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A REINVESTIGATION OF THE CHEMISTRY OF PINOL[1a] OXYGEN MIGRATION IN THE ELECTROPHILLIC ADDITIONS TO A 7-OXABICYCLO[3.2.1]OCT-2-ENE DERIVATIVE

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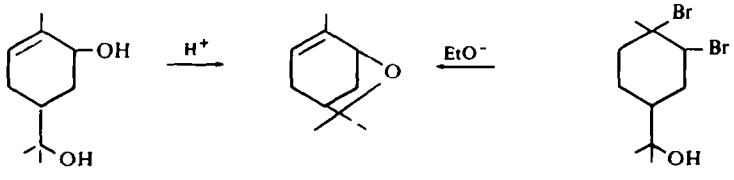
Abstract—The addition of bromine to pinol is shown to give 6,7-*diendo*-dibromocineole (**6**) which on treatment with hydrogen bromide is converted into "pinol tribromide" which is now formulated as 2,6-dibromo-4-(α-bromoisopropyl)-1-methyl-1-cyclohexanol (**7**). The reaction of cineole dibromide **6** with lead hydroxide, epoxidation of pinol with performic acid or hydrolysis of pinol oxide afford 6,7-*diendo*-dihydroxycineole **21**. Pinol epoxide on treatment with hydrogen chloride, hydrogen bromide or boron trifluoride is converted into the corresponding *diendo* 6-halo-7-hydroxycineole derivative. The reaction of pinol with potassium permanganate, osmium tetraoxide or nitrosyl chloride does not proceed with oxygen migration and yields pinol glycol **34** and chloro nitroso dimer **35**, respectively.

THE bicyclic ether 2,6,6-trimethyl-7-oxabicyclo[3.2.1]oct-2-ene (**1**), better known as pinol, is not found in Nature, but can be obtained from a variety of naturally occurring terpenes and played an important historical role in the development of the chemistry of terpenes such as α-pinene and α-terpineol.[2]

Pinol hydrate (**2**), available from a number of sources,[3,5,6–12] serves as a convenient precursor for the preparation of pinol (**1**). Pinol can also be prepared from α-terpineol dibromide,[12,13] α-terpineol chlorohydrin,[2] pinene glycol,[15] pinol glycol chlorohydrin,[14] and by reaction of nitrosyl chloride with pinene.[4]

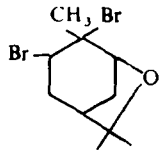
The structure of pinol was determined by chemical degradations performed by Wallach and Wagner,[2] and it is sufficient to point out that the NMR spectrum of pinol (Experimental) is in complete accord with the acepted structural assignment.



2 **1**

Pinol is best characterized by conversion to a highly crystalline dibromide which Wallach[4] formulated as **3** on the basis of its reconversion to pinol by the action of sodium metal. The dibromide is converted by hydrogen bromide in acetic acid into pinol tribromide, formulated as **4**.[5] The latter compound attracted our attention because its oxidation would afford a carvone tribromide isomer **5** in which the Br atoms would most likely be equatorial.*

* Two carvone tribromides are known and in both the α-bromo group is axial.[16]



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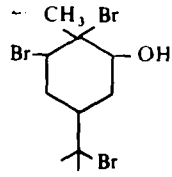

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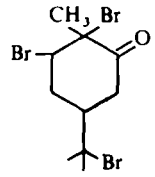
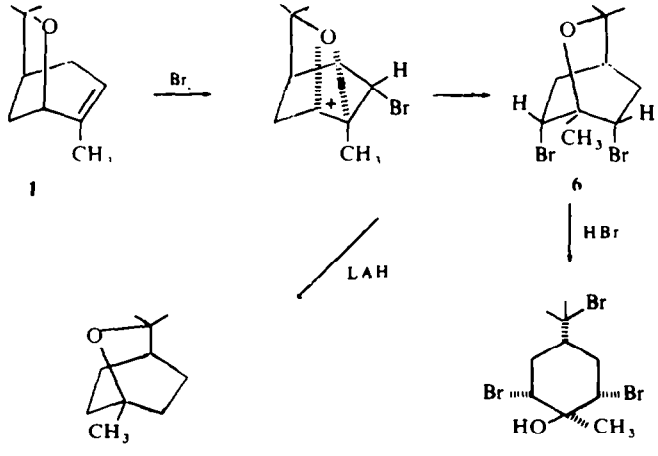


5

Three lines of reasoning led us to suspect and ultimately reject structure **3** for pinol dibromide and **4** for pinol tribromide. First of all, the addition of bromine to optically active pinol is known[14] to give inactive pinol dibromide. Secondly, attempts to oxidize pinol tribromide with a wide assortment of oxidizing agents met with no success. Thirdly, the NMR spectrum of pinol dibromide exhibited a singlet Me resonance at δ 1·46, while pinol tribromide displayed a similar signal at 1·55 ppm. These relatively high field chemical shifts are not consistent with the presence of a CH_3—C—Br moeity.

A consideration of possible mechanistic pathways for the bromine addition to pinol (Scheme I) suggested **6** as a reasonable structure for pinol dibromide and **7** for pinol tribromide. Structure **6** has a plane of symmetry and would account for the formation of optically inactive dibromide from active pinol. Compound **7** is a tertiary alcohol and would explain the stability of pinol tribromide toward oxidizing agents. Finally, the presence of a CH_3—C—O moeity is consistent with the NMR singlets at 1·46 and 1·55 mentioned above. The correctness of formulation **6** for pinol dibromide was demonstrated by LAH reduction to cineole (**8**). Pinol dibromide must now be renamed 6,7-dibromocineole, and henceforth will be referred to as such.

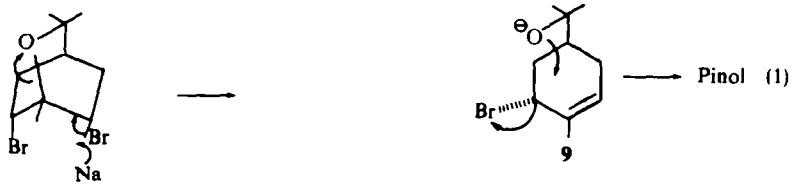


1 6 8 7

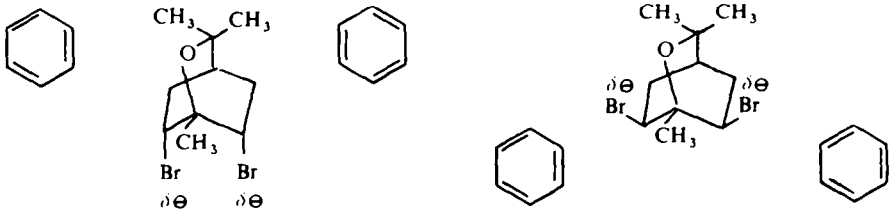
SCHEME 1

The conversion of cineole dibromide **6** to pinol by sodium is explained by a 1,2-elimination[17] generating alkoxide **9**. Intramolecular displacement of the allylic bromine atom in **9** by the oxide anion finds analogy in the formation of pinol by the

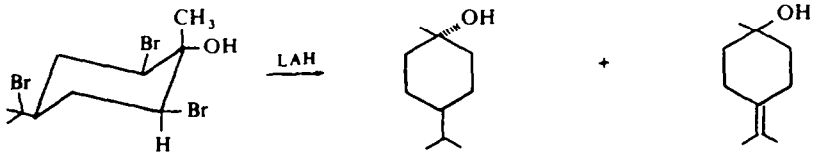
action of alkoxides on α-terpineol.[12, 13] It is of course conceivable that the conversion of **6** → **1** involves a concerted mechanism, and does not involve the intermediate **9**.



Direct evidence for the *diendo* configuration of cineole dibromide **6** is not available. However, the chemical shift for the *gem*-dimethyl group, 1·23 ppm is not markedly different from the chemical shift of 1·17 ppm displayed by the *gem*-dimethyl group of cineole (**8**). This observation is consistent with the *diendo* formulation since an appreciable downfield shift would be anticipated for the *diexo* bromide where the Br atoms closely approach the *gem*-dimethyl group. More significant is the observation that, in benzene, the *gem*-dimethyls are shifted upfield to 0·87 ppm, whereas the bridgehead Me remains at 1·48 ppm (1·47 ppm in $CDCl_3$). According to Ronayne and Williams[18] benzene will complex with a polar group in a manner such that the benzene molecules are situated as far as possible from the negative dipole in the molecule. On this basis the two possible pinol dibromides (NMR eliminates the *exo-endo* isomer) should give complexes A and B shown below. The marked shielding of the *gem*-dimethyl group and the failure to observe a shift of the bridgehead Me group is in accord with complex **A**.



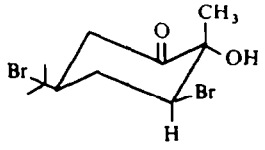
We turn next to the configuration of "pinol tribromide" (**7**). LAH reduction of this tribromoalcohol gave two alcohols in a ratio of 5·6 : 1. The minor product was tentatively identified as γ-terpineol **10** on the basis of its NMR spectrum, but complete characterization was not accomplished due to the lack of sufficient material. The major product, m.p. 42–44°, was identified as *cis-p*-methan-1-ol (**11**) on the bais of its m.p.,[19] NMR and mass spectra.[20] It is reasonable to assume that a change of



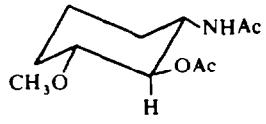
configuration has not occurred during the hydrogenolytic formation of **11** and that the bromoisopropyl and Me groups in "pinol tribromide" (**7**) are *cis*.

The NMR spectrum of "pinol tribromide" (**7**) displays a downfield ABX pair of doublets at 4·21 ppm, $J_{ax+bx} = 17$ Hz, which is indicative of two equivalent axial CHBr hydrogens. On this basis "pinol tribromide" must have the stereochemistry represented by structure **7a**.

A remarkable downfield shift of 1·15 ppm is observed for the CHBr protons when "pinol tribromide" is transformed into its acetate derivative **12**. This shift finds no parallel in the spectra of a wide variety of 2,6-dibromocyclohexanols and their acetate derivatives.[21] For example, the CHBr protons in *trans*, *trans*-2,6-dibromocyclohexanol and its acetate both resonate at 3·9 ppm. However, substantial downfield shifts of adjacent CH—X protons have been noted for the acetate of bromo alcohol **13**[22] and the N,N-diacetate of diacetylamino ether **14**.[23]

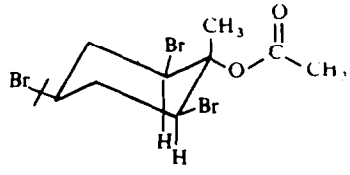


13



14

Examination of molecular models of **12** suggests the interaction between Me and acetate groups destabilizes conformations such as **15**, which ordinarily are favored in cases where Me is replaced by hydrogen, and permits high or exclusive population of conformations such as **16** where the acetate CO group closely approaches the adjacent axial hydrogens resulting in appreciable anisotropic deshielding.



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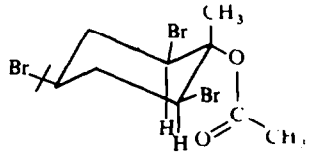
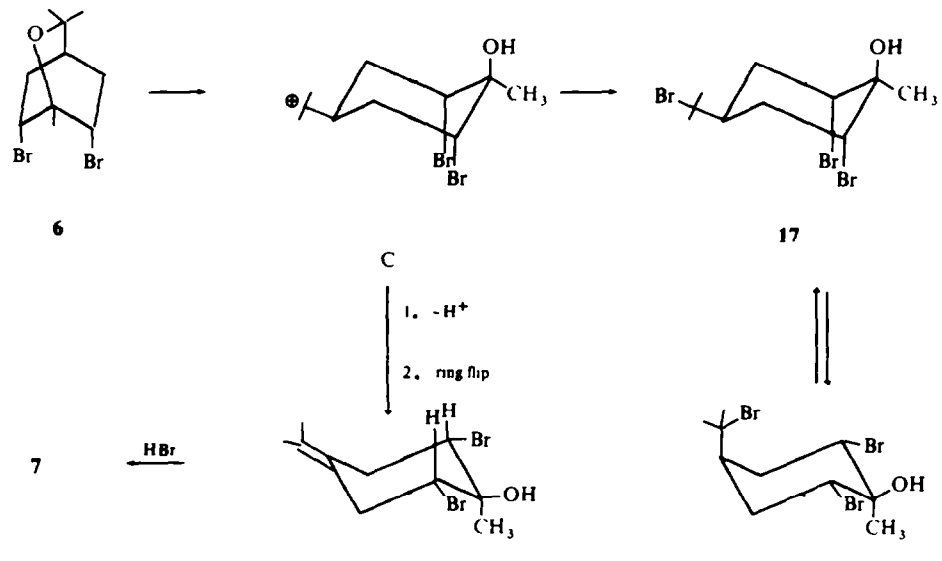


16

It is seen that the ether ring opening of "pinol tribromide" **7** by hydrogen bromide proceeds with inversion of configuration at C-4. To account for this we propose the isomerization pictured in Scheme 2. The reaction of cation C, produced by acid-catalyzed opening of the ether ring in **6**, with bromide ion would lead to the highly strain dibromo alcohol **17**. The large diaxial bromine interaction in **17** or ion C estimated to be about 4 kcal/mol[24] or the high conformational energy of the axial bromoisopropyl group in **17a**, might provide sufficient driving force for elimination to give unsaturated dibromo alcohol **18** which is eventually converted to "pinol tribromide" **7** by addition of hydrogen bromide.

The demonstration that pinol undergoes a molecular rearrangement on bromination reopens to investigation the chemistry of this bicyclic ether and places in question the correctness of structural assignments of many of its derivatives. It was of interest, therefore, to reexamine the known reactions of pinol in order to determine whether rearrangement occurs with other electrophilic reagents.



SCHEME 2

One compound which has definitely been assigned incorrectly is "*cis*-pinol glycol" regarded in the literature as structure **19**. This diol is obtained by hydrolysis of cineole dibromide **6** with lead hydroxide,[5] by acid catalyzed hydration of pinol epoxide (**20**),[25] and by hydroxylation of pinol with performic acid. On the basis of spectral and chemical evidence it is now shown to be 6,7-*diendo*-dihydroxycineole (**21**).

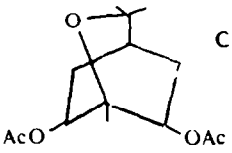
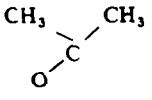
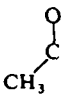
Oxidation of diol **21** by the Jones procedure[25] afforded the crystalline dione **22**. Reduction of this dione with LAH, followed by acetylation, afforded *exo-endo* diacetate **23a** and *diexo* diacetate **24a** in a ratio of 10:1. By resorting to bulkier reducing agents such as lithium aluminum tri-t-butoxy hydride, a mixture of keto-alcohol **25** and *exo-endo* diol **23** was produced. The isolation of keto-alcohol **25** could be avoided by extending the reaction period or employing a larger excess of reducing agent. Catalytic hydrogenation of the diketone gave a mixture of diols with **21** predominating.

Diol **21** displayed a dimeric type H-bonded stretching vibration at 2·82 μ, in addition to a weaker monomeric OH peak at 2·76 μ, which was not altered appreciably by dilution. Diols **23** and **24**, on the other hand, showed monomeric absorption when dilute solutions were examined. Furthermore, diol **21** gave a cyclic sulfite derivative **26** which provides chemical support for its *diendo* assignment.

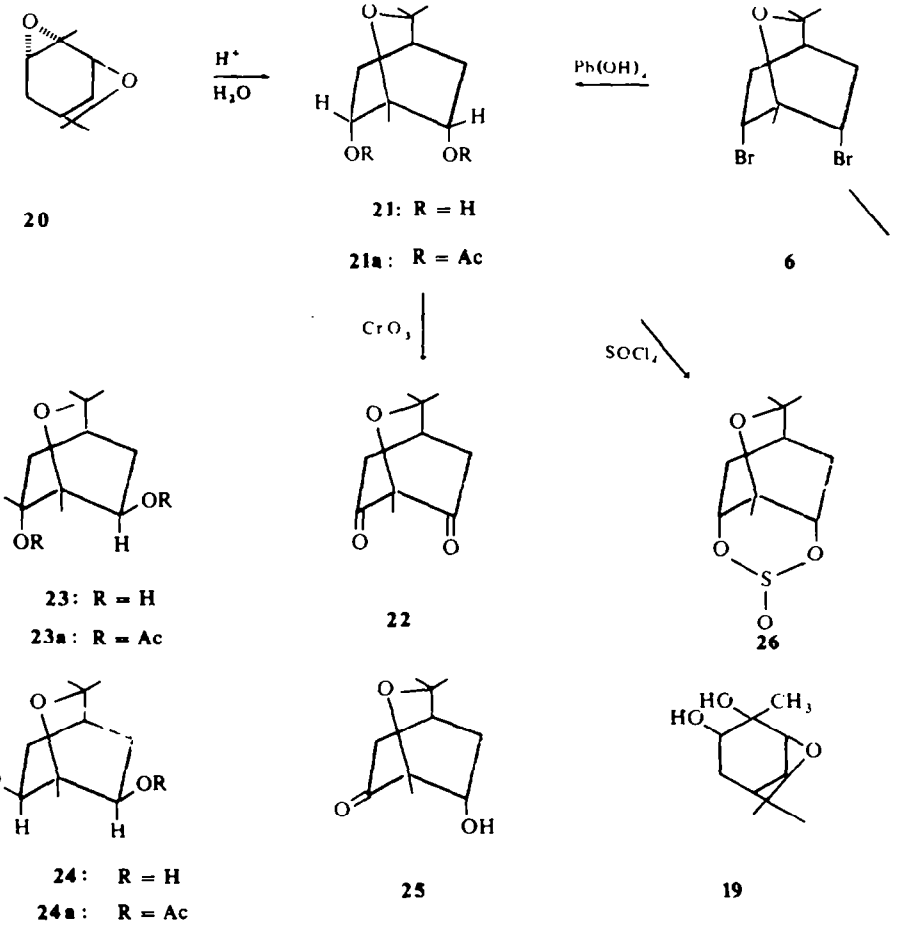
The NMR spectrum of diol **23** in DMSO showed two doublet OH signals and two CH—OH multiplets, whereas diol **21** in DMSO displayed a single OH doublet and a single CH—OH multiplet. The NMR spectra of the acetates **21a**, **23a** and **24a** are compared in Table 1 and provide additional confirmation of the *exo-endo* configuration in **23** and *diexo* configuration in **24**.

Wallach[5] reported the formation of the diacetate derivative of *cis*-pinol glycol on treatment of cineole dibromide with silver acetate. This transformation of **6** to the diacetate derivative **21a** has been confirmed. It is seen that in the reaction of cineole

TABLE 1. NMR SPECTRA OF 6,7-DIHYDROXYCINEOL DIACETATES:[a]

				H--C--OAc	CH_3--CO--O
Diendo	1·28	1·11	4·80 (q, 19 Hz)[b]		2·08
Exo-endo	1·28, 1·33	1·07	4·92 (two q, 32 Hz)[b]		2·07
Diexo	1·34	1·03	4·73 (q, 18 Hz)		2·12

[a] In parts per million (60 HMZ, internal TMS);
[b] Width at half peak height



20

21: R = H

21a: R = Ac

6

23: R = H

23a: R = Ac

22

26

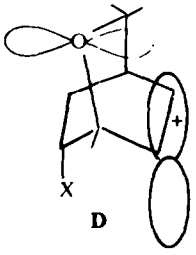
24: R = H

24a: R = Ac

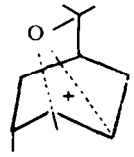
25

19

dibromide **6** with silver acetate and lead hydroxide the replacement of both Br atoms occurs with complete retention of configuration. This may be a consequence of the nucleophile entering from the less hindered side of the molecule or perhaps the stereochemistry of the reaction site is determined by participation of the ether O atom as pictured in ion **D** or **E**.



D



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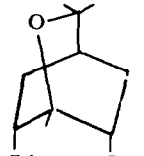
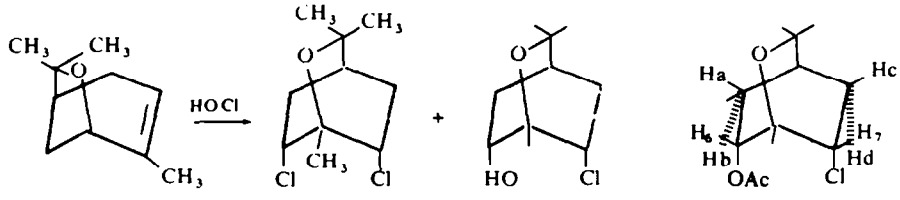
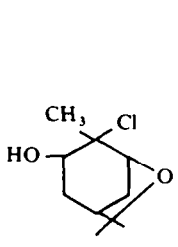


21a

The addition of hypochlorous acid to pinol in acetic acid afforded a mixture of *diendo*-6,7-dichlorocineole (**27**), 6-chloro-7-hydroxycineole (**28**) and 7-acetoxy-6-chlorocineole (**29**). The dichloride **27** was also obtained by the addition of chlorine to pinol. The chlorohydrin must have the cineole structure **28** rather than the pinol structure **30** suggested by Ginsberg[27] since oxidation according to the Jones procedure gave a chloroketone formulated as **31** on the basis of the presence of a doublet of doublets at 4·18 ppm attributed to a H—C—Cl proton.



27 **28** **29**



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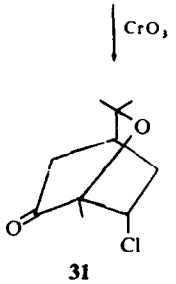
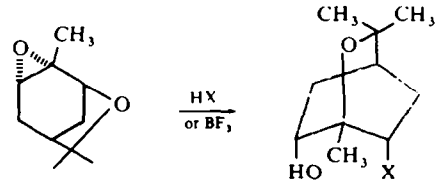


31

Chloroalcohol **28** exhibited a complicated two proton downfield signal centered at 4·0 ppm which could not be analyzed. Acetylation with acetic anhydride-pyridine at ambient temperature gave chloroacetate **29** which showed two doublets of quartets centered at 4·93 and 4·07 ppm. First order analysis of these signals gave $J_{H_6H_a} = 7{\cdot}0$ Hz, $J_{H_6H_b} = 10{\cdot}0$ Hz, $J_{H_6H_7} = 1{\cdot}9$ Hz, $J_{H_7H_c} = 5{\cdot}4$ Hz, and $J_{H_7H_d} = 10{\cdot}0$ Hz. The pertinent feature to be noted is the small long range coupling between H_6 and H_7. It is well established that long range coupling through four bonds is favored by a "W"

arrangement[28] and such an arrangement is only possible if H_6 and H_7 are both *exo*.

Pinol oxide affords chlorohydrin **28**, bromohydrin **32**, and fluorohydrin **33** on treatment with hydrogen chloride, hydrogen bromide, and boron trifluoride, respectively, demonstrating that shift of an O atom is common to all electrophilic ring openings of the epoxide ring.

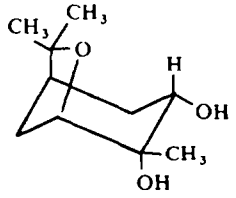


28: X = Cl

32: X = Br

33: X = F

The hydroxylation of pinol (**1**) with potassium permanganate[14] proceeds in a normal fashion to give *cis*-pinol glycol **34**.* Diol **34** is obtained in much higher yield by hydroxylation of **1** with osmium tetraoxide. Diol **34** exhibits a multiplet assigned to the C-3 proton which is partially superimposed on the H—C—O signal at C-1, however, the obvious broad nature of the signal, J_{tot} = 15 Hz, is indicative of an axial rather than an equatorial proton.



34

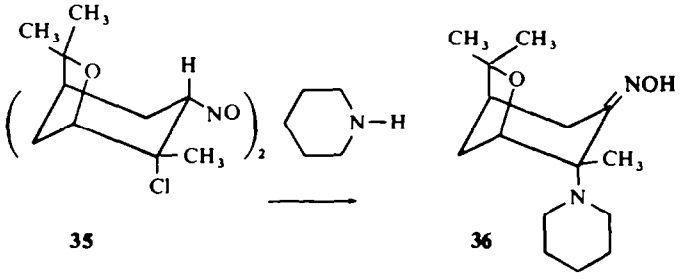
In view of the close parallel now found between pinol and other bicyclic olefins, such as norbornene, toward electrophilic agents it became of interest to determine whether pinol undergoes rearrangement on treatment with nitrosyl chloride. It is known that nitrosyl chloride adds in a *cis* manner from the *exo* side of norbornene and norbornadiene.[29]

The reaction of pinol with isoamylnitrite and hydrochloric acid according to Wallach's procedure[4] gave pinol nitrosochloride. Wallach regarded this compound as structure **35** and its NMR spectrum now demonstrates that this assignment is correct. Pinol nitrosochloride dimer **35** exhibits a singlet at 1·77 ppm characteristic of a Me group beta to a Cl atom. In addition, a doublet, J = 5 Hz, is observed at 4·08 ppm which is assigned to the C-1 proton adjacent to the ether oxygen and is analogous to the C-1 proton in pinol **1**. Examination of molecular models of these bicyclic compounds suggests the C-1 proton forms a dihedral angle approaching 90° with one of the adjacent methylene hydrogens resulting in a spin coupling constant

* The literature refers to this compound as *trans*-pinol glycol. The terms *cis* and *trans* were employed by early workers to designate the relative orientation of the substituents and the ether bridge.

close to zero; coupling with the other hydrogen of the methylene group gives rise to the observed doublet. The proton adjacent to the nitroso group appears as an ABX pair of doublets centered at 6·37, $J_{(AX+BX)}$ = 18 Hz, which is indicative of an axial hydrogen. This proton resonates at much lower field than that observed in the corresponding addition compounds of norbornene and norbornadiene and presumedly reflects the anisotropic effect of the neighboring O atom. It is seen that addition of nitrosyl chloride proceeds without rearrangement and although evidence is not available at this time it seems reasonable to place the Cl atom axial and assume that nitrosyl chloride has undergone *cis* addition to pinol in the same fashion that it does to norbornene.

Reaction of pinol nitrosochloride dimer with piperidine gave the piperidino oxime **36** in which the parent bicyclo[3.2.1]octyl ring system is retained.



35 **36**

EXPERIMENTAL

All b.ps and m.ps are uncorrected. NMR spectra were determined with a Varian Associates A-60 spectrometer. IR spectra were measured with Perkin–Elmer Model 221, 421, and Infracord spectrometers. Microanalyses were performed by Dr. C. S. Yeh and associates.

Pinol (**1**). To an ice cooled soln of α-terpineol (53 g; 0·34 mol) in hexane (400 ml) containing pyridine[30] (2 ml) Br_2 (57·5 g; 0·36 mol) was added slowly. The yellow soln was washed with 5% HCl, 5% $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated to give 106 g of a light yellow oil which was added at ambient temp under N_2 to a soln of NaOEt in EtOH (15·8 g Na added to 500 ml abs EtOH). The mixture was stirred at room temp for 5 days and was poured into water and extracted with ether. The ether extracts were washed with water and dried. The solvent was removed and distilled gave 11·6 g of pure pinol, b.p. 61–65° (2 mm) and 17·4 g of pinol contaminated with *ca* 25% of *p*-cymene, b.p. 65–67° (2 mm.) A redistilled sample showed b.p. 176–180°, n_D^{20} 1·4716; NMR (CCl_4) 1·14 and 1·25 (s's, 6, $(CH_3)_2$ C—O), 1·68 (d, 3, J = 2 Hz, $\underline{CH_3}C{=}CH{-}$), 3·88 (broad d, 1, CH—O), and 5·16 ppm (m, 1, CH=C).

Alternatively, *d*-carvone was converted in 37% yield to 8-hydroxycarvotanacetone, m.p. 40–42·5°, by the procedure of Rupe and Schlochoff.[31] LAH reduction of 8-hydroxycarvotanacetone gave pinol hydrate, m.p. 105–107°, in 90% yield. Pinol hydrate was warmed for 30 min with 15% H_2SO_4. Steam distillation, extraction of the distillate, and distillation gave pure (±)-pinol in 77% yield.

"*Pinol dibromide*," diendo-6,7-*dibromocineole* (**6**). To a stirred soln of **1** (8·16 g, 0·0537 mol) in CH_2Cl_2 (100 ml) at 0–5° soln of Br_2 (9·0 g; 0·0566 mol) in (15 ml) CH_2Cl_2 was added dropwise. After stirring 20 min the soln was washed with 10% Na_2CO_3 aq, dried ($MgSO_4$), and concentrated to leave 14·2 g of a pale yellow solid. Recrystallization from hexane and sublimation gave colorless prisms, m.p. 92–94°; Lit.[4] m.p. 94°; IR ($CHCl_3$) 6·82, 7·24, 8·88, 9·20, 10·30, and 11·72 μ; NMR ($CDCl_3$) 1·23 (s, 6, $(CH_3)_2C$—O), 1·46 (s, 3, CH_3—C—O), 1·64 and 2·6 (m's), and 4·16 (q, 2, J_{AX+BX} = 17 Hz, CHBr).

"*Pinol tribromide*" (**7**). To a warm soln of **6** (8·92 g) in glacial AcOH (9 ml), AcOH saturated with HBr (19 ml) was added. The soln was kept at 0° for 25 hr and the ppt was collected and washed thoroughly with water. The solid, 7·90 g (70%) after drying *in vacuo* over P_2O_5, was crystallized from hexane to give colorless needles, m.p. 160–161°; Lit.[5] m.p. 160; IR ($CHCl_3$) 2·8, 6·84, 7·22, 7·49, 8·78, 8·98, 10·71, and 11·45 μ; NMR ($CDCl_3$) 1·54 (s, 3, CH_3—C—O), 1·79 (s, 6, $(CH_3)_2C$—Br), 1·96–2·49 (m), and 4·15 ppm (q, 2 J_{AX+BX} = 15·5 Hz, CHBr).

"Pinol tribromide" was recovered from attempts to oxidize it with neutral and acidic potassium permanganate, N-bromosuccinimide, chromium trioxide in pyridine and acetone-sulfuric acid-water, and ruthenium tetraoxide.

Pinol tribromide acetate (**12**). A soln of "pinol tribromide" (400 mg) in acetyl chloride (10 ml) was stirred at ambient temp for 40 hr with 400 ml powdered Mg (750 mg). The mixture was filtered and the Mg was washed thoroughly with ether. Water was cautiously added to the filtrate and the aqueous phase was extracted with ether and the combined ether layers were washed with water and 10% Na_2CO_3 aq. The ether soln was dried ($MgSO_4$) and evaporated leaving 388 mg (82%) of a colorless solid. Recrystallization from hexane gave colorless crystals m.p. 160–162°; IR ($CHCl_3$) 5·8, 7·35, 8·95, 9·80, and 10·55 μ; NMR ($CDCl_3$) 1·57 (s, 3, CH_3—C—O), 1·77 (s, 6, $(CH_3)_2C$—Br), 2·09 (s, 3, CH_3CO), 2·17–2·43 (m), and 5·37 (q, 2, $J_{AX+BX} = 17$ Hz, —CH— Br). (Found: C, 33·38; H, 4·48; Br, 55·46. Calcd. for $C_{12}H_{19}Br_3O_2$: C, 31·13; H, 4·40; Br, 55·11%).

Lithium aluminium hydride reduction of cineole dibromide. A stirred slurry of LAH (2·50 g, 0·066 mol) in THF (50 ml) containing **6** (2·0 g, 0·0064 mol) was refluxed for 22 hr. The excess hydride was destroyed with sat. Na_2SO_4 aq and the mixture was filtered and the salts washed thoroughly with ether. The soln was dried ($MgSO_4$) and the solvent removed leaving 1·07 g of pale yellow oil. GLPC analysis (3 meter DEGS column at 90°) and separation indicated 3 components: the first eluted compound (47%) was identified as n-BuOH and arises by cleavage of the solvent; the second component eluted (49%) was shown to be 1,8-cineole by comparison of retention time, IR and NMR spectra with those of an authentic sample; the third component (4%) was not identified.

Lithium aluminum hydride reduction of "pinol tribromide". Compound **7** (2·0 g), was reduced with LAH (3·50 g) in THF as described to give 645 mg of a pleasant smelling liquid. GLPC analysis (DEGS column at 150°) indicated the presence of two components in a ratio of 5·6:1. The major component **11**, was collected and after recrystallization from pentane showed m.p. 42–44°, lit.[19] m.p. 42–44°; IR (neat) 3·0, 3·45, 6·9, 7·4, 10·3, 11·0, and 14·0 μ; NMR (CCl_4) 0·88 (d, 6, $J = 6$ Hz, $(CH_3)_2CH$), 1·15 (s, 3, CH_3—C—O), and 3·32 ppm (s, 1, OH); mass spectrum (75 ev) 156, and 71 (100%). (Found: C, 76·63; H, 13·19. Calcd. for $C_{10}H_{20}O$: C, 76·86; H, 12·90%).

The minor component was assigned as **10** on the basis of its NMR spectrum: 1·18 (s, 3, CH_3—C—O), 1·64 (broad s, 6, $(CH_3)_2C$=C), and complex multiplets between 1·93–2·5 ppm.

Reaction of diendo-6,7-*dibromocineole* (**6**) *with sodium.* A soln of **6** (1·30 g) in dry benzene (7 ml) was heated with Na (220 mg) for 19 hr.[4] Work-up gave 250 mg of oil which was shown by GLPC analysis on a DEGS column at 100° to be a mixture of two compounds in a ratio of 4:1. The major component was collected and was shown to be **1** by spectral analysis. The minor component was not identified.

6,7-endo,endo-*Dihydroxy cineole* (**21**)

A. *Dibromide* (**6**) *and lead hydroxide.* A mixture of (4·0 g), freshly prepared lead hydroxide (3·0 g) and water (60 ml) was refluxed for 1 hr. The soln was cooled and decanted from the solid which had not dissolved. The soln was extracted with chloroform, the chloroform was dried ($MgSO_4$) and evaporated under diminished pressure to leave a white solid. Recrystallization from hexane-EtOAc gave colorless needles, m.p. 122–124°; lit.[5] m.p. 124°, IR ($CHCl_3$) 2·79, 3·00, 7·33, 8·80, 9·08, and 10·22 μ; various dilutions of the diol in chloroform showed no variance in the relative intensities of the peaks at 2·76 and 2·82 μ; NMR ($CDCl_3$) 1·20 (DMSO) 1·10 (s, 6, CH_3—C—O), 1·13 (s, 3, CH_3—C— O), 4·74 (d, 2, $J = 7$ Hz, —OH).

C. *Hydroxylation of pinol.* To a stirred soln of 30% H_2O_2 (2·73 ml) formic acid (11·7 ml), **1** (3·0 g) was added over a 1 hr period. During the addition, the temp was maintained at 35–45° by means of a water bath. The mixture was stirred at ambient temp overnight and the volatile reagents were removed under diminished pressure. The resulting oil was stirred with dil NaOH aq at ambient temp for 1 hr, and then at 45–50° for 2 hr. The mixture was extracted with chloroform, the chloroform soln was dried and evaporated to give an off-white solid which was recrystallized from hexane-EtOAc to afford 1·85 g (50%) of colorless needles, m.p. 122–124°. The IR and NMR spectra of this solid were identical with those of the diol **21** prepared above.

C. *Acid hydrolysis of pinol oxide.* Pinol oxide was obtained by treating **1** with *m*-chloroperbenzoic acid and showed b.p. 47–51° (0·65 mm), n_D^{20} 1·4657; NMR (CCl_4) 1·10, 1·18, and 1·26 (s's, 9, CH_3—C—O), 1·82 (broad s, —CH— —CH_2—), 2·70 (m, 1, —C(O)—C—H), and 4·02 ppm (d, 1, —CH—O).

A soln of pinol epoxide (168 ml) in acetone (3 ml) water (2 ml) and 15% H_2SO_4 (1 ml) was stirred at ambient temp for 11 hr. On work-up there was obtained 71 mg (38%) of a pale yellow solid. Recrystallization

from hexane-EtOAc (Norit) afforded fine white needles, m.p. 124–126° whose IR and NMR spectra were identical with those of **21**.

Sulfite derivative **26** *of diol* **21**. To a cooled and stirred soln of $SOCl_2$ (284 mg; 2·1 mmol in pyridine (25 ml) was added dropwise a soln of **21** (372 mg: 2·02 mmol) in 6 ml pyridine. The mixture was stirred overnight, water was added, and the soln extracted with ether. The ether was washed with 5% HCl, saturated cadmium chloride soln, dried, and evaporated to afford 240 mg (51%) of sulfite which was purified by sublimation *in vacuo*, m.p. 138–140°; IR 8·10, 8·92, 9·40, 9·98, and 11·05 μ; NMR (CCl_4) 1·21 (s, 6, $(CH_3)_2C$—O), 1·54 (s, 3, CH_3—C—O), 1·85 (m, 1, J_{tot} = 12 Hz), 2·0–3·2 (m, 4), 4·33 (q, 2, J_{tot} = 20 Hz —CH—OSO—). (Found: C, 51·74; H, 7·17; S, 13·55. Calcd. for $C_{10}H_{16}O_4S$: C, 51·72; H, 6·89; S, 13·78%).

7-dicndo-*Dihydroxy cineole diacetate* (**21a**)

A. *Cineole dibromide and silver acetate*. A mixture of cineole dibromide (304 mg) silver acetate (550 mg) and AcOH (5 ml) was heated at 98° for 21 hr. NaBr (200 mg) was added and after stirring at room temp for 30 min the mixture was filtered. The filtrate was added to water and extracted with ether. The ether soln was washed with water, 10% Na_2CO_3 aq, dried ($MgSO_4$), and concentrated leaving 254 mg (96%) of a colorless oil which soon solidified. Recrystallization from hexane afforded fluffy white needles, m.p. 92° (Lit.[5] m.p. 97°); IR ($CHCl_3$) 5·78, 7·25, 7·8–8·3, 9·33, and 9·68 μ; NMR ($CDCl_3$) 1·11 (s, 3, CH_3—C—O), 1·29 (s, 6, $(CH_3)_2$—C—O), 2·10 (s, 3, O—CO—CH_3), 1·66 and 2·68 (complex m, —CH—, and —CH_2—), 4·92 (q, 2, J_{tot} = 14 Hz, CH—OAc).

In another experiment, a soln of 545 mg of cineole dibromide and 985 mg AgOAc in 20 ml glacial AcOH was stirred at rt for 28 hr. The usual workup afforded 508 mg of **21a**.

B. *Acetylation of diol* **21**. A soln of **21** (100 mg) in acetyl chloride (5 ml) was stirred at ambient temp with Mg powder (500 mg) for 30 hr. The soln was decanted and neutralized with $NaHCO_3$ aq. The mixture was extracted with ether and the ether soln was dried ($MgSO_4$), and evaporated leaving 133 mg (92%) of a white solid. Recrystallization from hexane gave **21a** as fluffy white needles, m.p. 90–92°.

1,3,3-*Trimethyl-2-oxabicyclo*[2.2.2]*octa-6,7-dione* (**22**). Oxidation of **21** (1·0 g) in acetone (20 ml) with Jones reagent (3 ml) gave crude diketone (557 mg). A pure sample of **22** was obtained by recrystallization from hexane, m.p. 122–126°, and sublimation *in vacuo*, m.p. 125–128°; IR 5·67, 5·76 μ; NMR ($CDCl_3$) 1·18 (s, 3, CH_3—C—O), 1·39 (s, 6, $(CH_3)_2$—C—O), 2·1–3·2 (complex m). (Found: C, 65·96; H, 7·93. Calcd. for $C_{10}H_{14}O_3$: C, 65·91; H, 7·74%).

Lithium aluminium hydride reduction of cineole-6,7-dione (**22**). To a stirred soln of LAH (150 mg; 3·96 mmoles) in ether (25 ml) was added dropwise a soln of **22** (200 mg; 1·10 mmoles) of ether (10 ml). The mixture was stirred at ambient temp for 30 min and then was worked up to yield 179 mg of white solid which showed a wide melting range and was not purified further.

A soln of crude diol (100 mg) in acetyl chloride (5 ml) was stirred with powdered mg (0·5 g) for 24 hr. The mixture was worked-up in the usual manner to give 128·6 mg of a colorless oil. GLPC showed the oil to be composed of two primary components in a ratio of 10:1. The major component, **23a**, was isolated by preparative GLPC as a solid, m.p. 58·0–59·5°; IR 5·75 μ; NMR ($CDCl_3$) 1·07 (s, 3, CH_3—C—O), 1·28 and 1·33 (s's, 6, $(CH_3)_2$—C—O), 2·07 and 2·12 (s's, 6, O—CO—CH_3), 1·69 and 2·55 (m's), 4·82 and 5·03 (pair of 4 line signals, 2, J_{tot} = 26 Hz, H—C—OAc). (Found: C, 62·09; H, 8·31. Calcd. for $C_{14}H_{22}O_5$: C, 62·19; H, 8·21%).

The minor component **24a**, was also isolated by preparative GLPC and purified by sublimation, m.p. 82–85°, IR 5·78 μ; NMR ($CDCl_3$) 1·03 (s, 3, CH_3—C—O), 1·34 (s, 6, $(CH_3)_2$—C—O), 2·12 (s, 6, O—CO—CH_3), 1·5–3·0 (m's, and 4·73 ppm (t, 2, J = 6 Hz, H—C—OAc).

Addition of a 1·0 M solution of LAH in ether to **22** (102 mg) followed by the usual work-up and analysis by VPC indicated the formation of 71% *exo-endo-* **23a**, 21% *diendo* **21a**, and 7% *diexo* **24a**.

When the LAH reduction was carried out in the presence of an equivalent of $AlCl_3$ the product was comprised of 69% *exo- endo-* **23a**, 24% *diendo* **21a**, and 7% of an unidentified acetate.

Catalytic hydrogenation of dione **22**. A mixture of **22** (311 mg) in EtOH (50 ml) and Raney Ni (1 g) was shaken at ambient temp for 11 hr in a Parr apparatus. The catalyst and solvent were removed and the residue was acetylated to give 327 mg yellow oil. Analysis on a Carbowax 20 M column at 180° indicated the presence of 90% of a mixture of **21a** and **23a**, and 10% of *diexo-***24a**.

When 1·02 g of **22** was reduced using PtO_2 as catalyst and AcOH as solvent, 889 mg of yellow semisolid was obtained. Recrystallization from hexane afforded 162 mg of *diendo-***21a** m.p. 82–87°, raised to m.p. 95–96° by a second recrystallization. Column chromatography of the mother liquors on silica gel gave **21a** (220 mg) *diexo-* **23a**, (45 mg) and unidentified yellow oil (170 mg) whose IR showed OH and CO indicating it was most likely a hydroxy-ketone.

6,7-*exo-endo*-Dihydroxycineole (**23**). A soln of **23a** (300 mg) LAH and (212 mg) in ether (50 ml) was refluxed under N_2 for 3 hr. The reaction was worked up in the usual fashion to give 214 mg (99%) of **23**, m.p. 162·5–164°. An analytical sample was obtained by recrystallization from hexane–EtOAc and showed IR 2·83, 2·91 μ; NMR ($CDCl_3$) 1·2 (s, 6, $(CH_3)_2$—C—O) m 1·31 (s, 3, CH_3—C—O), 3·91 (q, with superimposed t, 2, —CH—O); (DMSO) 0·99, 1·10, and 1·20 (s's, 9, CH_3—C—O), 4·19 (d, 1, J = 5·5 Hz, —OH), and 4·61 (d, 1, J = 5 Hz, —OH). (Found: C, 64·35; H, 9·58. Calcd. for $C_{10}H_{18}O_3$: C, 64·57; H, 9·67%).

Addition of hypochlorous acid to pinol. To an ice cooled soln of pinol (2·0 g) in 90% AcOH (15 ml) was slowly added (33 ml) 5·25% NaOCl aq. The mixture was stirred for 5 min and extracted with ether. The ether soln was washed with 5% NaOH aq, dried, and evaporated to leave a yellow oil from which a solid slowly crystallized. The solid, 119 mg, was removed and sublimed *in vacuo* to afford a pure sample of **27**, m.p. 75–78°; NMR 1·23 (s, 6, $(CH_3)_2$—C—O), 1·42 (s, 3, CH_3—C—O), 1·6–2·2 (m, 3), 2·6–3·1 (m, 2, —CH—C—Cl), 4·10 (d of d, 2, J_{AX} = 6 Hz, J_{BX} = 9·5 Hz, —CH—Cl). Addition of Cl_2 to pinol in chloroform gave the same **27** in 68% yield. (Found: C, 53·54; H, 7·22; Cl, 31·81. Calcd for $C_{10}H_{16}Cl_2O$: C, 52·81; H, 7·17; Cl, 31·84%).

A portion of the oil (310 mg) remaining after separation of **27** was chromatographed on florisil to give **27** (50 mg) **28** (120 mg) m.p. 49–51·5° (lit.[27] m.p. 52–54°); NMR 1·21 (s, 6, $(CH_3)_2$—C—O), 1·38 (s, 3, CH_3—C—O), 1·5–2·2 (m, 3), 2·26 (s, 1, —OH), 2·5–3·1 m, 2, *endo*-CH—C—O, —CH—C—Cl), 3·7–4·3 (m, 2, —CH—O, —CHCl); and 10 mg of acetate **29**, NMR ($CDCl_3$) 1·25 (s, 9, CH_3—C—O), 1·72 (m, 2), 2·06 (s, 3, CH_3—CO), 2·6–3·1 (m, 2), 4·06 (d of d of d, 1, —CH—Cl), and 4·92 (d of d of d, 1, —CH—OAC).

7-*Chloro*-1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]*octan*-6-*one* (**31**). A portion of the crude material (238 mg) obtained from the addition of hypochlorous acid to pinol was oxidized by the Jones procedure[26] and the product was chromatographed on 30 g silica gel. Elution with 15% ether–hexane gave **27** (40 mg) followed by **31** (102 mg). A pure sample of **31** was obtained by sublimation *in vacuo* and displayed m.p. 74·5–77° (lit.[27] m.p. 74–75·5°); IR (CCl_4) 5·72 μ; NMR 1·21, 1·28, and 1·31 (s', s, 9, CH_3—C—O), 1·7–2·3 (m, 2), 2·4–3·2 (m, 3), 4·18 (d of d, 1, J = 9·5 Hz and J = 4·1 Hz, CH—Cl).

endo-7-*Bromo*-endo-6-*hydroxycineole* (**32**). A soln of pinol oxide (500 mg) in chloroform (10 ml) was stirred vigorously with 47–49% fuming HBr (3 ml) at ice bath temp for 1 hr. The reaction was worked up in the usual fashion and the solvent was removed without heating above room temp, to afford **32** (630 mg, 77%) which gradually solidified; m.p. 50–51·5°; IR ($CHCl_3$) 2·79 μ; NMR ($CDCl_3$) 1·19 (s, 6, $(CH_3)_2$—C—O), 1·38 (s, 3, CH_3—C—O), 1·55 (m, 1), 2·7–2·9 (m, 1), 2·23 (s, 1, —OH), 3·98 (broad m, 2, CH—Br and CH—OH); mass spectrum, molecular ions at 248 and 250. (Found: C, 48·37; H, 6·65; Br, 32·68. Calcd for $C_{10}H_{17}BrO_2$: C, 48·19; H, 6·83; Br, 32·73%).

Similar treatment of pinol oxide with HCl afforded **28**.

6-*Fluoro*-7-*hydroxycineole* (**33**). A soln of pinol epoxide (100 mg) and a few drops BF_3- etherate in dry benzene (2 ml) was kept at ambient temp for 5 min and then washed with 5% $NaHCO_3$ aq and dried. The solvent was removed leaving an oil which slowly solidified. Sublimation *in vacuo* gave an analytical sample, m.p. 46–50°; IR 2·9 μ; NMR (CCl_4) 1·16, 1·30, 1·54 (s's, 9, CH_3—C—O), 2·94 (s, 1, —OH), 3·34–4·08 (complex m, 2, H—C—O and H—C—F). (Found: C, 63·58; H, 9·13; F, 10·12. Calcd for $C_{10}H_{17}FO$: C, 63·82; H, 9·09; F, 10·10%).

Hydroxylation of pinol, diol **34**

A. *Potassium permanganate.* To an ice cooled soln of $KMnO_4$ (2·30 g 0·0148 mol) and NaOH (0·40 g, 0·01 mole) in 40 ml water was added a soln of pinol (1·52 g, 0·01 mole) in t-BuOH (50 ml) and water (20 ml). Approximately 50 g cracked ice was added and the mixture was stirred vigorously for 5 min. A few drops of isopropyl alcohol was added and the mixture was filtered. The MnO_2 was washed well with ether, t-BuOH and water. The combined filtrate and washings were concentrated under diminished pressure and the residue was thoroughly extracted with hexane. On cooling the hexane soln deposited fine, white crystals of **34**, 96 mg, m.p. 127–129°; lit[14] m.p. 129°; IR ($CHCl_3$) 2·95, 9·35–9·7, and 9·97 μ; NMR ($CDCl_3$) 1·17, 1·26, and 1·33 (s's, 9, 3 CH_3), 1·5–2·2 (broad m's), 2·84 and 3·02 (broad s's, 2, —OH), 3·94 (d, 1, J = 3·5 Hz, H—C—O) superimposed on 3·8 (t or q, 1, H—C—O).

B. *Osmium tetraoxide.* To a soln of pinol (500 mg; 3·29 mmoles) in dry pyridine (5 ml) and freshly distilled THF (2·5 ml) at −78° was added a soln of osmium tetraoxide (845 mg, 3·33 mmoles) in THF (6 ml). The soln was allowed to stand at −78° for 2·5 hr, 200 ml ether was added, and the mixture was kept at −78° another 30 min to insure complete precipitation of the osmium complex. The ppt was filtered off, washed with ether and immediately dissolved in CH_2Cl_2 and treated with H_2S gas. The black ppt was removed and the solvent evaporated under diminished pressure to afford a solid. Recrystallization from hexane–

EtOAc afforded 258 mg colorless plates, m.p. 128–129° whose spectra were identical with those of **34** prepared as described above.

Pinol nitrosochloride dimer (**35**). To a cold soln of pinol (0·9 g) and isoamyl nitrite (1·4 ml) in AcOH (2 ml) was added dropwise conc HCl (1·2 ml). The mixture was kept at 0° for 30 min and the crystalline ppt, 570 mg (44%), was removed and washed with MeOH, m.p. 111–113°, lit.[4] m.p. 113°, IR ($CHCl_3$) 6·87, 7·22, 8·50, 9·97, 10·44, and 11·35 μ (very weak peaks at 3·05 and 6·09 μ indicated the presence of a small amount of oxime); NMR ($CDCl_3$) 1·26 and 1·46 (s's, 6, $(CH_3)_2$—C—O), 1·77 (s, 3, CH_3—C—Cl), 4·08 (d, 1, —H—C—O), and 6·38 ppm (q, 1, J_{tot} = 18·5 Hz, H—C—NO).

Pinol nitrolpiperidide (**36**) was prepared as described by Wallach[4] and was recrystallized from hexane–EtOAc to give colorless cubes, m.p. 158–159°; lit.[4] m.p. 154°; IR ($CHCl_3$) 2·80, 3·07, 7·32, 8·32, 8·99, 9·47, 9·84, 10·07, (bd, 1, H—C—O), and 9·76 ppm (s, 1, =NOH).

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