for 16 hr. The cooled mixture was washed twice with saturated $NaHCO_3$ solution and three times with H_2O and saturated brine and dried ($MgSO_4$). The benzene solutions were concentrated and then distilled through a short Vigreux column to give 26 g (85%) of **2a** as a colorless liquid: bp 125–129° (0.4 mm); uv max (C_2H_5OH) 221 nm (ϵ 4970); ir ($CHCl_3$) 1642 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.24 (s, 3) and 2.34 ppm (s, 3, 2 isoxazole-CH_3) and 3.95 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.10; H, 8.42; N, 5.72.

1,1-Ethylenedioxy-2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclohexane (2b).—This compound, prepared as described in the previous experiment from 2-[(3,5-dimethyl-4-isoxazolyl)methyl]-cyclohexanone,[3] was obtained in 86% yield as a colorless liquid: bp 126–132° (0.25 mm); uv max (C_2H_5OH) 222–223 nm (ϵ 4880); ir ($CHCl_3$) 1645 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.35 (s, 3) and 2.34 (s, 3, 2 isoxazole-CH_3), and 4.04 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.95; H, 8.25; N, 5.58.

1,1-Ethylenedioxy-2-(3-oxobutyl)cyclopentane (4a).—To a solution of 5.0 g (21 mmol) of **2a** in 100 ml of 3.2% ethanolic KOH solution was added 100 mg of 10% palladium on carbon catalyst and the resulting mixture was hydrogenated at atmospheric pressure and room temperature. After 8 hr, the uptake of hydrogen had ceased. The catalyst was removed by filtration and washed with fresh ethanol. The filtrates were concentrated at reduced pressure to approximately 30 ml. To this solution of the vinylogous amide **3a** was added 100 ml of 20% aqueous KOH solution and the resulting mixture was degassed, placed under nitrogen, and heated at reflux overnight. The cooled solution was extracted with benzene. The benzene solutions were washed with saturated brine and dried ($MgSO_4$). Solvent removal, followed by distillation, gave 3.52 g (83%) of **4a** as a colorless liquid: bp 85–90° (0.35 mm); no uv absorption; ir ($CHCl_3$) 1723 cm^{-1} (CH_3CO-); nmr ($CDCl_3$) δ 2.12 (s, 3, CH_3CO-), 2.45 (t, 2, J = 7 Hz, $-CH_2COCH_3$) and 3.90 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.73; H, 8.98.

1,1-Ethylenedioxy-2-(3-oxobutyl)cyclohexane (4b).—This compound, prepared by the method described in the previous experiment, was obtained in 84% yield as a colorless liquid, bp 96–101° (0.3 mm), which solidified upon standing to a white solid: mp 38–40°;[11] no uv absorption; ir ($CHCl_3$) 1710 cm^{-1} (CH_3CO-); nmr, ($CDCl_3$) δ 2.15 (s, 3, CH_3CO-), 2.45 (t, 2, J = 7 Hz, $-CH_2COCH_3$), and 3.96 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.19; H, 9.70.

4,4a,5,6,7,8-Hexahydronaphthalen-2(3*H*)-one (5b).—To a solution of crude keto ketal **4b**, prepared as described above from 6.00 g of isoxazole ketal **2b**, in 60 ml of methanol was added 6 ml of 4 *N* HCl and the resulting mixture was heated at reflux under nitrogen for 3 hr. The solution was cooled, poured into H_2O, and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried ($MgSO_4$). Solvent removal followed by distillation gave 2.73 g (76%) of colorless liquid: bp 70–76° (0.25 mm) [lit.[5] bp 135–138° (15 mm)]; uv max (C_2H_5OH) 237 nm (ϵ 14,100) and 308–310 (60); ir ($CHCl_3$) 1719, 1675 (~1:4, $-CH_2CO-$ and C=CHCO–) and 1625 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.85 ppm (s, 0.8, =CHCO–).

In a separate preparation, the crude octalone mixture was treated with 2,4-dinitrophenylhydrazine to give 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 2,4-dinitrophenylhydrazone, mp 170–172° (lit.[5] mp 168–170°), in 78% yield after crystallization from ethyl acetate.

2,3,7,7a-Tetrahydroindan-5(6*H*)-one (5a).—Crude 1,1-ethylenedioxy-2-(3-oxobutyl)cyclopentane (**4a**), prepared from 5.0 g of isoxazole ketal **2a**, was treated with HCl in ethanol as described in the preceding experiment. The resulting colorless oil [2-(3-oxobutyl)cyclopentanone (**7**), ir ($CHCl_3$) 1748 (cyclopentanoe C=O) and 1710 cm^{-1} (CH_3CO-)] was dissolved in 50 ml of 2% methanolic NaOH. The resulting solution was heated at reflux under nitrogen for 3 hr, cooled, diluted with H_2O, and extracted with benzene. The benzene extracts were washed with saturated brine and dried ($MgSO_4$). Solvent removal and distillation gave 1.64 g (57%) of **5a** as a colorless liquid: bp 60–68° (0.25 mm) [lit.[5] bp 80–81° (0.4 mm)]; uv max (C_2H_5OH) 237 nm (ϵ 13,090) and 310 (60); ir ($CHCl_3$) 1750 (weak, cyclopentanone C=O) and 1670 cm^{-1} (C=CHO–); nmr ($CDCl_3$) δ 3.20 (q, ~0.1, J = 14 Hz, $CH_2C=O$) and 5.88 ppm (q, ~0.95, J = 1 Hz, =CHC=O); semicarbazone mp 217–219° (1-butanol) (lit.[5] mp 214–219°).

Registry No.—**2a**, 34803-84-4; **2b**, 34769-83-0; **4a**, 34803-85-5; **4b**, 34769-84-1; **5a**, 1489-28-7; **5b**, 1196-55-0.

Acknowledgment.—We would like to express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche for their assistance in this work.

Compounds Affecting the Central Nervous System. I. Tropane-2β,3β-diol Derivatives. A Reverse Ester of Cocaine

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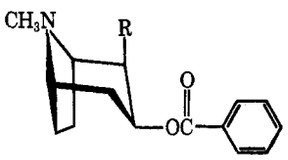
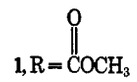
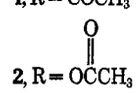
Investigation of all possible modifications of a known drug has been one of the approaches used to find better therapeutic agents. A drug having an ester group can typically be modified by formation of a "reverse ester." It appeared to us that the reverse ester **2** of cocaine (**1**)





1, R = $COCH_3$



2, R = $OCCH_3$

might have an activity profile more interesting than that of cocaine.

The most convenient intermediate for the preparation of **2** was tropane-2β,3β-diol (**7**), a compound first prepared by Einhorn and Fischer[1] and later characterized fully by Davies, Jones, and Pinder.[2] Large-scale preparation of **7** has now been achieved by permanganate oxidation of ethyl nortrop-2-ene-8-carboxylate (**5**) followed by reduction with $LiAlH_4$.

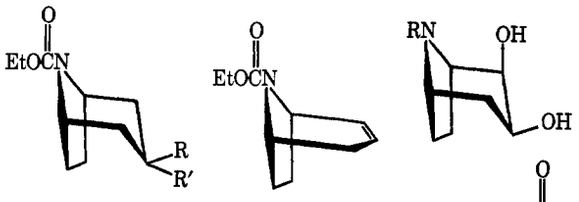
A method for the preparation of precursor **5** (see Experimental Section) involved dehydration of alcohol **3**. This alcohol, with its hydroxyl group in the axial position, was formed along with the equatorial epimer **4** (3:1 ratio) when ethyl 3-oxonortropane-8-carboxylate[3] was reduced catalytically (Pt in EtOH or HOAc) or by hydrides [$NaBH_4$ in MeOH or LiAl (*tert*-OBu)$_3$H in THF]. The role of the basic nitrogen in steric control of catalytic hydrogenation was illustrated here when tropan-3-one (basic N) was reduced catalytically (Pt in

(1) A. Einhorn and L. Fischer, *Chem. Ber.*, **26**, 2008 (1893).
(2) W. A. M. Davies, J. B. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3504 (1960).
(3) B. J. Calvert and J. D. Hobson, *ibid.*, 2723 (1965).

TABLE I
CHEMICAL SHIFTS, PPM ($CDCl_3$)

Compd	H_1	H_5	H_2	H_3	NCH_3	$OCCH_3$	C_6H_5
8[a,b]	3.1	3.1	3.8	4.9	2.4		7.3–8.3
9[c,d]	3.4	3.1	5.0	3.9	2.3		7.5–8.1
10[a,b]	3.3	3.1	5.0–5.5	5.0–5.5	2.4		7.0–8.1
12[a,d]	3.1	3.1	3.7	4.8	2.3	2.0	
13[a,d,e] (HCl salt)	4.0	4.0	5.2	5.2	2.9	2.3, 2.0	
2[a,b]	3.2	3.2	5.2	5.2	2.3	2.1	7.1–8.3
11[c,f]	3.4	3.2	5.1	5.1	2.3	1.9	7.3–8.2

[a] 60 MHz. [b] 20% solution. [c] 100 MHz. [d] 10% solution. [e] 11.7 ppm (NH^+), vanishes in D_2O; 2.9 ppm (d, 3 H, NCH_3) $\xrightarrow{D_2O}$ 2.9 ppm (s, 3 H, NCH_3). [f] 7% solution.

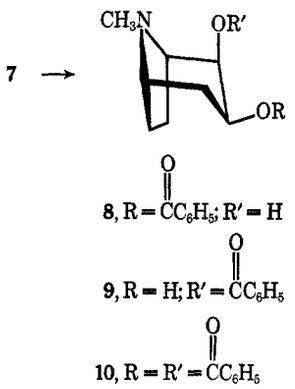


3, R = H; R′ = OH
4, R = OH; R′ = H
5
6, R = EtOC
7, R = CH_3

EtOH or HOAc) to give tropan-3α-ol as the exclusive product.[4]

The next phase of the problem involved benzoylation at C-3. On the basis of the difference in rates for acylation of equatorial *vs.* axial hydroxyl groups,[5] the desired 3β-benzoate (equatorial) should predominate. However, House, *et al.*,[6] have shown that a tertiary nitrogen atom adjacent to an axial hydroxyl group can increase the rate of acylation of the latter through acyl transfer from an intermediate acyl ammonium ion.

When diol **7** was treated with 1 equiv of benzoic anhydride in pyridine and the reaction mixture was worked up in the customary manner, the 3β-benzoate **8**



8, R = CC_6H_5; R′ = H
9, R = H; R′ = CC_6H_5
10, R = R′ = CC_6H_5

was isolated as the major product, together with a small amount of the 2β-benzoate **9** and a very small amount of dibenzoate **10**.

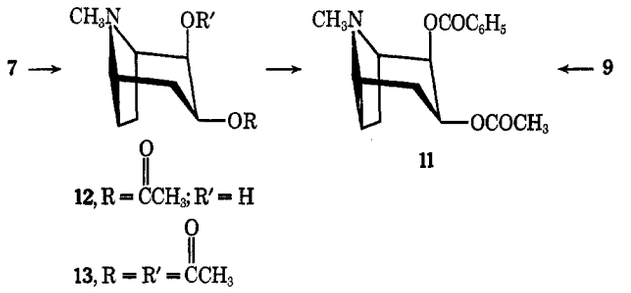
The 3β-benzoate **8** was readily identified by its physical properties. The infrared spectrum (CCl_4) of this 3-benzoate with its axial hydroxyl group at C-2 had a band at 3465 cm^{-1} that persisted even on dilution to a 0.001 *M* concentration, a characteristic of expected intramolecular hydrogen bonding with the nitrogen.[2]

Its nmr spectral signals are recorded in Table I and corroborating spin-decoupling experiments are described in the Experimental Section. Additionally, the C-1 and C-5 hydrogen signals were not separated. This symptom precludes the presence of a 2β-benzoyloxy group (see below and Table I).

The 2β-benzoate structure **9** was substantiated similarly. The infrared spectrum (CCl_4) had a band at 3610 cm^{-1}, which is characteristic of a nonbonded hydroxyl group.[2] When the benzoate is at the C-2 position, the C-1 hydrogen is deshielded and is resolved from the C-5 hydrogen (see Table I). Spin-decoupling experiments are described in the Experimental Section.

Acetylation of the 3-benzoate **8** then furnished the desired reverse ester **2**. It is evident that an axial C-2 acetoxyl group does not have a deshielding effect on the C-1 hydrogen, since the C-1 and C-5 hydrogens are unresolved. Thus it seems that the aromatic ring of compound **9** must be involved. Yet the 2β-carbomethoxy group of cocaine and the 2α-carbomethoxy group of pseudococaine both produce deshielding of the C-1 hydrogen; the C-1 and C-5 hydrogens are separated.[7]

In like manner, acetylation of the 2-benzoate **9** furnished a sort of backwards reverse ester, diester **11**.

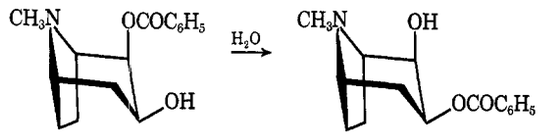


12, R = CCH_3; R′ = H
13, R = R′ = CCH_3
11

The nmr spectrum showed an unresolved multiplet for the hydrogens at C-2 and C-3, but showed resolved signals for the C-1 and C-5 hydrogens (Table I).

It is appropriate at this point to mention some observations related to the mechanism of benzoylation alluded to earlier. A sample of crude benzoylation product obtained after the usual work-up, which consisted of evaporation of the excess pyridine by warming *in vacuo* followed by addition of dilute aqueous base and extraction with ether, was converted directly to the monobenzoate monosilyl ether with *N*,*O*-bis(trimethylsilyl)acetamide. A glpc analysis indicated that the crude reaction mixture contained 3-monobenzoate **8**

(4) S. P. Findlay, *J. Org. Chem.*, **24**, 1540 (1959).
(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 216.
(6) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963).
(7) A. Sennema, L. Moat, A. J. Van Der Gugten, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, **87**, 1027 (1968).



9 8

and 2-monobenzoate **9** in a 6:1 ratio. It was found that a sample of the 2β-monobenzoate **9** in acetone-d_6 or $CDCl_3$, when treated with a drop of D_2O for 15 hr, had an nmr spectrum compatible with a 75% conversion to the 3β-monobenzoate **8**. There was an 80% conversion after 40 hr (ratio of methyl peak heights).

Therefore it appeared as if the ratio of monobenzoates produced after work-up reflected an equilibrium mixture of compounds, and that perhaps the 2β-monobenzoate **9** is the kinetic product as would be expected on the basis of the difference in rates of acetylation due to acyl ammonium involvement. To test this assumption, a sample of diol **7** in pyridine was treated with 1 equiv of benzoic anhydride in the usual manner. At the end of the time allotted for benzoylation an excess of acetic anhydride was added. Work-up in the usual manner, including thick layer chromatography, afforded an approximately 3:1 mixture of acetate benzoates. The minor product corresponded to **2** while the major compound was **11**. It is quite evident from this experiment that usual work-up of the benzoylation reaction caused the 2β-monobenzoate, the kinetic product, to rearrange to the more stable 3β-monobenzoate.

When this tandem experiment of benzoylation and acetylation without intermediate work-up was done in $CHCl_3$ instead of pyridine, **2** was the major product.

Acetylation of the diol **7** with 1 equiv of acetic anhydride gave 50% of recovered starting material and about 15% of the 3β-monoacetate **12**. Substantiation of the structure of **12** was accomplished by the same series of spin-decoupling experiments used to identify the 3-monobenzoate **8**. The infrared spectrum (CCl_4) had a band at 3464 cm^{-1} (persisting even after dilution to a 0.001 *M* concentration) which corresponded to the band observed in the spectrum of compound **8**.

Although tlc analysis of the mother liquor showed a major spot corresponding to diacetate **13** together with a minor spot of monoacetate **12**, preparative tlc furnished this diacetate in only 10% yield.

The reverse ester **2** of cocaine (**1**) was devoid of stimulative activity.

Experimental Section[8]

Ethyl (±)-1αH,5αH-Nortrop-2-ene-8-carboxylate (5). Method A.—A solution of 313.5 ml (3.33 mol) of ethyl chloroformate in 650 ml of C_6H_6 was added in 1 hr to 136.8 g (1.11 mol) of tropidine in 750 ml of C_6H_6 which was heated at 70°.[9] The mixture was then heated under reflux for 3 hr, diluted with Et_2O, and washed with 2 *N* HCl. The solution was dried (Na_2SO_4) and concentrated to an oily residue which was distilled under reduced pressure, affording **5** (48.4 g, 74% yield), bp 83–92° (0.25–1.0 mm).

Method B.—To a solution of 231.8 g (2.12 mol) of nortropidine[10] in 2.8 l. of H_2O held at 15° was added dropwise with stirring 228 g (2.12 mol) of ethyl chloroformate followed by a solution of 42.2 g (1.05 mol) of NaOH in 300 ml of H_2O. Another 228 g (2.12 mol) of ethyl chloroformate followed by 42.2 g (1.05 mol) of NaOH in 300 ml of H_2O was added. The two-phase system was stirred for another 0.5 hr at 15°. Et_2O was added, the layers were separated, and the organic layer was washed (dilute HCl) and dried (Na_2SO_4). Evaporation of the solvents and distillation of the residue gave 369.8 g (96%) of **5**, bp 68–74° (0.30–0.34 mm). The analytical sample boiled at 70–72° (0.15–0.20 mm), $n^{25}D$ 1.4875.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.28; H, 8.33; N, 7.72. Found: C, 66.5; H, 8.5; N, 7.6.

Method C.—Ethyl 3α-hydroxy-1αH,5αH-nortropane-8-carboxylate (**3**) (43.8 g, 0.22 mol) in 150 ml of $SOCl_2$ was heated under reflux for 2 hr and let stand overnight. The excess $SOCl_2$ was removed and the residue was distilled under reduced pressure to give **5** (20.5 g, 51% yield), bp 87° (0.5 mm).

Mixture of Ethyl (±)-1αH,5αH-Nortropan-3ξ-ol-8-carboxylates (3 and 4).—A solution of 100 g (0.50 mol) of ethyl (±)-3-oxo-1αH,5αH-nortropane-8-carboxylate[3] in 100 ml of THF was added dropwise to a suspension of 151.2 g (0.5 mol + 20% excess) of Li(*tert*-OBu)$_3$AlH with stirring at room temperature. After 3 hr of stirring, a saturated Na_2SO_4 solution was added carefully together with Et_2O. The layers were separated and the Et_2O layer was washed (2 *N* HCl and saturated NaCl), dried (Na_2SO_4), and concentrated. The residue (109.5 g) was crystallized from Et_2O–pentane, affording 43.8 g of 3α-ol **3**, mp 73–74°. The mother liquor was chromatographed on 2 kg of silica gel. The least polar fraction, obtained by elution with 3:1 Et_2O–pentane, gave (from Et_2O) another 24 g (68% yield) of **3**, mp 73–74°, R_f 0.3 (silica gel, Et_2O). In a repeat run a polymorph was obtained with mp 88–89.5°.

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.3; H, 8.5; N, 7.1.

The more polar fractions, eluted with Et_2O, gave 22.8 g (23%) of 3β-ol **4**, mp 63–64.5° (from Et_2O), R_f 0.17 (silica gel, Et_2O).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.0; H, 8.7; N, 7.0.

$NaBH_4$ in MeOH with work-up similar to that just described gave approximately the same isomer ratio. Low-pressure hydrogenation (PtO_2 in HOAc or EtOH) with monitoring by tlc appeared to give this same isomer ratio.

Preparation of (±)-1αH,5αH-Tropan-3α-ol from Ethyl (±)-3α-Hydroxy-1αH,5αH-nortropane-8-carboxylate (3).—A solution of 1.00 g of **3** in 30 ml of Et_2O was added to 0.5 g of $LiAlH_4$ in 100 ml of Et_2O with stirring. After 15 hr of reflux, 3 ml of H_2O was added and the mixture was filtered. Concentration of the filtrate afforded 0.74 g of (±)-1αH,5αH-tropan-3α-ol, the ir spectrum of which was identical with that of an authentic sample. Recrystallization from Et_2O–EtOH gave material of mp 63–64° (reported[4] mp 63–64°; the melting point of (±)-1αH,5αH-tropan-3β-ol is 109–110° [4]).

Ethyl (±)-2β,3β-Dihydroxy-1αH,5αH-nortropane-8-carboxylate (6).—A solution of 91 g of $KMnO_4$ and 91 g of $MgSO_4$ in 1.5 l. of H_2O was added to a solution of 100 g of ethyl (±)-1αH,5αH-nortrop-2-ene-8-carboxylate (**5**) in 4 l. of 95% EtOH over a period of 1.5 hr while the temperature was maintained at −5 to −2°. The mixture was stirred for 3 min. A solution of 62 g of sodium metabisulfite in 185 ml of H_2O was added over 5 min. The mix was filtered through Sulka Flox and the filtrate was concentrated *in vacuo*.

The residue was dissolved in 600 ml of $CHCl_3$ and the solution was washed with 100 ml of H_2O, dried over K_2CO_3, and treated with Darco G-60. The $CHCl_3$ was evaporated and the residue was dissolved in 150 ml of Et_2O. This solution was cooled and filtered. The product weighed 55.6 g (47%), mp 88–89° after drying at 40° *in vacuo*. No more product could be obtained from the filtrate. The analytical sample, recrystallized from Et_2O, melted at 93–94°.

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.8; H, 7.9; N, 6.4.

(8) All melting points were determined in capillary tubes and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer except for the high-dilution measurements, which were done with a Beckman IR-7 instrument. Nmr spectra were measured in $CDCl_3$ with a Varian A-60 spectrometer using Me_4Si as an internal reference. Spin-decoupling experiments were done with a Varian HA-100 instrument using a Hewlett-Packard audiooscillator 4204A. The mass spectrum reported was measured with a Jeolco JMS-1-OSC mass spectrograph. Column chromatography was done with 100–200 mesh silica gel obtained from the Davison Co., Baltimore, Md. Preparative tlc was done using 20 × 40-cm plates coated with a 1-mm thickness of Brinckmann PF 254 silica gel. The analytical plates were coated with the same gel.

(9) Method of E. Jucker and A. Lindenmann, Swiss Patent 442,318 (1967).

(10) R. Willstätter and F. Iglauer, *Chem. Ber.*, **33**, 1640 (1900).

(±)-1αH,5αH-Tropane-2β,3β-diol (7).[1,2]—A solution of 2.15 g (0.01 mol) of diol **6** in 30 ml of THF was added to 100 ml of THF containing 1 g of $LiAlH_4$. The solution was heated under reflux for 15 hr. (It was found later that reflux for 1 hr was sufficient.) H_2O was carefully added and the mixture was extracted with a 2:1 mixture of $CHCl_3$–EtOH. The organic layer was dried (Na_2SO_4) and concentrated to afford 1.45 g of residue. The residue crystallized from a small volume of Et_2O to give 1 g of diol **7**, mp 104–108°. Concentration of the filtrate gave another 0.18 g, mp 104–108° (77% yield).

The analytical sample, obtained from a similar experiment, melted at 105–107°.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.0; H, 9.6; N, 8.8.

Benzoylation of (±)-1αH,5αH-Tropane-2β-3β-diol (7).—A solution of 8.9 g (0.04 mol) of benzoic anhydride in 62 ml of pyridine was treated with 6.2 g (0.04 mol) of the diol **7** all at once and the resulting solution was heated on a steam bath for 2 hr. The excess pyridine was removed by heating *in vacuo*. Et_2O and dilute NaOH were added to the residue and the layers were separated. The Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and concentrated *in vacuo* to afford 7 g of oily residue which crystallized. Recrystallization from Et_2O afforded 3.57 g of impure **(±)-1αH,5αH-tropane-2β,3β-diol 3-benzoate (8)**, mp 92–95°. A second crop of crude 3-benzoate (0.36 g, mp 90–91°) was also obtained. The mother liquor was put on ten silica gel thick-layer plates which were developed with 25:24:1 Et_2O–pentane–*i*-$PrNH_2$. Elution of the more polar uv-absorbing band with Et_2O and recrystallization of it from Et_2O afforded another 1.0 g of monobenzoate **8**, mp 93–95° (46% total). Recrystallization of the total **8** from Et_2O gave 4.3 g, mp 93–94°. The filtrate will be referred to below as mother liquor A.

Further recrystallization of **8** in a similar experiment gave an analytical sample, mp 95–97°, ir (CCl_4, 0.05–0.001 *M*) 3465 and 1722 cm^{-1}.

In a spin-decoupling experiment on **8**, irradiation of the methylene region caused the signal of the furthest downfield aliphatic hydrogen (–$CHOCOC_6H_5$, 4.9 ppm) to be simplified from a multiplet to a doublet [J = 3.5 Hz, H-2(e), H-3(a) coupling]. There was no change in the character of the H-2 signal. Irradiation of the H-2 triplet at 3.8 ppm collapsed the H-3 multiplet at 4.9 ppm to a quartet having J = 7 and 10 Hz [H-3(a), H-4(e) and H-3(a), H-4(a) coupling, respectively]. Irradiation of the H-3 multiplet at 4.9 ppm collapsed the H-2 triplet to a doublet [J = 3.5 Hz, H-1(e), H-2(e)]. There was no change in the character of the H-1 signal.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33; N, 5.36. Found: C, 69.1; H, 7.4; N, 5.3.

The cyclohexanesulfamate salt of **8**, prepared in acetone, melted at 205–207° dec (from MeOH).

Anal. Calcd for $C_{15}H_{19}NO_3 \cdot C_6H_{13}NO_3S$: C, 57.24; H, 7.33; S, 7.28. Found: C, 57.4; H, 7.5; S, 7.2.

Partial concentration of mother liquor A caused precipitation of 0.1 g of **(±)-1αH,5αH-tropane-2β,3β-diol 2-benzoate (9)**, mp 128–132°. Glpc analysis of the trimethylsilyl ether derivative prepared with *N*,*O*-bis(trimethylsilyl)acetamide (on a methyl silicone gum column, OV-1) indicated that this sample contained 7% of the 3-benzoate **8**. An analytical sample, prepared by recrystallization from Et_2O in an identical experiment, melted at 136.5–137.5°: ir (CCl_4, 0.05–0.001 *M*) 3610 and 1726 cm^{-1}.

In a spin-decoupling experiment, irradiation of the H-3 signal at 3.9 ppm collapsed the triplet at 5.0 ppm to a doublet [J = 3 Hz, H-1(e), H-2(e)]. Irradiation of the H-2 signal at 5.0 ppm simplified the H-3 multiplet at 3.9 ppm and the H-1 multiplet at 3.4 ppm. Irradiation of the H-1 signal at 3.4 ppm collapsed the H-2 signal at 5.0 ppm to a doublet [J = 4.2 Hz, H-2(e), H-3(a)]. Irradiation of the methylene region simplified the H-3 signal at 3.9 ppm.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33; N, 5.36. Found: C, 69.0; H, 7.3; N, 5.3.

In an identical experiment a portion of the crude reaction mixture was silylated and put through an OV-1 glpc column as described above. The process indicated a 6:1 ratio of 3-monobenzoate **8** to 2-monobenzoate **9**.

The partially concentrated mother liquor A, from which **9** was removed, was subjected to preparative plate chromatography. The less polar uv-absorbing band afforded 0.60 g of **(±)-1αH,5αH-tropane-2β,3β-diol dibenzoate (10)**, mp 92–93° from hexane–Et_2O. This product was analyzed as its hydrochloride salt, mp 273° dec (from acetone).

Anal. Calcd for $C_{22}H_{23}NO_4 \cdot HCl$: C, 65.73; H, 6.02; Cl, 8.83. Found: C, 65.6; H, 6.0; Cl, 8.9.

Equilibration of 2-Monobenzoate 9 to a Mixture of 2- and 3-Monobenzoates 8 and 9.—A 5% solution of 1αH,5αH-tropane-2β,3β-diol 2-benzoate (**9**) in acetone-d_6 in an nmr tube was treated with a drop of D_2O. The solution was scanned at 0, 15, and 40 hr and after 6 days (Table II).

TABLE II

Compd	0 hr	15 hr	40 hr	6 days
	Aromatic peak height			
2-Benzoate **9**	100	20	23	15
3-Benzoate **8**	0	80	77	85
	Methyl peak height			
2-Benzoate **9**	100	25	20	21
3-Benzoate **8**	0	75	80	79

This conversion was also observed in $CDCl_3$ with a drop of D_2O.

Acetylation of (±)-1αH,5αH-Tropane-2β,3β-diol (7).—A solution of 4 g (0.025 mol) of diol **7** in 25 ml of pyridine was treated with 2.54 g (0.25 mol) of Ac_2O at room temperature overnight. The excess pyridine was removed by heating *in vacuo*. Dilute NH_4OH and Et_2O were added. The layers were separated and the Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and concentrated to afford 2.7 g of oily residue A. The aqueous layer was extracted with a mixture of $CHCl_3$–EtOH (2:1) to give 2.02 g (50%) of starting glycol **7**.

Residue A crystallized in Et_2O–pentane to give 0.76 g (15%) of **(±)-1αH,5αH-tropane-2β,3β-diol 3-acetate (12)**, mp 85–88°. Tlc analysis of the mother liquor (silica gel, Et_2O–*i*-$PrNH_2$ 98:2) showed a large spot at R_f 0.45 corresponding to diacetate **13** and a small spot at R_f 0.40 corresponding to 3-monoacetate **12**.

The recovered glycol **7** was reprocessed with Ac_2O to give another 0.22 g (9%) of 3-monoacetate **12**, mp 84–86°. Recrystallization from Et_2O gave the analytical sample, mp 85–86.5°, ir (CCl_4, 0.05–0.001 *M*) 3464 and 1744 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.21; H, 8.63; N, 7.02. Found: C, 60.2; H, 8.6; N, 7.0.

In a spin-decoupling study on **12**, irradiation of the H-2 signal at 3.7 ppm collapsed the H-3 signal at 4.8 ppm to a quartet [J = 10 and 8 Hz, H-3(a), H-4(a) and H-3(a), H-4(e), respectively]. Irradiation of the H-3 signal at 4.8 ppm collapsed the H-2 signal at 3.7 ppm to a doublet (J = 3.5 Hz; H-1, H-2). Irradiation of the methylene region collapsed the H-3 signal at 4.8 ppm to a doublet (J = 3.5 Hz, H-2, H-3). The signals of the C-1 and C-5 hydrogens were not resolved.

The total mother liquor residues (2.3 g) from isolation of the 3-monoacetate were further acetylated with 10 ml of Ac_2O and 15 ml of C_5H_5N overnight at room temperature. Work-up as above afforded 1.03 g of oily **(±)-1αH,5αH-tropane-2β,3β-diol diacetate (13)**. Chromatography on four silica gel preparative plates (Camag DSFO coating) using two passes of 97:3 Et_2O–*i*-$PrNH_2$ gave a principal band containing 0.62 g (10%) of oily diacetate **13**. Its HCl salt melted at 253° dec (from acetone).

Anal. Calcd for $C_{12}H_{19}NO_4 \cdot HCl$: C, 51.87; H, 7.27; Cl, 12.78. Found: C, 51.8; H, 7.3; Cl 12.7.

(±)-1αH,5αH-Tropane-2β,3β-diol 2-Acetate 3-Benzoate (2).—A solution of 10 g (0.038 mol) of 3-monobenzoate **8** in 100 ml of C_5H_5N was treated with 50 ml of Ac_2O and heated on the steam bath for 4.5 hr. Excess reagents were removed by warming *in vacuo*. Dilute NaOH and Et_2O were added. The layers were separated and the Et_2O layer was washed (saturated NaCl), dried (Na_2SO_4), and concentrated to give 11.5 g of oil that crystallized when fresh ether was added. Filtration afforded 6.3 g of **2**, mp 101.5–103°. A second crop of 3.5 g, mp 99–101.5°, was obtained upon concentration of the mother liquor (85% yield).

The analytical sample from an identical experiment melted at 101.5–103.5° (from Et_2O); R_f 0.21 (silica gel; Et_2O–pentane–*i*-$PrNH_2$ 50:47:3).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.30; H, 6.98; N, 4.61. Found: C, 67.5; H, 7.1; N, 4.6.

The cyclohexanesulfamate salt of **2**, prepared in and recrystallized from acetone, melted at 159–165°.

Anal. Calcd for $C_{17}H_{21}NO_4 \cdot C_6H_{13}NO_3S$: C, 57.25; H, 7.11; S, 6.65. Found: C, 57.2; H, 7.2; S, 6.3.

(±)-1αH,5αH-Tropane-2β,3β-diol 2-Benzoate 3-Acetate (11). Method A (from the 3-Acetate).—A solution of 0.80 g (4 mmol) of (±)-1αH,5αH-tropane-2β,3β-diol 3-acetate (**12**) in 5 ml of C_5H_5N was treated with 0.91 g (4 mmol) of benzoic anhydride at room temperature overnight. The usual work-up afforded 1.1 g of oily residue. Chromatography on four silica preparative plates using 50:47:3 Et_2O–pentane-*i*-$PrNH_2$ (R_f 0.36) followed by recrystallization from hexane gave 0.50 g of poorly formed crystals of 2-benzoate 3-acetate **11**, mp 91–95°. From wet ether, **11** formed a hydrate as beautiful, massive prisms which reverted to an oil when dried *in vacuo*. The air-dried prisms melted at 90–102° with bubbling and their nmr spectrum showed an excess of two hydrogens, presumably from H_2O. The mass spectrum gave a molecular ion peak at *m/e* 303 with abundant ions at *m/e* 244 ($M^+ - OAc$), 198 ($M^+ - OBz$), and 105 (OBz), and very intense peaks at *m/e* 17 (OH) and 18 (H_2O).

Anal. Calcd for $C_{17}H_{21}NO_4 \cdot H_2O$: C, 63.53; H, 7.22; N, 4.35. Found: C, 63.5; H, 7.3; N, 4.2.

Method B (from the 2-Benzoate).—A solution of 0.10 g (0.4 mmol) of (±)-1αH,5αH-tropane-2β,3β-diol 2-benzoate (**9**) in 5 ml of C_5H_5N and 2.5 ml of Ac_2O was heated on the steam bath for 2 hr. The usual work-up afforded 0.12 g of **11** as an oil that crystallized from hexane, mp 96–99°. A sample recrystallized from wet ether melted at 92–102° (bubbling). The nmr and ir spectral curves and the tlc R_f value were all identical with those of **11** prepared by method A. A mixture melting point was undepressed.

Method C (from the Diol).—A solution of 0.48 g (3.1 mmol) of diol **7** in 20 ml of C_5H_5N was treated with 0.72 g (3 mmol) of benzoic anhydride and the solution was heated on a steam bath for 2.5 hr. Ac_2O (4 ml) was added and the mixture was heated for 2 hr more. The usual work-up afforded 0.72 g of an oily residue. Tlc analysis (silica gel; Et_2O–pentane-*i*-$PrNH_2$ 50:47:3) showed a major spot with R_f 0.36 and a minor spot with R_f 0.21. Chromatography on four preparative plates using the same solvent system gave 0.50 g (54%) of the R_f 0.36 oil which crystallized as prisms from wet Et_2O. It was found to be identical with **11** by means of nmr, ir, mixture melting point, and tlc.

The band of R_f 0.21 material furnished 0.17 g of oil which crystallized from Et_2O and proved identical with the 2-acetate 3-benzoate **2** by the usual criteria.

When the experiment just described was repeated using $CHCl_3$ as the solvent instead of pyridine, tlc analysis of the product indicated that **2** was the major product.

Registry No.—**2**, 33780-46-0; 2 cyclohexanesulfamate, 33780-47-1; **3**, 33780-48-2; **4**, 33780-49-3; **5**, 33780-50-6; **6**, 33780-51-7; **7**, 33780-52-8; **8**, 33886-15-6; **8** cyclohexanesulfamate, 33886-16-7; **9**, 33872-63-8; **10**, 33780-53-9; **10** HCl, 33780-54-0; **11**, 33780-55-1; **12**, 33780-56-2; **13** HCl, 33780-57-3.

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A Simple Synthesis of 4-Hydroxycyclohexanone

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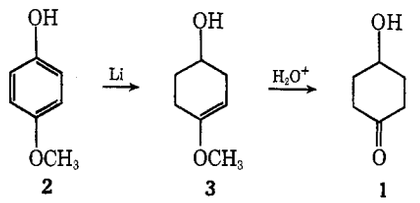
Recently in our laboratory we have found it desirable to prepare synthetically useful quantities of 4-hydroxycyclohexanone (**1**). We therefore had need of a simple high-yielding route to this compound. Jones and Sondheimer[2] developed a route, later modified by Trager,[3] which required the selective oxidation of a protected 1,4-cyclohexanediol. This multistep synthesis gave only a 25% yield based upon the starting diol and was not suited to our purpose.

Fried[4] has shown that phenols can be reduced under Birch conditions provided that high enough concentrations of Li in ammonia are used. The high concentrations of Li are required presumably because of the high potential barrier to formation of the dianion radical, which must come from the initially produced phenoxide anion.

When *p*-methoxyphenol (**2**) was subjected to reduction with lithium in ammonia (3.6 *M* Li), there was isolated after work-up the crude enol ether **3** which was directly hydrolyzed in 0.1 *N* HCl to afford **1** in 89% yield after distillation. The mole ratio of lithium to the phenol appears to be critical. When the mole



2 **3** **1**

ratio was reduced from 11:1 to 6:1 (both still 3.6 *M* in Li), considerable quantities of 1,4-cyclohexanedione are formed. This high-yielding simple route can be easily adapted to large scale reactions and renders this valuable synthetic intermediate (**1**) readily available.

Experimental Section

4-Hydroxycyclohexanone (**1**).—Liquid ammonia (100 ml) after distillation through a KOH tower was collected with stirring in a thoroughly dry three-neck flask at −78°. The NH_3 inlet was replaced by a N_2 inlet and the remainder of the reaction was run under nitrogen. The reaction flask was allowed to warm to −50° and Li (2.5 g, 0.36 g-atom) was added all at once. After this, *p*-methoxyphenol (4.0 g, 32.2 mmol) in anhydrous ether (25 ml) was added to the ammonia solution over a period of 5 min. The reaction mixture was stirred at −50° for 45 min, absolute ethanol (1.9 ml, 32 mmol) was added, and stirring was continued for an additional 1 hr. Absolute ethanol (4 ml) was added at 30-min intervals until the blue color was discharged. A total of 25 ml of ethanol was used.

After the ammonia had been evaporated, saturated NH_4Cl (200 ml) was added to the residue, and the resulting brown solution was cooled in an ice bath. Concentrated HCl was added dropwise until the pH of the solution was approximately 1. This acidic solution was then heated to 50° for 1 hr to effect hydrolysis of the enol ether **3**. The cooled aqueous solution was extracted with $CHCl_3$ (8 × 50 ml), saturated with NaCl, and then reextracted. After drying and removal of solvent, 4.96 g of a brown oil was isolated. Distillation at 93° (0.3 mm) yielded 3.25 g (89%) of 4-hydroxycyclohexanone: M^+ 114; ir (neat) 5.95 (C=O), 2.98 μ (OH); nmr ($CDCl_3$–TMS) δ 4.16 (m, α to hydroxyl), 1.77–2.84 (m, ring CH_2 protons); 2,4-dinitrophenylhydrazone mp 152–153° (lit.[1] mp 150–151°).

Registry No.—**1**, 13482-22-9.

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