REDUCTIVE TRANSFORMATION OF A HYDROXYIODOKETONE OF 8-AZABICYCLO[3.2.1]OCTANE INTO 7-AZABICYCLO[2.2.1]HEPTANE WITH LITHIUM ALUMINIUM HYDRIDE¶

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ABSTRACT

1α,4β-Diodo-2α-acetoxytropan-3-one (2) and 1α-iodo-2α-acetoxytropan-3-one (3), which comprise 64% of products emerging from the lead tetraacetate oxidation of tropan-3α-ol in presence of iodine, were subjected to lithium aluminium hydride reduction. The expected 2.3-dihydroxytropane was not obtained. Instead, a diol which was not prone to periodate oxidation, containing one primary and one secondary alcoholic groups was obtained. It was assigned the 1-hydroxymethyl-2α-hydroxy-7-methyl-7-azabicyclo[2.2.1]heptane structure (8), on the basis of spectroscopic evidences (ir, nmr and mass spectrometry) and some chemical transformations [formations of a cyclic sulfite (9), an epichlorohydrin (11) and 1-methyl-2α-hydroxy-7-methyl-7-azabicyclo[2.2.1]-heptane (12)]. The reaction is understood as an initial β-elimination process, triggered by the delivery of hydride ion to the carbonyl function in the sequence 3 → 21 → 22, yielding a highly reactive enolate aldehyde (22) which is prone to an immediate internal aldol condensation (22) → (23) ⇄ (24), affording the observed diol (8) on further reduction of the aldehydic group by $LiAlH_4$. The reductive deiodination of (3) into 2α-acetoxytropine (2b) or into 2α-hydroxytropan-3-one (25) was smoothly achieved by means of hydrogenation over Raney Nickel on mild basic conditions.

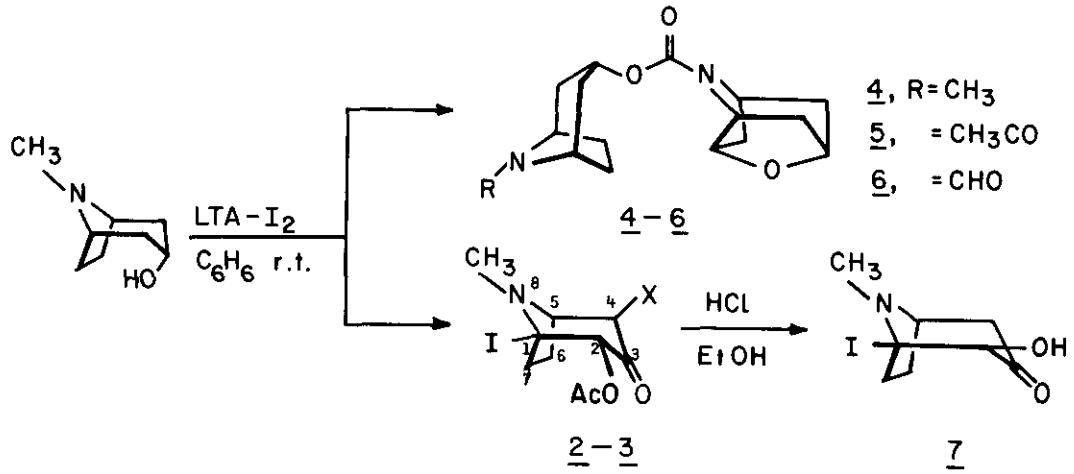
Unlike the tropane derivatives (1, 26-28) which under electron impact enter into two distinctly different modes of fragmentation, the 7-azabicyclo[2.2.1]heptane framework in (8)-(12) characteristically favor one mode by which carbon-2 and carbon-3 are lost and the methylene pyrrolenium ion emerges as the most prominent ion in their spectra.

¶Dedicated to Professor Tetsuji Kametani on the occasion of his retirement.

The emergence of 1α,4β-diiodo-2α-acetoxytropan-3-one (2, 55%) and 1α-iodo-2α-acetoxytropan-3-one (3, 9%), together with three dimeric products: (4, 18%), (5, 12%), and (6, 4%), from the lead tetraacetate oxidation of tropan-3α-ol (1) in presence of iodine (see scheme 1) was reported earlier in a preliminary communication.[1,2] This paper concerns a study of an anomalous reaction encountered in an attempt to convert (3) into 2α,3α-dihydroxytropane desired for a structural elucidation study.

The major $C_{10}H_{13}I_2O_3N$ (2, m.p. 185°, yellowish-green) product was easily converted to the mono-iodo product (3, colorless) on short exposure to aqueous $NaHSO_3$ solution. The nmr spectrum of of (2) displays three signals attributable to the existing three different protons, as follows: (i) a double-doublet at τ4.75; (ii) a singlet at 5.45, and (iii) a q at 6.32. The signals of methylene protons appear in the 7.3-8.8 region. The signal at 5.45 disappears on passage to (3), whereas the quintet at 6.32 changes to a multiplet on 2 → 3 conversion. In the iodo-ketol (7, see scheme 1), the proton at C-2 α to the hydroxyl resonates at τ 5.90 (instead of 4.75 for the same proton in 3). It is thus evident that the quintet for (2) should be assignable to the bridgehead proton (C-5), and the singlet at τ 5.45 to C_4-H in (2). The presence of a carbonyl function on C-3 will be evident in the sequel. The reduction of (3) with $LiAlH_4$ was rapid and smooth, affording a colorless $C_8H_{15}O_2N$ compound demonstrating no tendency to undergo C-C cleavage on oxidation with periodic acid. Its ir spectrum indicates the presence of hydroxyl absorptions

SCHEME 1



at 3340 cm^{-1} (sharp) and at 1055 and 1022 cm^{-1} (C-O). Its physical properties were not consistent with those of 2β,3α-, 2β,3β-, and 3α,6β-dihydroxytropanes recorded in the literature.[7] Nmr study indicated that the new reduction product in essence contain a N-methyl group (τ 7.85, s, D_2O) attributable to 7-azabicyclo[2.2.1]heptane framework, and only one bridgehead proton (τ 6.81, t, D_2O). It displayed resonances (6H between τ 7.3 and 8.7 (methylene protons); a singlet (2H) at τ 5.85 attributable to methylene protons α to OH; a double-doublet at τ 5.25 (1H) assignable to a tertiary proton α to OH; a triplet at τ 6.81 (1H) assignable to a bridgehead proton. The new diol reacted with CH_3I to give a methiodide, in which the bridgehead proton in the starting compound experience downfield shift to τ 5.95, displaying two distinctly different methyl proton resonances around τ 6.9, consistent with structure (8).

In analogy to 1,2- and 1,3-diols, (8) entered readily into ester exchange reaction with dimethyl sulfite at 120° to yield a six-membered cyclic sulfite.[8] It is well established that 1.3-cyclic sulfites prefer the rigid chair conformation with the S=O bond axial.[9] The stretching frequency of an *axial* S=O in a 6-membered cyclic sulfites occurs at 1190 ± 5 cm^{-1}, and at 1230 cm^{-1} for an *equatorial* S=O.[9] On this basis we assigned an *axial* S=O to the cyclic sulfite from (8) since it displays a strong absorption band at 1200 cm^{-1} and should therefore be formulated as having structure (9).

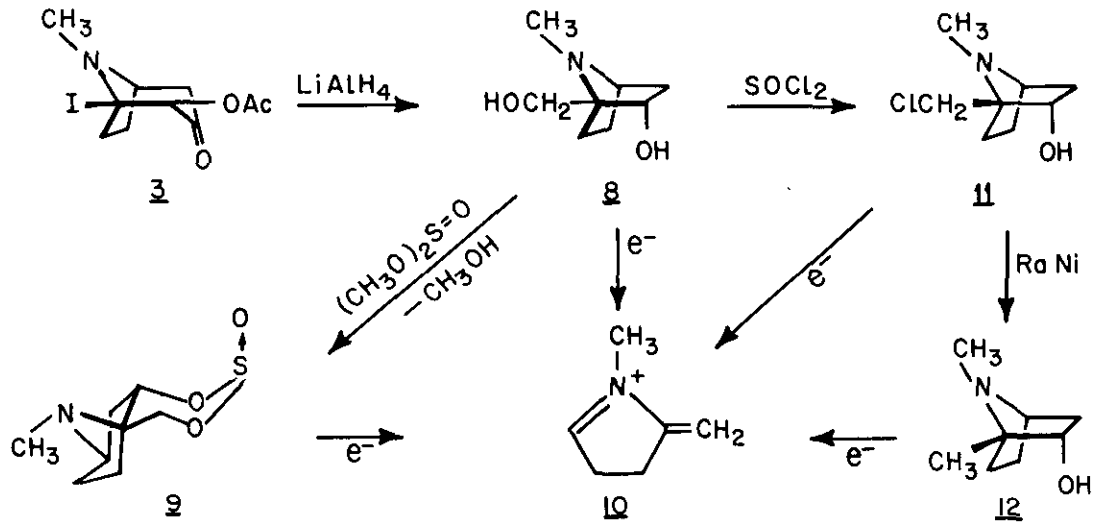
The *axial* C-2 proton in (9) is disposed parallely to the *axial* S=O bond and therefore is expected to experience deshielding effect, as is the case ($\Delta\delta$ = 33.6 Hz),[10] indeed.

The mass spectrum of (9) does not exhibit a molecular ion peak ($M^{+\cdot}$), but it shows a peak at m/e 139 (38%), corresponding to a M-SO_2 fragment, and a base peak at m/e 96 (100%) corresponding to N-methyl 2-methylenepyrrolenium ion (10).[11]

The presence of two distinctly different types of alcoholic group is implied from the emerging chlorohydrin of structure (11), from the reaction of (8) with $SOCl_2$, whereby only the primary alcohol underwent the chlorination reaction. On catalytic hydrogenation with the aid of Raney Nickel W-2[12] the chlorohydrin (11) was hydrogenolyzed to give the corresponding amino-alcohol (12). The signal appearing at τ 6.30 (2H, d,J=2Hz) in (11), attributable to the CH_2Cl protons, does not appear in the nmr spectrum of (12). Instead, a singlet at τ 8.72 (3H) appears in conformity with structure (12) (see Scheme 2).

Unlike (9), diol (8) itself, as well as its derivatives, (11) and (12), all exhibit the respective molecular-ion peaks and a base peak at m/e 96, probably of structure (10).[13]

SCHEME 2

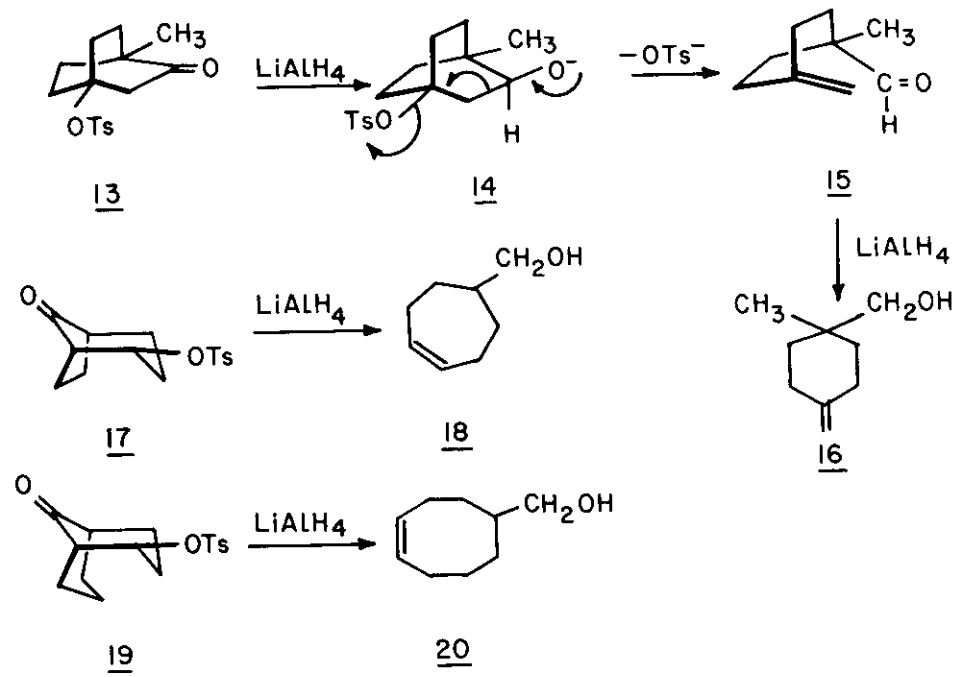


REACTION MECHANISM

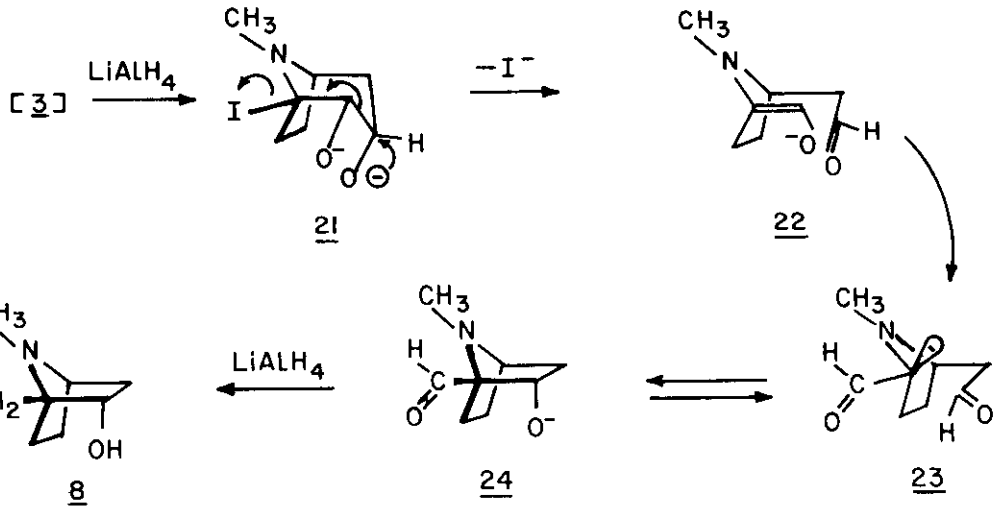
Clearly, the chemical events involved in the (3) → (8) conversion comprise most likely bond-breaking of the C-I and the C-C types, and consequently two types of bond-forming processes, of the C-C and C-H types. The breakings of the C-I and the C-C bonds in (3) could be the sequence of a synchronous process resembling the 13 → 16, 17 → 18, and the 19 → 20 fragmentations initiated by $LiAlH_4$.[14] *The 13 → 16 conversion is understood to be triggered by delivery of the hydride ion to the carbonyl function, followed by a synchronous β-elimination in the sequence 13 → 14 → 15 → 16 (see Scheme 3). Analogous events in (3) should lead to an enolate ion (22) of a pyrrolidine-dialdehyde species (23) in the sequence 3→21→22⇄23 (see Scheme 4). The respective dialdehyde from (23) could not be isolated since its carbanion oribtal is perfectly aligned for carbanion attack on the aldehydic carbon to effect C-C bond formation to yield the mono-aldehyde (24) which on further reduction with $LiAlH_4$ affords the rearranged diol (8).*

It is clear from the foregoing that to effect deiodination in (3) one must avoid the formation of a di-anion such as (21). Towards this end we tried to apply the catalytic hydrogenation methods,[15] *which proved to be most successful. Depending on conditions, we were able to obtain either the 2α-hydroxytropan-3-one (25), or, the 2α-acetoxytropan-3α-ol (26), which, in turn, could be reduced to tropan-2α-ol (28), either by the Huang-Minlon method (modified Wolff-Kishner),*[16]

SCHEME 3



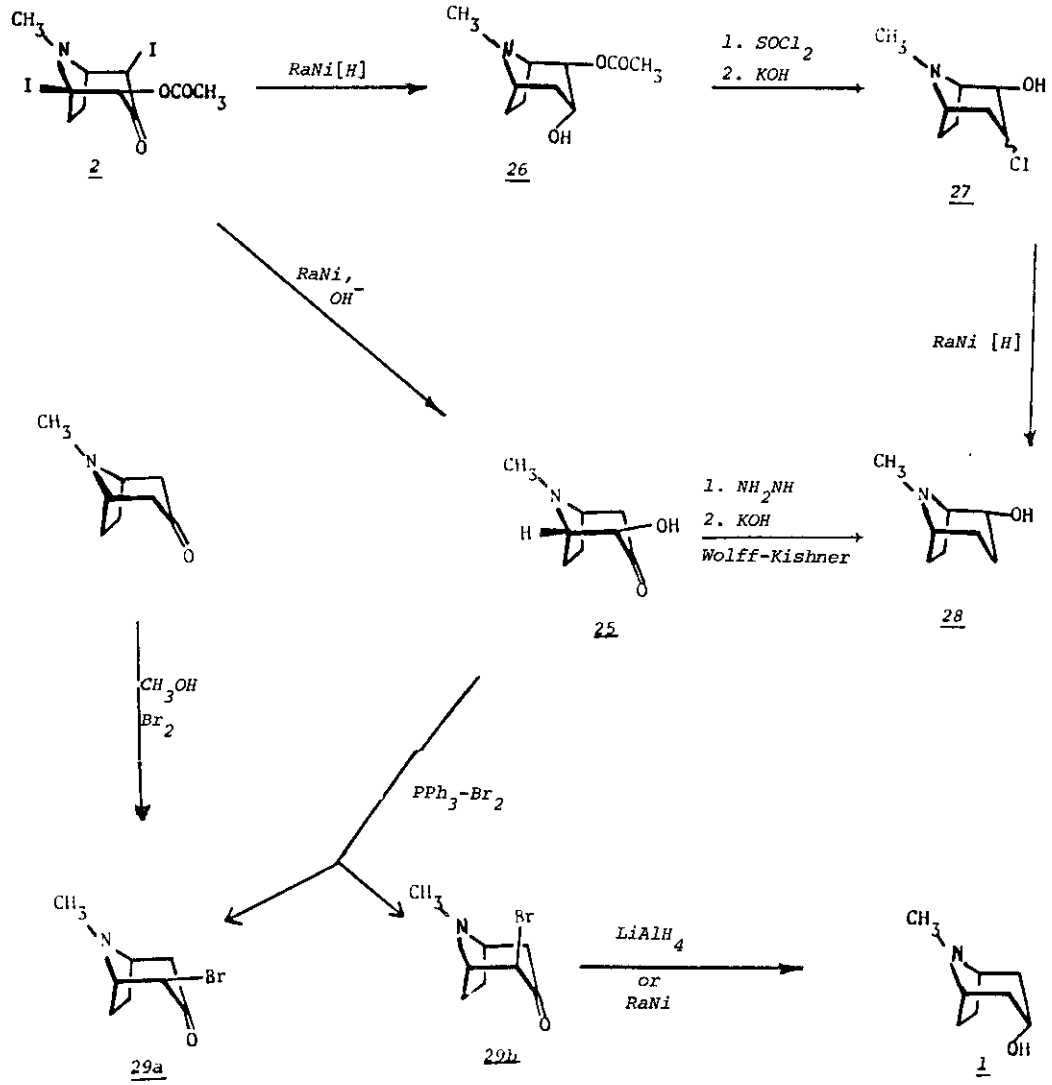
SCHEME 4



25 → *28*, *or, via chlorination-Raney-Nickel hydrogenation in the sequence* *26*→*27*→ *28* *(see Scheme 5).*[17] *This clearly indicates that the acetoxy group in (2), or in (3), resides on carbon-2.*

To establish conclusively the site of the carbonyl in (2) or in (3), the hydroxy-ketone (25) was first converted into 2α-bromotropan-3-one (29) by means of bromine-triphenylphosphine complex[18,19]*, and then reduced to tropan-3α-ol by* $LiAlH_4$ *(see Scheme 5).*

SCHEME 5



MASS SPECTRA.

Under electron impact, all compounds included in this study produce the respective molecular ions, the relative abundances of which vary dramatically with the bicyclic framework and substitution. Examining of Table 1 reveals that change of framework from 8-azabicyclo[3.2.1]octane (1, 26-28)

Table 1. Relative Peaks of Prominent Ions in Mass Spectra of compounds 1, 8-12, 26-28.

Compound	Molecular Ion m/e (%)	$M-C_2H_4$ m/e (%)	m/e	Base Peak m/e	Structure
Tropan-3α-ol (1)	141 (24)	113 (20)	96 (72)	82	
Tropan-2α-ol (28)	141 (52)	113 (8)	-	96	
2α-Acetoxytropan-3α-ol (26)	199 (26)	171 (2)	156 (24)	95	
3-Chloro-2α-acetoxytropane (27)	175 (3) 177 (1)	-	140 (74)	82	
Diol (8)	157 (8)	129 (2)	-	96	10
Cyclic Sulfite (9)	203 (0)	-	139 (38)	96	10
Chlorohydrin (11)	175 (23) 177 (9)	147 (2)	140 (7)	96	10
Methylamino alcohol (12)	141 (41)	113 (5)	-	96	10
Methiodide of diol-8	-	-	171 (9) 157 (18)	142	

to 7-azabicyclo[2.2.1]heptane (8-12) imply in general lowering of molecular-ion stabilities, probably because of increase in internal strain. In the 8-azabicyclo[3.2.1]octane series, an introduction of the 2α-acetoxy substituent close to hydroxyl group at C(3) causes no significant change in the molecular-ion stability against tropan-3α-ol, but, on the other hand, replacement of the hydroxyl by a chlorine group (from 26 to 27) entails dramatic drop in the molecular-ion stability. The case is just the opposite in the bicyclo[2.2.1]heptane series indicating that the replacement of the primary hydroxyl group (8) by a chlorine atom (compound 11) augments the relative abundance of the molecular-ion. Positional change of the hydroxyl group in (1) from C(3) to C(2) (from 1 to 28) appears to enhance considerably the molecular-ion stability. Another aspect worthy of note relates to modes of fragmentation. Two important modes of rupture of the bicyclic framework operate in tropane series. One, rupture of the C(5)-C(7) bond causing the loss of carbon atoms 6 and 7; the second, rupture of the alternate C(1)-C(2) bond leading to appearance of pyrrolenium ions, of which (10) is a representative.[13] In the bicyclo[2.2.1]heptane series (8-12) only the second mode of mass spectral fragmentation appears to be prominent. This behaviour is understandable, since primary cleavage is likely to be

favored between the two functionalized carbon atoms[20] (C-1 and C-2) in (8)-(12). A prominent-ion m/e 139 in the mass spectrum of (9) correspond to M-SO_2 which is characteristic of cyclic sulfites.[11]

A complete change in the mass spectral fragmentation patterns occurs when the diol (8) is converted to the respective methiodide. The base peak in the spectrum of the methiodide occurs at m/e 142, assignable to an ionic fragment [M-CH_3I-CH_3] resulting from losses of CH_3I and CH_3 radical. This suggests that cleavage of C-C bond next to a nitrogen atom is no longer favored when it is quaternarized. However, this is not the case with picrates which exhibit the molecular-ion and the base peak of the free base.

The mass spectra of the iodo-hydroxytropanones (2, 3 and 7) merits a more thorough discussion which will be enunciated in a forthcoming communication.[21]

EXPERIMENTAL SECTION.

Infrared (ir) spectra were recorded on a Perkin-Elmer 237 spectrometer and uv spectra on a Unicam Model Sp 800A spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained with Jeol C-60-H, and with Varian HA-100 instruments with an Me_4Si internal standard. Mass spectra were taken on a Varian MAT CH-5 spectrometer using the direct inlet system. The electron energy was maintained at 70 eV and the ionization current was maintained at 20 μA. The abundances of ions from primary fragmentations are given in percentages relative to the highest peak in the spectrum (base-peak). Thin layer chromatographies were performed on silica gel plates.

Chemicals. Lead tetraacetate was prepared according to the literature.[22] Thionyl chloride was purified by the method of Friedman and Wetter.[23]

Raney Nickel 28 in water is a product of W.R. Grace & Co. Davison Chemical So. Pittsburg, Tennessee. Raney Nickel W-2 was prepared according to Mozingo.[12] Silica gel for column chromatography, a product of Hopkins and Williams Lab Reagents. Kieselgel G.F.$_{254}$ (KGF$_{254}$) a product of E. Merck, Darmstadt, Germany.

Lead Tetraacetate (LTA) Oxidation of Tropan-3α-ol (1) in presence of Iodine. Isolation of 1α,4β-diiodo-2α-acetoxytropan-3-one (2) and 1α-iodo-2α-acetoxytropan-3-one (3). To a saturated solution of iodine (76.2 gr, 0.3 moles) in dry benzene (300 ml) was added at 20°C freshly prepared LTA[18] (266 gr, 0.6 moles) portionwise with stirring during 15 min., and then a solution of chemically pure tropan-3α-ol (42.3 gr., 0.3 moles) in dry benzene (300 ml) was added dropwise

over 30 minutes. Stirring was continued for 48 hrs. at r.t. At the first three hours, the appearance of a viscous brown precipitate was noted, which after a few hrs. was transformed into a yellow powder. The supernatant was filtered, the precipitate washed with benzene and treated separately, from which compounds (4), (5) and (6) were isolated and characterized. The filtrates and washings are combined and its volume reduced to 60 ml by evaporation. After standing in a cold room, green-yellow crystals (40 g) of (2) crystallized out of solution and were collected by filtration. Recrystallization from either ethanol or CCl_4 yielded crystals, m.p. 184-185°C; ir (KBr): 1760, 1745 (C=O), 173 (ester), 1050s (C-O) cm^{-1}; nmr ($CDCl_3$, in τ) 4.75 (1H, dd, H-2), 5.45 (1H, s, H-4), 6.32 (1H, qu, H-5), 7.25 (3H, s, N-CH_3), 7.95 (3H, s, $COCH_3$). Anal. Calcd. for $C_{10}H_{13}I_2NO_3$: Mol.wt. 449; C, 26.74; H,2.92; N,3.12; I,56.53. Found: C,26.93; H,2.86; N,3.09; I,56.90.

Isolation of 1α-iodo-2α-acetoxytropan-3-one (3). The filtrate remaining after separation of (2) was concentrated and the undistillable residue was dissolved in $CHCl_3$, chromatographed on silica gel column (1 kg), using first 70:30 mixture of petruleum ether (40-60°)-ether, and then ether as developing solvents. The residue obtained after removal of the solvent was recrystallized from CCl_4, yielding colorless crystals (3), m.p. 137°; ir (KBr) cm^{-1}: 1760 (C=O), 1730 (ester), 1060 m, 1035 (C-O); nmr ($CDCl_3$ τ): 4.70 (1H, dd, H-2), 6.25 (1H, m, H-5), 7.25 (3H, s, N-CH_3), 7.92 (3H, s, $COCH_3$). Anal. Calcd. for $C_{10}H_{14}INO_3$: Mol.wt. 323.14; C,37.17; H,4.37, N, 4.33; I,39.28. Found: Mol.wt. 323 (mass spectra); C,36.92; H,4.25; N,4.24; I,39.25.

Picrate of 1α-iodo-2α-acetoxytropan-3-one melted at 191-193°. Anal. Found for $C_{16}H_{17}IN_4O_{10}$, C,35.87; H,3.24; N,10.20; I,23.37.

The hydrochloride [(2)·HCl], m.p. 198-202; ir(cm^{-1}) (KBr): 2500 (N-H), 1770 (C=O), 1750 (ester), 1070 m, 1045 m (C-O); nmr (D_2O, τ): 4.55 (1H, H-2), 5.5 (1H, H-5), 6.82 (3H, s, N-CH_3), 7.9 (3H, s, $COCH_3$).

The hydroiodide [(2)·HI], m.p. 207-210°. Anal. Found for $C_{10}H_{15}I_2NO_3$: C,27.54; H,3.58; N,3.06; I,56.00.

Conversion of (2) into (3). A solution of 5 gr of (2) in 200 ml $CHCl_3$ was shaken with a solution of 5 gr $NaHSO_3$ in 5 ml H_2O for 90 min. The organic layer was separated, the solvent was removed and the residue (3.62 gr) was recrystallized from CCl_4, yielding (3), m.p. 134-6°.

Formation of 1α-iodo-2α-hydroxytropan-3-one (7). Acid hydrolysis of (3). To a solution of 4 gr of (3) in 500 ml pure ethanol was added a saturated solution of hydrogen chloride in 30 ml ethanol. The mixture was refluxed for 2 hrs. and the resulting blue solution was cooled and left to crystallize yielding 3.78 gr. of a grey material, identified as 1α-iodo-2α-hydroxy-tropan-3-one hydrochloride, m.p. 214° (from ethanol). Ir (cm^{-1}) (KBr): 2550, 2620 ($\overset{+}{N}H$), 1762 (C=O), 1082m, 1055m (C-O); nmr (D_2O, τ): 5.7 (1H, dd, H-2), 5.5 (1H, m, H-5), 6.92 (3H, s, $N-CH_3$). Anal. Found for $C_8H_{13}ClINO_2$: C,30.28; H,4.10; N,4.21; I,40.60.

The free base (7), m.p. 154-156° (from petroleum ether 40°) was obtained after neutralization of the aqueous solution of (7)·HCl by K_2CO_3. IR (cm^{-1}) (KBr): 3480, 3150 (OH), 1752 (C=O), 1065, 1040 (C-O); nmr ($CDCl_3$, τ): 5.9 (1H, dd, H-2), 6.23 (1H, m, H-5), 7.28 (3H, s, $N-CH_3$). Anal. Found for $C_8H_{12}INO_2$: C,34.23; H,4.21; N,4.81; I,45.24. Mol.wt. 281.

Preparation of 1-Hydroxymethyl-2α-hydroxy-7-methyl-7-azabicyclo[2.2.1]heptane (8) from $LiAlH_4$ Reduction of (3). To a solution of 13.1 gr. of (3) in 1.5 lit. of dry ether was added portionwise (30 min.) with stirring lithium aluminium hydride (3.3 gr.) and the stirred reaction mixture was left at r.t. for 12 hrs. Excess of $LiAlH_4$ was destroyed by first adding dropwise a 1:1-mixture of ethanol:ether (100 ml) and then 50 ml H_2O. After filtration and removal of the solvent from the filtrate, the crude diol (8) was first crystallized from acetone and then from $CHCl_3$, yielding 4.7 gr. (74%) of colorless crystals, m.p. 188-189°.
Ir (cm^{-1}) (KBr): 3340 (OH), 1085s, 1055s, 1032m, 1020m (C-O); nmr (pyridine d_5, δ in τ): 5.25 (1H, d.qr, H-2), 5.85 (2H, s, OCH_2), 6.81 (1H, t, H-4), 7.66 (3H, s, $N-CH_3$); (in DMSO d_6): 6.11 d.qr , 6.28s, 6.81t, 7.85s. Anal. Found for $C_8H_{15}NO_2$: C,61.13; H,9.46; N,9.01; Mol.wt. 157 (ms).

The hydroiodide, m.p. 240-242°, was prepared by dissolving 181 mg of (8) in 20 ml 40%-HI at 45°, removal of H_2O in vaccuo, and recrystallization from ethanol-ether. Ir(cm^{-1})(KBr) : 3375 (OH), 2840, 2580 ($\overset{+}{N}H$), 1080s, 1045s, 1060m, 1025m; nmr (D_2O, τ) 5.5 (1H, H-2), 5.97 (1H, t, H-4), 6.15 (2H, s, CH_2O), 7.25 (3H, s, $N-CH_3$). Anal. Found for $C_8H_{16}INO_2$:C,33.60; H,5.83; N,4.95; I,44.96.

The picrate of (8) melted at 243-245°, and the benzoate had m.p. 131-133°.

1-Chloromethyl-2α-hydroxy-7-methyl-7-azabicyclo[2.2.1]heptane (11). Diol (8) (0.5 gr.) was dissolved in 5 ml. of purified $SOCl_2$, and 0.5 ml of DMF (dried over KOH) was added, and the resulting mixture was refluxed for 22 hrs.[11] Excess $SOCl_2$ is removed first by evaporation (vaccuo) and then with

the aid of acetone. This yielded 450 mg of the hydrochloride of the chlorohydrin (11), m.p. 220°. Ir (cm^{-1}) (KBr): 3230 (OH), 2740, 2770($\overset{+}{N}H$), 1085m, 1065s, 1040m, 1010m (C-O), 750 (C-Cl); nmr (D_2O, τ) 5.4 (1H, H-2), 6.0 (1H, H-4), 6.05 (2H, s, CH_2-Cl), 7.25 (3H, s, N-CH_3). Anal. Found for $C_8H_{15}Cl_2NO$: C,44.78; H,6.73; N,6.28, Cl,33.10.

The free base (11), m.p. 76-81° (from petruleum-ether 40°), resulted after adding K_2CO_3 to the aqueous solution of the hydrochloride. Ir (cm^{-1}) (neat) : 3100-3350 (OH), 1080s, 1030s (C-O), 740 (C-Cl); nmr (pyridine d_5, τ): 5.42 (1H, d.qr, H-2), 6.08 (2H, d J 6 Hz, CH_2-Cl), 6.85 (1H, t, H-4), 7.82 (3H, s, N-CH_3); in $CDCl_3$: 5.78(d.qr H-2), 6.3(d J 2 Hz CH_2-Cl), 6.80(t H-4), 7.82s (N-CH_3). Anal. Found for $C_8H_{14}ClNO$: C,54.49; H,8.10; N,7.29; Cl,19.30.

1.7-Dimethyl-2-hydroxy-7-azabicyclo[2.2.1]heptane (12). Into a hydrogenation bottle of Parr Hydrogenator is placed a mixture of the chlorobydrine (11) hydrochloride (422 mg), 20 ml of H_2O, 300 mg K_2CO_3 and 3 gr. Raney Nickel W-2 and then subjected to usual catalytic hydrogenation under 1.5 atmospheric pressure of H_2 for 1 hr. at r.t. After the usual work up the chloroform solution of the product was dried (Na_2SO_4), the solvent removed and the pure product (12) was obtained (185 mg) in the form of its hydrochloride [(12)·HCl], m.p. 308-312° (dec.). Ir (cm^{-1}) (KBr): 3290 (OH), 2770, 2570($\overset{+}{N}$-H), 1080s, 1060m, 1030m, 1010m (C-O); nmr ($CDCl_3$, τ): 5.5 (1H, d.qr, H-2), 6.12 (1H, t, H-4), 7.35 (3H, s, N-CH_3), 8.45 (3H, s, CH_3-C). Anal. Found for $C_8H_{16}NClO$: C,53.71; H,8.86; N,7.84; Cl,20.30.

The free base (12) exhibited peaks in the nmr spectrum at ($CDCl_3$, τ) : 6.15 (1H, d.qr, H-2), 6.88 (1H, t, H-4), 7.85 (3H, s, N-CH_3), 8.82 (3H, s, CH_3-C).

7.7-Dimethyl-1-hydroxymethyl-2-hydroxy-7-azabicyclo[2.2.1]heptane Iodide. Methiodide of (8). Method (a). To a solution of 470 mg (8) in 70 ml acetone, 1 ml of methyl iodide is added, well shaken, left for 48 hrs. at r.t., and the colorless small crystals (465 mg.) of the methiodide were collected. More crystals (290 mg.) were obtained on concentration of the supernatent solvent, m.p. 325-328° (dec.) (from EtOH). Method (b). Methyl iodide (1 ml.) was added to a solution containing 450 mg. of (8), K_2CO_3 (700 mg.), ethanol (50 ml.) and H_2O (30 ml.), and the mixture was refluxed for 12 hrs., cooled, and the crystalline precipitate of the methiodide was collected m.p. 323-326°. Ir (KBr) (cm^{-1}): 3350 (OH), 1055, 1030 (C-O); nmr (D_2O,τ): 5.4 (1H, H-2), 5.9 (1H, H-4), 6.03 (2H, s, CH_2-O), 6.9 (6H, two s,CH_3-$\overset{+}{N}$-CH_3. Anal. Found for $C_9H_{18}NIO_2$: C,35.82; H,6.04; N,4.46; I,42.06.

Cyclic Sulfite (9) from ester exchange between diol (8) and dimethyl sulfite. Diol (8) (770 mg.) was allowed to enter into the ester exchange reaction with 1 ml. of dimethyl sulfite at 120° for 3 hrs. After cooling, the reaction product was triturated with petroleum-ether 40° and the resulting solid compound was recrystallized from acetone to yield a dihydrate of (9), m.p. 245-290° (hygroscopic). Ir(KBr)(cm^{-1}): 1200 (S=O), 1045, 1062 (C-O); nmr (D_2O, τ) : 5.55 (H-2), 6.2 (H-4), 6.25 (2H, OCH_2), 7.0 ($N-CH_3$); in $DMSO_{d_6}$: 5.2, 6.0, 6.06, and 6.85 ($N-CH_3$).

2α-Acetoxytropan-3-one. Reductive de-iodination of (3). A solution of (3) (4 gr) in ethanol (120 ml) was mixed with a solution of K_2CO_3 (1.68 gr.) in H_2O (2 ml), to which was then added 46 gr. of Raney Nickel 28 (suspended in 20 ml H_2O). The resulting mixture was stirred for 30 min. at r.t., then filtered and washed with ethanol. The liquid product (2.26 gr.) left after removal of ethanol was subjected to preparative thin-layer chromatography on plates of kieselgel G.F.$_{254}$ (E. Merck, Darmstadt, Germany), using $CHCl_3$ as developing solvent (Rf ∿ 0.15) to afford 2α-acetoxytropan-3-one (1.88 gr.) in a liquid form. Ir(neat)(cm^{-1}): 1740 (C=O), 1050, 1030 (C-O); nmr (neat, τ): 5.14 (1H, quintet, H-2), 6.52 (1H, d-like , H-1), 7.0 (1H, d-like, H-5 , 7.62 (3H, s, $N-CH_3$), 8.0 (3H, s, $COCH_3$). Anal. Found for $C_{10}H_{15}NO_3$: C,60.63; H,7.80; N,7.35. It is characterized by its conversion into its hydrochloride m.p. 224-226° (dec.). Anal. Found for $C_{10}H_{16}ClNO_3$: C,51.23; H,6.85; N,5.73; Cl, 15.31.

2α-Hydroxytropan-3-one (25). The acid hydrolysis of 2-acetoxytropan-3-one to 2α-hydroxytropan-3-one (25) was effected by refluxing an ethanolic solution of the keto-acetate (3.5 gr. in 130 ml. EtOH) to which a saturated solution of gaseous HCl in 30 ml dry EtOH was added, for 5 hrs. After the usual work up, the corresponding hydrochloride was isolated, m.p. 242° (dec.) (from ethanol). Ir(KBr) (cm^{-1}) : 3350, 3320 (OH), 2600, 2550 (NH), 1765 (C=O), 1080 (C-O); nmr (D_2O, τ) 5.6 (H-1), 6.18 (H-5), 7.1 (3H, s, $N-CH_3$). Anal. Found for $C_8H_{14}NClO_2$: C,49.96; H,7.45; Cl, 18.45.

The free base (25) was freed from its hydrochloride in the way already described here, m.p. 101-103° (from petroleum ether 40°). Ir(KBr)(cm^{-1}): 3400 (OH), 1740 (C=O), 1060 (C-O); nmr ($CDCl_3$): 7.02 (d-like, H-5), 6.1 (quintet, H-1). Anal. Found for $C_8H_{13}NO_2$: C,61.70; H,8.64; N,9.02.

The picrate of (25) melted at 211° (dec.). Anal. Found for $C_{14}H_{16}N_4O_9$: C,43.68; H,4.20; N,14.36.

2α-Acetoxytropan-3α-ol (26), m.p. 79-81° (benzene-petroleum-ether), was obtained (90% yield) as a consequence of the catalytic reduction of (3) (3 gr.) in 96% EtOH-H_2O (260 ml) containing K_2CO_3 (1.26 gr.) and 30 g. W-2 Raney Nickel at 15°C, under 1.5 atmospheric pressure of H_2 during 90 min. After the usual work up the liquid crude product was purified by thin-layer chromatography (Kieselgel G.F.$_{254}$). Ir(KBr)(cm^{-1}): 3420, 3110 (OH), 1720 (acetate), 1070w, 1045s (C-O); nmr ($CDCl_3$, τ): 4.8 (H-2, quartet), 5.2 (H-3, quintet), 6.83 (H-1, quintet), 7.15 (H-5, d-like), 7.55 (N-CH_3, s), 7.95 (COCH_3, s). Anal. Found for $C_{10}H_{17}NO_3$: C,60.0; H,8.64; N,7.28.

2α-Acetoxy-3-chlorotropane (27) resulted from refluxing (26) (1 g) with purified $SOCl_2$ containing DMF (1 ml.) during 22 hrs., followed by a work up already described above. It could not be induced to crystallize. Ir(neat)(cm^{-1}): 3560, 3350 (OH), 1060, 1045 (C-O); nmr ($CDCl_3$, τ): 5.32 (H-2, quint.), 6.12 (H-3, m), 6.78 (H-1 quart.), 6.96 (H-), 7.68 (N-CH_3, s). Anal. Found for $C_8H_{14}ClNO$: C,54.05; H,8.39; N,7.38; Cl,19.65.

Tropan-2α-ol (28). (a) *From catalytic reduction of* (27). An ethanolic solution of (27) (200 mg., in 0.4 ml of EtOH), and aqueous potassium carbonate (100 mg. in 2 ml. of H_2O) were mixed with 8 gr. Raney Nickel 28 and subjected to hydrogenation under 3.2 atmospheric pressure of H_2 at 25°C. As a consequence of the usual work up, pure tropan-2α-ol (28), m.p. 45-48°, could be obtained either *via its hydrochloride salt*, m.p. 266° (dec.), or from its *picrate*, m.p. 267°. (b) *From Wolff-Kishner reduction (Huang-Minlon modification) of 2α-hydroxytropan-3-one* (25). To a solution of (25) (1.5 gr.) in 15 ml. of EtOH, 2.3 gr. hydrazine hydrate was added, and then the mixture heated for 2 hrs. at 105°C. Solvent was removed by evaporation, and powdered K_2CO_3 (2.3 gr.) was added and the mixture was heated to 100° for 2 hrs., and an additional 1 hr., at 150°C, yielding 400 mg. of tropan-2α-ol, m.p. 45-48°. Ir (CCl_4)(cm^{-1}): 3330, 3625 (OH), 1062s (C-O); nmr ($CDCl_3$, τ): 6.2 (H-2, m), 6.95 (H-1 and H-5), 7.8 (N-CH_3, s). Anal. Found for $C_8H_{15}NO$: C,67.96; H,10.67; N,9.96.

The hydrochloride exhibited nmr signals in D_2O at (τ) : 6.0 (H-2), 6.2 (H-1 and H-5), 7.2 (N-CH_3, s). Anal. Found for $C_8H_{16}NClO$: C,53.83; H,9.15; N,7.70; Cl,20.00. Our 2α-hydroxytropane, and, both its hydrochloride and picrate,[13] showed identity in all respects with an authentic specimen kindly supplied by Professor R.L. Clark.[20]

2α- and 2β-Bromotropan-3-one (29a and 29b). To a cooled (ice-water) suspension of triphenylphosphine (860 mg.) in acetonitrile (35 ml), bromine (0.17 ml.) is added to produce the

$(C_6H_5)_3P \cdot Br_2$ complex. It was then allowed to react with 2α-hydroxytropan-3-one (25) (0.5 gr.) dissolved in 10 ml. of diethyleneglycol, first at r.t. for 10 min. and then at 72°C for 2 hrs. After cooling, removal of solvent and triphenyl oxide by washing with hot C_6H_6, a mixture(700 mg) of hydrochlorides of (29a) and (29b) was obtained, m.p. 288-290° (from ethanol). The separated free bases (29a) (400 mg. Rf ∿ 0.2) and (29b) were obtained by way of thin-layer chromatography on kieselgel-254, and ether as developing solvent.

2α-Bromotropan-3-one (29a), ir (KBr)(cm^{-1}) : 1750 (C=O), 720 (C-Br); nmr ($CDCl_3$, τ), 5.77 (H-2, d), 6.5 (H-1, d), 6.88 (H-5, d), 7.55 ($N-CH_3$, s).

2β-Bromotropan-3-one (29b), ir (KBr)(cm^{-1}) : 1718 (C=O), 700 (C-Br); nmr ($CDCl_3$, τ) : 5.05 (H-2, d), 6.5 (H-1, d), 6.88 (H-5, d), 7.39 ($N-CH_3$, s).

Conversion of (29a) + (29b) to (1). The hydrobromide salts of (29a) and (29b) (600 mg.) are dissolved in 10 ml. of H_2O to which is added an aqueous solution of K_2CO_3 and 7.5 gr. of Raney Nickel 28. The mixture was hydrogenated under 3.3 atm. H_2 during 90 min. and then worked up in the usual manner, yielding tropan-3α-ol (300 mg.) exhibiting identity in all respects with an authentic sample.

2α-, and 2β-Bromotropan-3-ones (29a and 29b), together with 2β,4β-dibromotropan-3-one and 2β-hydroxytropan-3-one, could be obtained through bromination of tropan-3-one by the method of Nickon[15] followed by thin-layer chromatography.

The bromo-tropanones (29a) and (29b) could be converted back into tropan-3-one by mixing 600 mg. of the respective hydrobromides in water (20 ml.) containing K_2CO_3 (350 mg.) and 7.5 gr. of Raney Nickel 28, and subjecting the resulting mixture to catalytic hydrogenation (3.3 atmosp. H_2 pressure, for 30 min.) followed by the usual work up.

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resulted in a doublet with J=11 Hz[5], clearly indicating strong spin interaction between the single proton C_2-βH and exo-endo protons on carbon-7 ("folded" or "zigzag" interaction[6]). Significantly, the C_4-αH which is disposed at 80°(Hehedral angle) relative to C_5-H, exhibits no spin interaction with C_7-H, as expected.

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