 18. Entropic discrimination between seven- and eight-membered cyclic transition states was invoked in an intramolecular cycloaddition of another *N*-(5-alkenyl)nitrone.[31]

Entropic discrimination between six- and seven-membered cyclic transition states may also account for the cyclizations of nitrones [36] (R^1 = H, R^2 = OH; R^1 = OH, R^2 = H) to adducts **25** and **29**. The unidirectional cycloadditions of [36] ($R^1 = R^2$ = H)[7] and of the related nitrone which led ultimately to luciduline[32,33] precedent the cyclizations yielding **25** and **29**. In stereomodels of the three *N*-(4-alkenyl)nitrones [36] (R^1 = H, R^2 = OH; R^1 = OH, R^2 = H; $R^1 = R^2$ = H) the planes of the nitrones were nearly parallel to those of the olefins.

The planes of nitrones and olefins were not parallel but perpendicular in stereomodels of the *C*-(3-cyclohexenyl)-nitrones corresponding to the *N*-(4-alkenyl)nitrones [36]. In stereomodels of the *C*-(3-cyclohexenyl)nitrones, the dipoles were pseudoaxial in conformers having the closest approach of dipoles to dipolarophiles. Although perpendicularity of the planes of dipoles to those of dipolarophiles should prevent intramolecular cycloadditions,[30] we do not know if the *N*-(4-alkenyl)nitrones [36] isomerized to the corresponding *C*-(3-cyclohexenyl)nitrones. The closely related *N*-ethyl-*C*-(3-cyclohexenyl)nitrone does not undergo intramolecular cycloaddition in hot xylene. Instead, this nitrone rearranges to *N*-ethylcyclohex-3-ene-1-carboxamide.[23]

Dynamic ^{13}C NMR Spectroscopy of 3-Isopropyl- and 3-Benzyl[3]manxine-6,9-diols (2 and 3).[26] The ^{13}C NMR spectra of **2** and **3** were temperature dependent, and we recorded fast-exchange spectra when we heated the solutions of **2** and **3** to about 65 °C. Cooling caused coalescence of all of the azabicycloundecane ring carbon

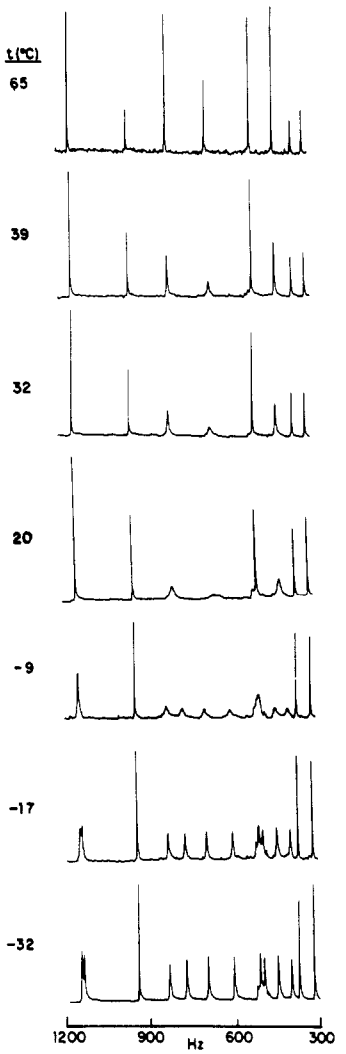


Figure 1. DCMR spectra of 3-isopropyl[3]manxine-6,9-diol (**2**; in $CDCl_3$).

resonances, until at −32 and −43 °C slow-exchange spectra resulted. Then the spectra of **2** and **3** showed 13 and 15 lines, respectively. Figure 1 shows the changing chemical shifts of C_1–C_{10} of **2**.

Compounds **2** and **3** changed their symmetry groups from C_1 at low temperature to C_2 at high temperature. Therefore the members of the five common pairs of carbon in both compounds must have exchanged environments in degenerate conformational equilibria (Scheme VI). We think unidirectional inversions of the three three-atom bridges mediated the exchanges but do not know if the inversions were concerted.

The conformations represented in Scheme VI reflect our observation that compound **2** was intramolecularly H bonded in solution. The conformations also reflect the agreement[34] that the least energetic cyclooctane conformation has the boat–chair (BC) geometry. Each of the cyclooctane rings of three bicyclo[3.3.3]undecane molecules (including manxine hydrochloride)[37] does have the BC conformation in the solid state.[35-37] One or more flattened bridges in the solution conformation(s) of **2** and **3** might

(28) Gössinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96–103.
(29) Trybulski, E. J.; Tufariello, J. J. *J. Org. Chem.* **1974**, *39*, 3378–3384.
(30) Carlsen, P. H. J.; Padwa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3862–3864.
(31) Bakker, B. H.; Oppolzer, W.; Siles, S.; Snowdon, R. L. *Tetrahedron Lett.* **1979**, 4391–4394.
(32) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722–6723.
(33) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755–2762.
(34) Dyllick-Brenzinger, R.; Olsen, H. *J. Am. Chem. Soc.* **1981**, *103*, 704–706.
(35) Murray-Rust, J.; Murray-Rust, P.; Watt, C. I. F. *Tetrahedron* **1980**, *36*, 2799–2806.
(36) Byrn, S. R.; Missavage, R. J.; Paul, I. C.; Wang, A. H.-J. *J. Am. Chem. Soc.* **1972**, *94*, 7100–7104.
(37) Leonard, N. J.; Coll, J. C.; Wang, A. H.-J.; Missavage, R. J.; Paul, I. C. *J. Am. Chem. Soc.* **1971**, *93*, 4628–4630.

also be consistent with our observations of the conformational mobilities of these compounds. We hope to publish our values of the Eyring parameters for the conformational mobilities of **2** and **3** separately.

Experimental Section

General Methods. Uncorrected melting points of amino- and azabicyclic diols were determined in sealed tubes on a Mel-Temp apparatus; all others were determined on a Kofler block (Thomas, Model 40). IR spectra ($\nu(CH_2Cl_2)$, cm^{-1}) were recorded on a Perkin-Elmer 727B spectrophotometer, ^1H NMR and proton-decoupled ^{13}C NMR spectra (δ, parts per million downfield from Me_4Si; $CDCl_3$ solutions except as noted; coupling constants in hertz) on Varian T-60, CFT-20, EM-390, and XL-100 instruments, and medium-resolution mass spectra on a Varian CH5 spectrometer. High-resolution mass spectra were recorded on a Varian MAT 312 instrument. E. Merck F-254 silica gel plates were used for TLC; developed plates were visualized in I_2 vapor. For column chromatography, silica gel (100 g/g, 0.063–0.200 mm) was purchased from E. Merck and basic alumina from Woelm. Alumina was deactivated with H_2O to grade IV. Unoptimized yields are reported.

Cycloadditions of *N*-Methylnitrone to 1,5-Cyclooctadiene, 1,4-Cyclohexadiene, and 1,3-Cyclohexadiene. In a molar ratio of 0.3:1.25:0.25:0.25, paraformaldehyde, the diene, *N*-methylhydroxylamine hydrochloride, $(i\text{-}Pr)_2NEt$, and ethanol (250 mL) were boiled 26–42 h under reflux; the solvent and excess diene were distilled under reduced pressure. The residue in H_2O (450 mL) was extracted with $CHCl_3$ (9 × 50 mL), washed with H_2O and brine, dried (Na_2SO_4), filtered, and distilled. Distilled isoxazolidines were characterized spectroscopically and were then used in the next step.

2-Methyl-2,3,3a,4,5,8,9,9a-octahydro-3*H*-cycloocta[*d*]isoxazole (8) was a colorless liquid: bp 58–60 °C (0.15 mm); yield 61%; mass spectrum, *m/e* (relative intensity) 167 (7, M^+), 60 (100); ^1H NMR 5.62 (br m, H_6 and H_7, 2 H), 4.18 (br m, H_{9a}, 1 H), 3.52–1.38 (envelope) and 2.67 (NCH_3) (total of 14 H).

2-Methyl-2,3,3a,4,7,7a-hexahydro-3*H*-1,2-benzisoxazole (10) was a colorless liquid: bp 37 °C (0.05 mm); yield 55% (from 1.7 mol of MeNHOH·HCl); mass spectrum, *m/e* (relative intensity) 139 (12, M^+), 60 (100); ^1H NMR 5.80 (br m, H_5 and H_6, 2 H), 4.35 (br m, H_{3a}, 1 H), 2.89–2.58 (envelope) and 2.67 (NCH_3) (total of 5 H), 2.36–1.91 (envelope, 5 H).

2-Methyl-2,3,3a,4,5,7a-hexahydro-3*H*-1,2-benzisoxazole (11) was a colorless liquid: bp 28–34 °C (0.05 mm); yield 78%; ^{13}C NMR (assignment, relative intensity, width at half-height): 132.6 (C_6 or C_7, 46, <0.5), 127.4–124.0 (C_7 or C_6, 11, 4.5), 75.0–72.0 (C_{7a}, 15, 3.0), 66.2–63.2 (C_3, 12, 3.5), 45.9 (NCH_3, 120, <0.5), 40.2 (C_{3a}, 42, <0.5), 26.6–25.2 (C_4 or C_5, 25, 1.5), 23.3 (C_5 or C_4, 41, 0.5); ^1H NMR 6.05 (d of br sextets, collapsed to a dq by irradiation at 4.32, H_6, $J_{6\text{-}7a} = 2$, $J_{6\text{-}5\alpha}$ or $J_{6\text{-}5\beta} = 3$, $J_{6\text{-}5\beta}$ or $J_{6\text{-}5\alpha} = 4$, $J_{6\text{-}7} = 10$), 5.81 (d of quintets, collapsed to a dt by irradiation at 4.32 and to a q by irradiation at 2.3–1.6, H_7, $J_{7\text{-}5\alpha} = J_{7\text{-}5\beta} = 2$, $J_{7\text{-}7a} = 3$, $J_{7\text{-}6} = 10$), 4.32 (br, s, $w_{h/2} = 13$ (75 °C), collapsed to a br d by irradiation at 5.81, $J_{7a\text{-}3a} = 12$, H_{7a}), 3.23 (br, H_{3a}), 2.84–2.40 ($H_{3\alpha}$ and $H_{3\beta}$) and 2.70 (NCH_3) (total of 5 H), 2.30–1.26 (envelope, $2H_4$ and $2H_5$); mass spectrum, *m/e* (relative intensity) 139 (12, M^+), 60 (100).

2-Phenyl-2,3,3a,4,5,8,9,9a-octahydro-3*H*-cycloocta[*d*]isoxazole (9) was prepared from 1,5-cyclooctadiene, *N*-phenylhydroxylamine, and paraformaldehyde in EtOH as described for **8**. Compound **9** was a red liquid [bp 132–137 °C (0.15 mm)] and was isolated by distillation and purified by chromatography over silica gel (elution with 9:1 $CHCl_3$–hexanes): yield 12%; mass spectrum; *m/e* (relative intensity) 229 (22, M^+), 106 (100); ^1H NMR 7.53–6.82 (m, C_6H_5, 5 H), 5.60 (br m, H_6 and H_7, 2 H), 4.27 (br m, H_{9a}, 1 H), 3.74 (dd, $J_{3\alpha\text{-}3\beta} = 10$, $J_{3\alpha\text{-}3a}$ or $J_{3\beta\text{-}3a} = 7$, $H_{3\alpha}$ or $H_{3\beta}$, 1 H), 3.23 (dd, $J_{3\alpha\text{-}3\beta} = 10$, $J_{3\beta\text{-}3a}$ or $J_{3\alpha\text{-}3a} = 6$, $H_{3\beta}$ or $H_{3\alpha}$, 1 H), 2.83–1.37 (envelope, 9 H).

MCPBA Oxidations of Isoxazolidines 8–11. Oxidations of isoxazolidines **8–11** and isolation of *N*-hydroxytetrahydrooxazines **14**, **24**, and **28** were done as described by Le Bel and co-workers.[12] After elution from alumina (activity IV) with chloroform, the oily crude products were characterized spectroscopically and were then used directly in the next step; only compound **14** crystallized.

3-Hydroxy-3,4,4a,5,6,9,10,10a-octahydro-2*H*-cycloocta[*e*]oxazine (14) was obtained as a white solid in a yield of 95%; a sample was crystallized from Et_2O: mp 112–114 °C; ^1H NMR 5.70–5.25 (br m, olefin); mass spectrum, *m/e* (relative intensity) 183 (17, M^+), 166 (62, M - OH), 67 (100). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.60; H, 9.22; N, 7.49.

3-Hydroxy-3,4,4a,5,8,8a-hexahydro-2*H*-1,3-benzoxazine (24) was an oil which was used directly in the next step: ^1H NMR 5.90–5.34 (br m, olefin); mass spectrum, *m/e* (relative intensity) 155 (7, M^+), 79 (100).

3-Hydroxy-3,4,4a,5,8,8a-hexahydro-2*H*-1,3-benzoxazine (28) was an oil which was not characterized but which was used immediately in the next step.

Oxidation of Isoxazolidine 9. The oily product (4.69 g) of oxidation of **9** (5.81 g) with MCPBA in CH_2Cl_2 as described by Le Bel and co-workers[12] was eluted from alumina by 99:1 $CHCl_3$–MeOH and was used directly in the preparation of **23**: IR 3520, 3370 (OH), 1590; ^1H NMR 7.6–6.5 (m, C_6H_5), 5.85–5.35 (dt, olefin H), 4.66 (br d, $J = 9$), 4.21 (t, $J = 7$), 3.98 (br s), 3.25–1.05 (envelope).

Observation of Nitrone [15]. A solution of **14** and Me_4Si in CD_3OD was prepared, and its ^1H NMR spectrum was recorded; the solution was allowed to stand at 25 °C for 21 h, when its spectrum was rerecorded. In addition to the signals of **14**, it then showed a new AB quartet assigned to the nitrone protons of [**15**]: δ_A 6.67, δ_B 6.63; $J_{AB} = \pm 7$. The quartet could still be observed after more than 8.75 months at 25 °C.

Intramolecular Cycloadditions. Solutions (0.2–1.1 M) of the products of oxidation of isoxazolidines **8–11** in 2-Me-2-BuOH were boiled 18–72 h under reflux in N_2. The cooled solutions were concentrated, and the residues were chromatographed over silica gel or used directly in the next step.

7-Hydroxy-2-methyl-2-aza-3-oxatricyclo[6.3.0^{1,8}.0^{4,11}]undecane (16) was eluted first by 97.5:2.25:0.25 $CHCl_3$–MeOH–NH_4OH; it was a yellow liquid [bp 81–84 °C (0.1 mm)], pure by TLC and ^1H NMR, and was obtained in a yield of 21%; ^1H NMR 6.1 (OH, ex), 4.4 (br d, CHON, $J = 9$), 3.9 (m, CHOH), 3.7–3.5 (m, CHN), 3.4–3.0 (m, 1 H), 2.7–2.4 (1 H), 2.67 (s, NCH_3), 2.2–1.3 (envelope, 8 H); mass spectrum *m/e* (relative intensity) 183 (47, M^+), 166 (18, M - OH), 42 (100).

9-Hydroxy-3-aza-12-oxatricyclo[4.3.2.1^{3,6}]dodecane (17) was eluted second from the foregoing column: colorless solid; mp 187–197 °C dec; yield 32%; crystallized from EtOAc; ^1H NMR 4.34 (dd, $J = 7$ and 8, H_{12}), 3.94–3.57 (m, H_9), 3.37–3.07 (overlapping, 2 H), 2.89–1.46 (envelope, 3 H); mass spectrum, *m/e* (relative intensity) 183 (28, M^+), 166 (19, M - OH), 41 (100). Anal. Found for $C_{10}H_{17}NO_2$: C, 65.71; H, 9.38; N, 7.71.

9-Hydroxy-3-aza-12-oxatricyclo[3.3.3.1^{3,6}]dodecane (18) was eluted last from the foregoing column; it was a viscous, yellow oil, obtained in a yield of 12%, and it crystallized from EtOAc: mp 174–180 °C; ^1H NMR 4.28 (br t, $J = 4$, H_{12}), 3.47–2.38 (envelope, 6 H), 2.25–1.05 (envelope, 10 H); mass spectrum, *m/e* (relative intensity) 183 (59, M^+), 166 (11, M - OH), 41 (100). Anal. Found for $C_{10}H_{17}NO_2$: C, 65.42; H, 9.27; N, 7.40.

7-Hydroxy-2-phenyl-2-aza-3-oxatricyclo[6.3.0^{1,8}.0^{4,11}]undecane (23) was obtained from 5.81 g of **9**, was eluted by 99.5:0.5 $CHCl_3$–MeOH, and was rechromatographed over alumina. Eluted by 75:25 hexanes–Et_2O, it was a clear red oil, pure to TLC: yield 27% (from **9**); ^1H NMR 7.4–6.8 (m, C_6H_5), 4.89 (d, $J = 10$, CHOH) and 4.65 (br d, $J = 9$, CHON) (total of 2 H), 4.3–3.8 (overlapping m, CHN and CHOH, 2 H), 3.2–2.5 (overlapping m, 2 H), 2.3–1.3 (envelope, 8 H); mass spectrum, *m/e* (relative intensity) 245 (90, M^+), 77 (100).

8-Hydroxy-3-aza-10-oxatricyclo[3.3.1^{1,5}.1^{3,6}]decane (25) was eluted by 95:4.5:0.5 $CHCl_3$–MeOH–NH_4OH and was obtained as a tacky yellow solid, pure by TLC, ^1H NMR, ^{13}C NMR, in a yield of 54% from **10**: ^{13}C NMR 80.7, 68.8, 63.2, 54.5, 37.8, 36.1, 34.5, 28.2; ^1H NMR 4.53 (m, H_6), 4.10 (m, H_8), 3.60 (br d, $J = 15$, 1 H), 3.16 (s, 2 H), 2.82 (dd, $J = 15$, 4, 1 H), 2.62–2.00 (envelope, 5 H including OH), 1.78 (dd, $J = 12$, 4, 1 H), 1.42 (br d, $J = 12$, 1 H); mass spectrum, *m/e* (relative intensity) 155 (16, M^+), 59 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.55; H, 8.96; N, 8.93. An acceptable microanalytical value for hydrogen was not obtained.

9-Hydroxy-3-aza-6-oxatricyclo[3.3.1^{1,5}.1^{3,6}]decane (29) was

eluted by 95:4.5:0.5 $CHCl_3$–MeOH–NH_4OH and was obtained as brown crystals, pure by TLC, in a yield of 49% from **11**. Two crystallizations from EtOAc gave light yellow prisms: mp 231–232 °C; ^{13}C NMR 80.8, 66.5, 59.3, 54.3, 45.0, 36.4, 27.1, 21.8; ^1H NMR 4.50 (dd, J = 6, 3, H_6), 3.94 (d, J = 5, H_9), 3.77 (d, J = 12, 1 H), 3.32 (dd, J = 4.5, 13.5, 1 H), 3.25–3.05 (overlapping, OH), 2.25–2.53 (envelope, 3 H), 2.12–1.20 (envelope, 5 H); mass spectrum, m/e (relative intensity) 155 (22, M^+), 138 (20, M - OH), 59 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.02. Found: C, 62.05; H, 8.35; N, 9.04.

Compound **29** was further characterized as the 9-tosylate **30** [mp 128.0–129.0 °C (EtOAc)], which was prepared with *p*-toluenesulfonyl chloride (py): IR 1190, 1180; ^1H NMR 7.83 (d, J = 8, 2 H), 7.38 (d, J = 8, 2 H), 4.64 (br d, J_{9-5} = 5, H_9), 4.48 (br dd, $J_{6-7\alpha}$ or $J_{6-7\beta}$ = 4, J_{6-5} = 5, H_6), 3.58 (d, J = 11, 1 H), 3.34–2.84 (envelope, 3 H), 2.73 (5 br lines of a sextet, $J_{5-6} = J_{5-9} = 5$, $J_{5-4\alpha}$ = 11, $J_{5-4\beta}$ <2, H_5), 2.48 (s, CH_3), 2.20–<0.50 (envelope, 5 H); mass spectrum, m/e (relative intensity) 309 (9, M^+), 138 (M - TsOH, 100).

Hydrogenolyses of Tricycloadducts 16, 17, 23, 25, and 29. These adducts (0.2–3.5 M in EtOH) were hydrogenolyzed in Parr shakers at 25 °C with 10% Pd on C under an initial H_2 pressure of 4 atm.[8] When TLC showed the absence of starting materials (4–8 days), the mixtures were filtered, and the filtrates were concentrated. The oily residues were ground under Et_2O, and the products were isolated by filtration. Compound **6** gave acceptable microanalytical values for a hemihydrate although no discrete signals attributable to hydrated water could be detected in ^1H NMR spectra of **6** and **7**. For solubility, ^1H NMR spectra of **6** and **7** were recorded in Me_2SO-d_6.

9-(Methylamino)bicyclo[4.2.1]nonane-2,5-diol (4) was isolated as a colorless solid, pure by TLC, in a yield of 61% from **16**. It was purified by sublimation at 100 °C (0.05 mm): mp 144–146 °C; ^{13}C NMR, (Me_2SO-d_6) 73.7, 67.4, 43.5, 35.7, 27.6, 25.3; mass spectrum, m/e (relative intensity) 185 (13, M^+), 150 (21), 70 (100). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 61.03; H, 9.93; N, 7.00. Acceptable microanalytical values could not be obtained. M^+ for $C_{10}H_{19}NO_2$: Calcd. 185.1415; Found: 185.1409.

3-Azabicyclo[4.3.2]undecane-6,9-diol (1) was isolated as a solid, pure by ^1H NMR, in a yield of 53% from **17** and was purified by sublimation at 150 °C (0.15 mm). It had no discrete melting point (sealed tube inserted at 25 °C, decomposition at 150–220 °C; inserted at 200 °C, decomposition at 202–220 °C): ^{13}C NMR (Me_2SO-d_6) 71.3 (d), 46.5 (t), 40.4 (d), 28.0 (t), 26.1 (t); mass spectrum, m/e (relative intensity) 185 (14, M^+), 168 (8, M - OH), 44 (100); M^+ calcd for $C_{10}H_{19}NO_2$ m/e 185.1415, found m/e 185.1405. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.33; N, 7.56. Found: C, 58.67; H, 9.38; N, 7.08. Acceptable microanalytical data could not be obtained.

9-(Cyclohexylamino)bicyclo[4.2.1]nonane-2,5-diol (5). After hydrogenation accompanied by hydrogenolysis of **23** and chromatography on silica gel (elution with 95:4.5:0.5 $CHCl_3$–MeOH–NH_4OH), pure (TLC and ^1H and ^{13}C NMR) **5** was isolated as yellow crystals in a yield of 65% from **23**. Crystallized from EtOAc, **5** had the following: mp 89.5–90.5 °C; ^{13}C NMR 75.8, 65.0, 58.1, 33.7, 28.4, 26.3, 26.0, 25.1; mass spectrum, m/e (relative intensity) 253 (11, M^+) 236 (12, M - OH), 56.3 (100). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.14; H, 10.75; N, 5.30.

3-Azabicyclo[3.3.1]nonane-6,8-diol (6) was isolated as a yellow solid, pure by TLC and ^1H NMR, in a yield of 42% from **10**. Purified by sublimation at 100 °C (0.05 mm), it was a colorless solid: mp 218–221 ° dec; ^{13}C NMR 67.6, 44.7, 41.5, 34.4, 29.6; mass spectrum, m/e (relative intensity) 157 (33, M^+), 140 (91, M - OH), 42.9 (100). Anal. Calcd for $C_8H_{15}NO_2 \cdot 0.5H_2O$: C, 57.80; H, 9.70; N, 8.43. Found: C, 58.06; H, 9.77; N, 8.32.

Compound **6** was further characterized as a triacetate (prepared with Ac_2O in py); mp 125.0–126.0 °C (Et_2O–CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.18; H, 7.31; H, 4.94.

3-Azabicyclo[3.3.1]nonane-6,9-diol (7) was isolated as a colorless solid, pure by TLC, in a yield of 69% from **29**. Purified by sublimation at 140 °C (0.2 mm), it had the following: mp 172–174 °C; ^{13}C NMR 69.6, 57.0, 43.3, 41.4, 37.5, 33.1, 29.9, 26.4; mass spectrum, m/e (relative intensity) 157 (14, M^+), 140 (66, M - OH), 42 (100). Anal. Found for $C_8H_{15}NO_2 \cdot 0.5H_2O$: C, 58.16; H, 9.14; N, 8.37. An acceptable value for hydrogen was not obtained.

N-Alkylations and Zinc Reductions of Tricycloadducts 17 and 18. Acetone solutions (0.1 M) of adducts **17** and **18** containing excesses of 2-iodopropane or benzyl chloride were boiled 4.5–28 h under reflux, cooled, and filtered. The precipitates in HOAc–H_2O (3:2, 5 mL/1.6 mmol of adduct) were treated with excesses of Zn dust (0.64 g/1.64 mmol of adduct) at 90 °C for 3 h. The cooled mixtures were decanted from the Zn nodules which were washed with 1 N HCl; the diols **2, 3, 20,** and **21**, respectively, were isolated from the cooled, combined, acidic solutions by basification and extraction with $CHCl_3$.

3-Isopropyl[3]manxine-6,9-diol (2) was crystallized from EtOAc: mp 80–84 °C; ^1H NMR (ambient temperature) 4.10–3.85 (m, CHOH), 3.15–2.45 (envelope), 1.95–1.50 (envelope), 1.05 (d, J = 6.6, CH_3), 1.04 (d, J = 6.6, CH_3); ^{13}C NMR (65 °C) 72.2 (d, CHOH), 58.4 (d, Me_2CH), 49.1 (t, CH_2N), 39.6 (d, CH), 29.1 (t, CH_2CH), 23.6 (t, CH_2CHOH), 19.5 (q, CH_3), 16.6 (q, CH_3); mass spectrum, m/e (relative intensity) 227 (6, M^+), 210 (7, M - OH), 72 (100). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.62; H, 10.78; N, 5.90.

3-Benzyl[3]manxine-6,9-diol (3) was isolated as an oil, pure by TLC and ^{13}C NMR: ^{13}C NMR (66 °C) 138.2, 129.4, 128.6, 127.6, 71.8, 65.7, 53.4, 39.1, 28.9, 23.4; ^1H NMR (ambient temperature) 7.32 (m, 5 H), 4.04 (m, 2 H), 3.77 (d, J = 13, $PhCH_AH_B$), 3.57 (d, J = 13, $PhCH_AH_B$), 3.10–2.45 (envelope), 2.1–1.3 (envelope); mass spectrum, m/e (relative intensity) 275 (0.6, M^+), 258 (2, M - OH), 91 (23), 43 (100); M^+ calcd for $C_{17}H_{25}NO_2$ m/e 275.1885, found m/e 275.1862.

3-Isopropyl-3-azabicyclo[4.3.2]undecane-6,9-diol (20) gave colorless crystals: mp 54–55 °C (from EtOAc); ^1H NMR 4.0–3.7 (br m), 3.3–1.25 (envelope), 1.05 (d, J = 7.5, $(CH_3)_2CH$); ^{13}C NMR 75.4, 56.9, 51.4, 41.5, 28.9, 27.4, 17.6; mass spectrum, m/e (relative intensity) 227 (11, M^+), 212 (100, M - CH_3). Anal. Found for $C_{13}H_{25}NO_2$: C, 68.68; H, 10.96; N, 6.34.

3-Benzyl-3-azabicyclo[4.3.2]undecane-6,9-diol (21) gave colorless crystals: mp 89.0–90.5 °C (from EtOAc); ^1H NMR 7.35 (s, 5 H), 3.8–3.95 (br m, 2 H), 3.51 (s, CH_2Ph, 2 H), 3.30 (dd, J = 4.5, 13.5, CH, 2 H), 2.6–1.32 (envelope, 14 H); ^{13}C NMR 138.2, 129.6, 128.7, 127.6, 74.3, 65.2, 56.3, 41.5, 29.0, 27.2; mass spectrum, m/e (relative intensity) 275 (5, M^+), 91 (100). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.00; H, 9.03; N, 4.81.

Dynamic ^{13}C NMR Spectroscopy. The ^{13}C spectra were obtained on a Varian FT-80A spectrometer, operating at 20 MHz and equipped with a 5-mm probe. The instrument was locked to the deuterium resonance of the $CDCl_3$ solvent, and proton-noise decoupling was used throughout. Each spectrum comprised approximately 2000 pulses with a 60° flip angle. A sweep width of 5000 Hz, an acquisition time of 1 s, and a delay time of 0.1 s were used. The temperature was maintained with a standard Varian temperature control unit. Each sample was allowed to equilibrate in the probe for about 30 min before data acquisition. Sample temperature was measured directly by using a low-loss immersible thermocouple before and after each run. Beginning and end temperatures never varied more than 2 °C, and the average was used in calculations.

Infrared Dilution Experiments. IR dilution experiments with compound **2** were done with a Perkin-Elmer Model 180 spectrophotometer over a ten-fold concentration range. Compound **2** showed ν 3605 (sh, free OH) and 3340 cm^{-1} (br, H-bonded OH) in $CDCl_3$ solution, and the ratio of intensities of the 3605- and the 3340-cm^{-1} bands became constant after a fivefold dilution of the sample.

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Registry No. 1, 80301-20-8; 2, 80301-21-9; 3, 80301-22-0; 4,

80301-23-1; **5**, 80301-24-2; **6**, 80301-25-3; **6** triacetate, 80301-26-4; **7**, 80301-27-5; **8**, 80301-28-6; **9**, 80301-29-7; **10**, 80301-30-0; **11**, 80301-31-1; **14**, 80301-32-2; **15**, 80301-33-3; **16**, 80301-34-4; **17**, 80301-35-5; **18**, 80301-36-6; **20**, 80301-37-7; **21**, 80301-38-8; **23**, 80301-39-9; **24**, 80301-40-2; **25**, 80301-41-3; **28**, 80301-42-4; **29**, 80301-43-5; **30**, 80301-44-6; 1,5-cyclooctadiene, 111-78-4; 1,4-cyclohexadiene, 628-41-1; 1,3-cyclohexadiene, 592-57-4; *N*-methylnitrone, 54125-41-6; *N*-phenylnitrone, 4745-47-5.

Hydroboration. 59. Thexylchloroborane–Methyl Sulfide. A New Stable Monohydroborating Agent with Exceptional Regioselectivity

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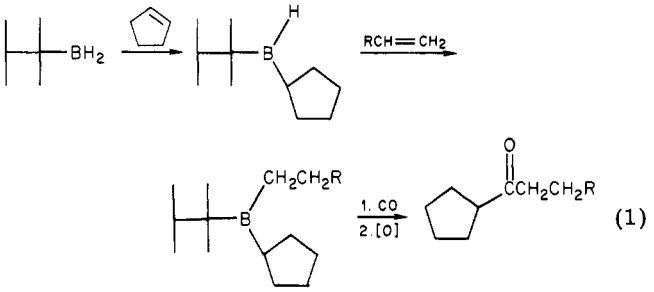
Under selected conditions, the hydroboration of 2,3-dimethyl-2-butene with 1 equiv of $BH_2Cl{\cdot}SMe_2$ proceeds cleanly in solution (CH_2Cl_2, $ClCH_2CH_2Cl$, Et_2O) or under neat conditions to give exclusively the monohydroboration product, thexylchloroborane–methyl sulfide (ThxBHCl·SMe_2). Stock solutions of ThxBHCl·SMe_2 in CH_2Cl_2 or Et_2O have unusual thermal stability at ambient temperatures or below. The hydroboration of reactive olefins, such as terminal or unhindered disubstituted alkenes, with ThxBHCl·SMe_2 proceeds quantitatively with high regiospecificity in CH_2Cl_2, $ClCH_2CH_2Cl$, Et_2O, and THF to produce isomerically pure thexylalkylchloroborane intermediates. Subsequent oxidation produces the desired alcohols in nearly quantitative yield with high regiospecificity. With less reactive olefins, such as 1-methylcyclopentene, cyclohexene, or α-pinene, ^{11}B NMR showed that the desired thexylalkylchloroborane products were contaminated with alkyldichloroborane species, indicating that a significant amount of product redistribution had occurred. This was reflected in a lower observed regioselectivity in the hydroboration of some less reactive alkenes with ThxBHCl·SMe_2.

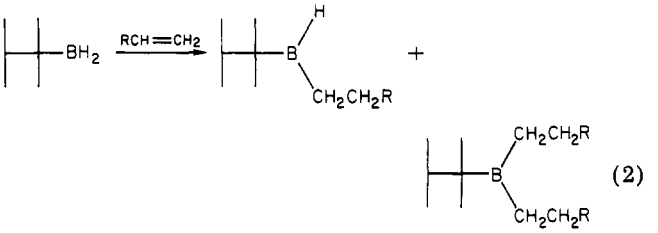
The thexyl (2,3-dimethyl-2-butyl, Thx) group is a particularly valuable blocking group in several reactions where coupling of two alkyl groups on boron is desired. For example, sequential hydroboration with thexylborane provides highly pure unsymmetrical trialkylboranes. Subsequent carbonylation or cyanidation produces the corresponding unsymmetrical ketones in high yield[2] (eq 1).



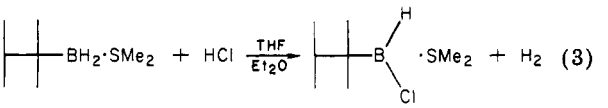
(1)

In this sequence, it is important to introduce first a relatively hindered alkene, such as cyclopentene or 2-methyl-1-butene, since treatment of thexylborane with unhindered terminal alkenes cannot be controlled to give exclusively monohydrboration[3] (eq 2). Consequently, this approach fails when one attempts to stitch together two different primary alkyl groups.

Two solutions to this problem utilizing thexylchloroborane (ThxBHCl) derivatives have recently been developed independently. Zweifel and Pearson have reported the successful synthesis of thexylchloroborane–methyl sulfide from thexylborane–methyl sulfide and hydrogen chloride[4] (eq 3). This reagent hydroborates terminal alkenes cleanly and quantitatively.



(2)



(3)

An alternative approach, developed in this laboratory, provides a direct route to this new reagent via hydroboration. The monohydroboration of 2,3-dimethyl-2-butene with various monochloroborane complexes has been examined in detail.[5] Whereas monomeric ThxBHCl·THF could be obtained cleanly from $BH_2Cl{\cdot}THF$, the product resulting from hydroboration of 2,3-dimethyl-2-butene with $BH_2Cl{\cdot}OEt_2$ was demonstrated to be a rapidly equilibrating mixture of $ThxBH_2$, $ThxBCl_2$, and $ThxBHCl{\cdot}OEt_2$. Treatment of either of these reagents with terminal alkenes led to complex mixtures in which the desired thexylalkylchloroborane was contaminated with significant amounts of trialkylborane and alkyldichloroborane species.

On the other hand, monohydroboration of 2,3-dimethyl-2-butene with $BH_2Cl{\cdot}SMe_2$ in methylene chloride proceeded cleanly to give pure thexylchloroborane–methyl

(1) (a) Graduate research assistant on temporary academic leave from Monsanto Agricultural Products Co. (b) Postdoctoral research associate, Purdue University. (c) Postdoctoral research associate on a grant from Albany International Chemicals Division.

(2) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5285–5287. Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 129–138. For a review of the synthetic applications of thexylborane, see: Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77–89.

(3) Brown, H. C.; Negishi, E.; Katz, J.-J. *J. Am. Chem. Soc.* **1975**, *97*, 2791–2798.

(4) Zweifel, G.; Pearson, N. R. *J. Am. Chem. Soc.* **1980**, *102*, 5919–5920.

(5) Brown, H. C.; Sikorski, J. A. *Organometallics* **1982**, *1*, 28–37.

0022-3263/82/1947-0863$01.25/0