differ from those in circular muscles of the eye.

The geometry of the amino alcohol portion of cholinergic antagonists based on tropane and piperidine has been shown to influence the antimuscarinic potencies of these esters—at least at sites in the guinea pig ileum—but the order of the effect is smaller than that caused by variations in the acyloxy moiety, and much smaller than that of absolute configuration in the case of amino alcohols esterified with chiral alcohols (*e.g.*, *l*-tropyl α-methyltropate is 50 times more active than the dextro isomer on rat gut).[18] In sharp contrast, the potencies of cholinergic *agonists* are greatly dependent upon the configuration and structure of the amino alcohol portion of the molecule as witnessed by the relative activities of (*R*)- and (*S*)-β-methylacetylcholine[19] and *cis*- and *trans*-2-acetoxycyclopropyltrimethylammonium iodide.[20] Hence the results presented here support the view that cholinergic agonists and their antagonists occupy different receptors[17,21] although evidence of competitive interactions between agonist-antagonist pairs points to their sharing a common anionic site.

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Compounds Affecting the Central Nervous System. 2.[1] Aromatic Acetals of Tropanediols

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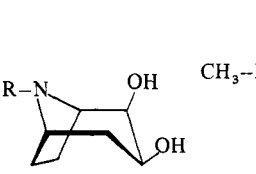
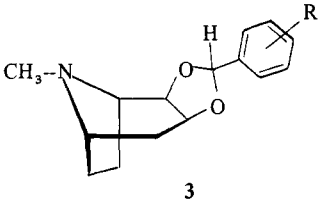
A series of acetals prepared from tropane-2β,3β-diol and variously substituted benzaldehydes was found to produce CNS stimulation and to reverse reserpine-induced eyelid ptosis. These acetals formed as pairs which were isomeric about the benzylic C. Configurational assignments were made on the basis of their nmr spectra. The acetals of ecgoninol and pseudoecgoninol were included in this study.

It is always a considerable pleasure to find that a chemical intermediate or a simple derivative of a compound under study has interesting biological activity. 1α*H*,5α*H*-Tropane-2β,3β-diol (**1**) was reported recently[1] as an intermediate in the preparation of a "reverse ester" of cocaine. Benzylidene acetals (**3** and **4**) of this diol, the subject of this paper, are central nervous system stimulants. They were prepared by the reaction of a variety of benzaldehydes with diol **2** followed by reduction of the *N*-ethoxycarbonyl group to Me.



1, R = CH_3
2, R = EtO_2C



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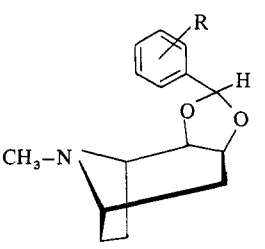
R as in Table II



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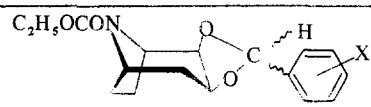
R as in Table II

Table I lists the 8-ethoxycarbonyl acetals which were prepared. In each case acetal formation gave essentially equal quantities of 2 products which were isomeric about the benzylic C. The configuration of the Ph group is designated β when it lies on the same side of the molecule as the N and α when the converse is true. The basis for configurational assignment is discussed later. Generally, the isomers with the aromatic ring in the α configuration crystallized spontaneously from the reaction mixtures. Purification of the β isomers was then accomplished by plate or column chromatography.

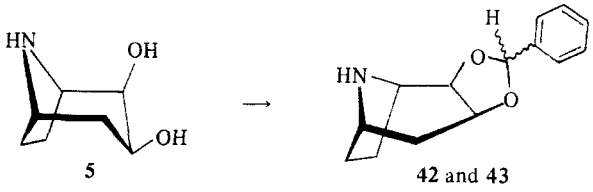
Table I

Compd	X	Isomer α- or β-phenyl	Nmr,[a] δ ppm, O_2CH	R_f[b]	Formula	Analysis	Solvent	Mp, °C
								
8[c]	H	α	6.06	0.78[d]	$C_{17}H_{21}NO_4$	C, H, N	Cyclohexane	87–90 (prisms) 85–87 (needles)
9[c,e]	H	β	5.88	0.73[d]	$C_{17}H_{21}NO_4$	C, H, N		
10[c]	*p*-OCH_3	α	6.01	0.65[f]	$C_{18}H_{23}NO_5$	C, H, N	Et_2O	97–98
11[c]	*p*-OCH_3	β	5.84	0.54[f]	$C_{18}H_{23}NO_5$	C, H, N	Et_2O	88–89
12[g]	*p*-Cl	α	6.02	0.63[f]	$C_{17}H_{20}NO_4Cl$	C, H, N	Et_2O	101–102
13[h]	*p*-Cl	β	5.85	0.53[f]	$C_{17}H_{20}NO_4Cl$			
14[g]	*p*-F	α	6.02	0.48[i]	$C_{17}H_{20}NO_4F$	C, H, F	Et_2O	98–99
15[h]	*p*-F	β	5.84	0.58[i]	$C_{17}H_{20}NO_4F$			
16[j]	*p*-NO_2	α	6.09	0.54[i]	$C_{17}H_{20}N_2O_6$	C, H, N	Et_2O	97–98
17[h]	*p*-NO_2	β	5.91	0.45[i]	$C_{17}H_{20}N_2O_6$			
18[k]	*p*-OCF_3	α	6.06	0.53[f]	$C_{18}H_{20}NO_5F_3$	C, H, F		
19[k]	*p*-OCF_3	β	5.88	0.45[f]	$C_{18}H_{20}NO_5F_3$			
20[l]	*p*-OAc	α	6.07	0.38[i]	$C_{19}H_{23}NO_6$	C, H, N	Et_2O	90–94
21[l]	*p*-OAc	β	5.89	0.31[i]	$C_{19}H_{23}NO_6$			
22[c,m]	*p*-$OCH_2C_6H_5$	α	5.95	0.42[i]	$C_{24}H_{27}NO_5$	C, H, N	Et_2O	113–115
23[c,m,n]	*p*-$OCH_2C_6H_5$	β	5.77	0.37[i]	$C_{24}H_{27}NO_5$			
24[o]	*m*-$OCH_2C_6H_5$	α		0.44[f,p]	$C_{24}H_{27}NO_5$			
25[o]	*m*-$OCH_2C_6H_5$	β		0.41[f,p]	$C_{24}H_{27}NO_5$			

[a] In $CDCl_3$, $(CH_3)_4Si$, internal standard. [b] Silica gel tlc. [c] Isomers sepd on thick-layer plates. [d] Solvent system (Et_2O–*n*-C_5H_{12}–*i*-$PrNH_2$, 25:24:1). [e] Short path distn (0.005–0.01 mm); $n^{25}D$ 1.5350. [f] Solvent system (Et_2O–*n*-C_5H_{12}–*i*-$PrNH_2$, 47:50:3). [g] Crystallized as a single isomer from crude reaction mixt. [h] Pure isomer was not isolated. [i] Solvent system 100% Et_2O. [j] Column chromatography (silica gel, Et_2O–*n*-C_5H_{12}–*i*-$PrNH_2$, 25:72:3). [k] Distd and characterized as a mixt 4:5; α:β isomers (short path distn; 165–173° (0.03–0.04 mm), $n^{26}D$ 1.4907. [l] Prepd from *p*-acetoxybenzaldehyde;[2] crystd from Et_2O as a mixt (3:1; α:β Ph isomers). [m] See Experimental Section for special prep. [n] Best sample obtained contd 16% of α-Ph isomer. [o] Crude mixt reduced without characterization. [p] The tlc spots were not assigned to a particular isomer in this case.

Compounds **22** and **23** of Table I are exceptional in that they were prepared from **20** and **21**, respectively, through hydrolysis of the Ac groups followed by benzylation of the resulting phenols.

Table II lists the *N*-Me acetals prepared in this study. Most of these were formed from the corresponding *N*-ethoxycarbonyl analogs using $LiAlH_4$ or AlH_3[3] as reducing agents. Production of the secondary amines **42** and **43** required initial hydrolysis of the urethane function of **2** to form diol **5** followed by acetal formation. Phenols **38–41** were formed from the corresponding benzyl ether urethanes



5 **42 and 43**

by LAH reduction followed by catalytic debenzylation.

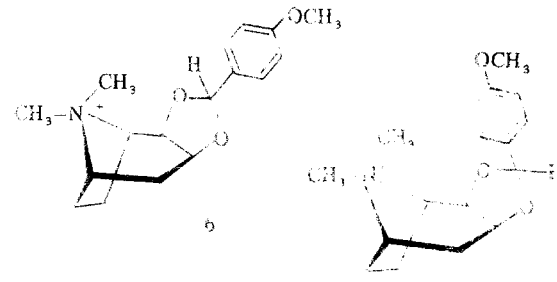
Compounds **44** and **45** are C-2 homologs of the above series, being derived from ecgoninol and pseudoecgoninol, respectively. Compound **44** has been reported by Fodor and Kovács[4] in the form of its benzenesulfonate salt. The acetal of pseudoecgoninol (**45**) failed to form under the conditions used by these workers.

Examination of the nmr spectra of the α and β aromatic acetals of Table I (nonbasic N) revealed that the benzylic H peaks of the isomeric pairs were well isolated from interference and appeared at characteristic positions which were 0.17–0.18 ppm apart.[5] The upfield position of the benzylic H of the β-Ph isomer may be the result of a sterically induced ring distortion which moves that H further into the shielding cone of an adjacent O.[6] These benzylic H peaks were useful for determination of isomer ratios in mixtures of these isomers.

When one isomer of such an α and β pair was converted to the corresponding *N*-Me analog, there was a significant downfield shift of the benzylic H (0.18 ppm average) whereas the other isomer showed a slight (0.07 ppm average) upfield shift upon similar transformation. A footnote summarizes the shifts observed.†

The major shift in the benzylic H accompanying this chemical transformation is associated with a major change in the electronic character of the β face of the molecule and thus the isomer associated with that shift (downfield) may be assigned the β-H and α-Ph configuration.

Confirmation for this configurational assignment is found in the nmr spectra of the methiodides of a pair of these isomeric amines. When the methoxyaromatic group is α and away from the 2 Me groups as in **6**, these methyls appear close together at 3.62 and 3.71 ppm. But when this

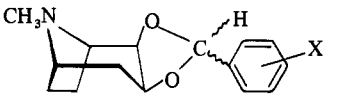
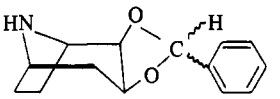
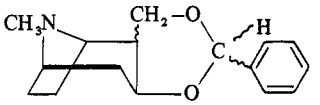


6

†Shift in benzylic H going from EtO_2CN to CH_3N (Δδ, ppm)

Ring substituent	α-Phenyl	β-Phenyl
H	+0.17	−0.10
p-OCH_3	+0.23	−0.11
p-Cl	+0.14	−0.10
p-F	+0.18	−0.06
p-NO_2	+0.18	−0.01
p-OCF_3	+0.19	−0.02

Table II

Compd	X	Isomer α- or β-phenyl	Nmr, δ ppm O_2CH	Nmr, δ ppm CH_3	R_f[a]	Formula	Analysis	Solvent	Mp or bp (mm), °C	Refractive index
										
26[b]	H	α	6.23	2.32[e]	0.70[d]	$C_{15}H_{19}NO_2$	C, H, N		122–130 (0.01–0.003 mm)	$n^{25}D$ 1.5466
27[b,c]	H	β	5.78	2.39[e]	0.73[d]	$C_{15}H_{19}NO_2$	C, H, N		114–128 (0.002–0.004 mm)	$n^{27}D$ 1.5474
28[b]	*p*-OCH_3	α	6.24	2.30[e]	0.41[f]	$C_{16}H_{21}NO_3$	C, H, N	Et_2O	76–77	
29[b]	*p*-OCH_3	β	5.73	2.40[e]	0.44[f]	$C_{16}H_{21}NO_3$	C, H, N	Et_2O–pentane	47–48	
30[g]	*p*-Cl	α	6.16	2.36[e]	0.51[f]	$C_{15}H_{18}ClNO_2$	C, H, Cl	Hexane	63–64	
31[g,h]	*p*-Cl	β	5.75	2.40[e]	0.59[f]	$C_{15}H_{18}ClNO_2$	C, H, Cl		(0.02–0.04 mm)	$n^{25}D$ 1.5535
32[i]	*p*-F	α	6.20	2.34[e]	0.36[f,j]	$C_{15}H_{18}FNO_2$	C, H, F		128–141 (0.01 mm)	$n^{25}D$ 1.5304
33[i]	*p*-F	β	5.78	2.40[e]	0.45[f,j]	$C_{15}H_{18}FNO_2$				
34[k]	*p*-NO_2	α	6.27	2.36[e]		$C_{15}H_{18}N_2O_4$	C, H, N	Et_2O	102–103	
35[l]	*p*-NO_2	β	5.90	2.40[e]		$C_{15}H_{18}N_2O_4$				
36[m]	*p*-OCF_3	α	6.25	2.39[e]	0.42[f]	$C_{16}H_{18}F_3NO_3$	C, H, F	Et_2O	117.5–119	
37[l]	*p*-OCF_3	β	5.84	2.44[e]	0.52[f]	$C_{16}H_{18}F_3NO_3$				
38[n]	*p*-OH	α	5.86	2.20[o]	0.49[p]	$C_{15}H_{19}NO_3$	C, H, N	Et_2O	218–220	
39[q]	*p*-OH	β	5.62	2.27[o]	0.53[p]	$C_{15}H_{19}NO_3$	C, H, N	Et_2O	174.5–175.6, 214–216	
40[r]	*m*-OH	α	5.92	2.25[o]	0.45[p,j]	$C_{15}H_{19}NO_3$	C, H, N	MeCN	212–225	
41[r]	*m*-OH	β	5.66	2.29[o]	0.49[p,j]	$C_{15}H_{19}NO_3$				
										
42[s]		α	6.13[e]		0.31[f,j]	$C_{14}H_{17}NO_2$	C, H, N		122–150 (0.025–0.035 mm)	$n^{25}D$ 1.5592
43[s]		β	5.87[e]		0.38[f,j]	$C_{14}H_{17}NO_2$				
										
44[t]		2β-Config	5.53[u]	2.35		$C_{16}H_{21}NO_2$	C, H, N	Hexane	82.5–85	$[\alpha]^{25}D$ +6°[v]
45[t]		2α-Config	5.70[u]	2.15		$C_{16}H_{21}NO_2$	C, H, N	Cyclohexane	57–61	$[\alpha]^{25}D$ −33°[v]

[a] Silica gel tlc. [b] Obtained from LAH redn of single isomer. [c] Contains 10% of α-Ph isomer. [d] Solvent system Et_2O-*i*-$PrNH_2$, 49:1. [e] $CDCl_3$-internal standard $(CH_3)_4Si$. [f] Solvent system, Et_2O-*n*-C_5H_{12}-*i*-$PrNH_2$, 47:50:3. [g] Obtained from AlH_3 redn of pure isomer (10–15 min). [h] Obtained from thick-layer chromatography on silica gel. [i] Obtained from AlH_3 redn of mixt of isomers (20 min). Isomers were not sepd. [j] Isomers not assigned to R_f values. [k] Obtained from AlH_3 redn of single isomer (45 min). [l] Obtained from AlH_3 redn of mixt, β isomer not isolated. [m] Obtained from AlH_3 redn of mixt. α-Ph isomer crystd from reaction mixt. [n] Obtained from LAH redn of **22** followed by hydrogenolysis with Pd/C. [o] DMSO-d_6, internal standard $(CH_3)_4Si$. [p] Solvent system THF-*i*-$PrNH_2$, 97:3. [q] Obtained from LAH redn of **23** followed by hydrogenolysis with Pd/C. [r] Obtained by LAH redn on mixt of **24** and **25** followed by hydrogenolysis with Pd/C. Did not separate mixt. [s] Distd and characterized as a mixt (see Experimental Section). [t] See Experimental Section. [u] No evidence of isomeric mixt at benzyl C. [v] 1% in $CHCl_3$.

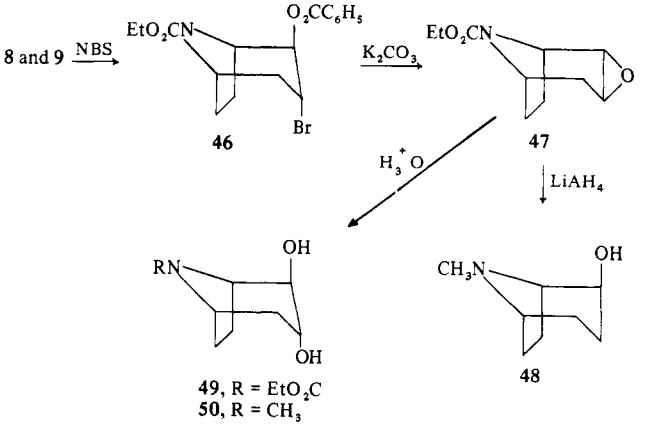
aromatic group is β as in **7**, it is in a position to shield one of the Me groups so that the methyls appear widely separated at 3.82 and 3.38 ppm.

It is curious that the nmr spectra of the ecgoninol acetals **44** and **45** show single benzylic H peaks. These products may have the thermodynamically more stable equatorial phenyl configurations.

In all the acetals reported here the C-1 and C-5 hydrogens were visible as separated peaks. For example, in the α-Ph isomer **26** these peaks appeared at 3.50 and 3.20 ppm with specific assignment uncertain. In the β-Ph isomer **27** they appeared at 3.58 and 3.20 ppm.

The R_f values of the α isomers in the urethanes of Table I were uniformly greater than those of the β isomers with the exception of the *p*-F isomers **14** and **15** (spots for **24** and **25** were not assigned). However, in the *N*-Me series of Table II the reverse was true in all of the 5 pairs whose tlc spots were identified.

When a mixture of the nonbasic, isomeric acetals **8** and **9** was treated with NBS in the presence of $BaCO_3$, acetal cleavage occurred with formation of a *single* bromoester (81%). Its nmr spectrum supported the positions and configurations of substituents as shown in **46**. This is consistent with the observation by Hanessian and Plessas[7] that "internal *O*-benzylidene acetals such as those joining vicinal *cis*-OH groups of a cyclic sugar derivative give isomeric *trans*-bromobenzoates." In the present case steric factors direct formation of the single product.



Aqueous alcoholic K_2CO_3 transformed this bromoester into 2β,3β-epoxide **47**, the β configuration of which was confirmed by reduction (LAH) to tropan-2β-ol[8] (**48**).

Hydrolysis of epoxide **47** gave the desired diaxial diol **49**

Table III. Effect of Benzylidenedioxy Tropanes on Reserpine-Induced Ptosis and the Overt Behavior of Mice

Compd	Dose, mg/kg ip	Prevention test MPS[a]	Prevention test PV[b]	Reversal test MPS[a]	Reversal test PV[b]	Overt behavior in mice, ip[e]
26	10			2.5	0.06	Locomotor stimulation, biting, squeaking, tapering off at 30 min at 30 and 50 mg/kg
	30	2.9	0.23	2.5	0.05[d]	
	50	1.9	0.01[d]	1.9	0.01[d]	
	Control[c]	3.3		3.4		
27	30	3.3	0.72	2.5	0.10	Questionable mild locomotor stimulation at 30 min at 30 and 50 mg/kg
	50	2.9	0.33	2.4	0.08	
	Control[c]	3.3		3.3		
28–29 mixt	1			3.4	0.88	At 30 and 50 mg/kg, convulsions, tremors, biting, squeaking, hyperexcitability. In combination with reserpine, 3/8 dead at 0.5 hr on prevention test
	10			2.1	0.03[d]	
	30	2.6	0.23	1.1	0.000[d]	
	50	2.6	0.23	1.0	0.002[d]	
	Control[c]	3.1		3.3		
30	1			3.6	0.72	At 30 and 50 mg/kg, convulsions, tremors, squeaking, and questionable locomotor stimulation; 1/8 dead in 3 hr in combination with reserpine in prevention and reversal tests
	10			2.8	0.06	
	30	3.0	0.72	2.4	0.02[d]	
	50	2.6	0.34	2.4	0.03[d]	
	Control[c]	3.1		3.4		
32–33 mixt	30	3.0	0.79	3.0	0.19	Hypersensitive to touch at 30 and 50 mg/kg
	50	3.0	0.64	2.9	0.19	
	Control[c]	3.3		3.4		
34	30	3.1	0.96	2.9	0.27	At 30 and 50 mg/kg, locomotor stimulation, tremors, biting, squeaking, for about 0.5 hr; mild stimulation at 3 and 5 hr; 1/8 dead in 0.5 hr in combination with reserpine on reversal test
	50	3.0	0.38	2.4	0.05[d]	
	Control[c]	3.4		3.3		
36	1			3.0	0.16	At 50 mg/kg, tremors. In combination with reserpine (reversal test), jumping, hyperexcitability, locomotor effects
	10			2.9	0.10	
	30	3.5	0.57	2.8	0.04[d]	
	50	3.3	1.00	2.8	0.04[d]	
	Control[c]	3.3		3.5		
38	30	3.1	0.72	2.6	0.13	Mild locomotor stimulation at 30 and 50 mg/kg
	50	3.1	0.72	2.1	0.006[d]	
	Control[c]	3.3		3.4		
39	30	3.4	0.72	3.1	0.44	Mild locomotor stimulation at 30 and 50 mg/kg
	50	3.3	0.72	2.9	0.19	
	Control[c]	3.3		3.4		
40–41 mixt	30	3.5	0.57	3.0	0.27	No stimulation
	50	2.6	0.44	2.0	0.01[d]	
	Control[c]	3.3		3.4		
42–43 mixt	1			3.1	0.79	Mild locomotor stimulation at 30 and 50 mg/kg
	10			2.8	0.06	
	30	2.9	0.38	2.1	0.02[d]	
	50	2.5	0.08	2.4	0.02[d]	
	Control[c]	3.3		3.4		
44	0.5	3.1	0.50	2.9	0.19	Lethal at 50 mg/kg. 1/5 dead in 0.5 hr at 30 mg/kg; clonic convulsions, tremors, biting, squeaking
	1	2.9	0.23	2.3	0.01[d]	
	10	2.3	0.02[d]	1.9	0.01[d]	
	30	1.6	0.01[d]	1.4	0.002	
	Control[c]	3.1		3.3		
45	0.5	3.4	0.32	3.0	0.32	Lethal at 10 mg/kg
	1	3.4	0.79	2.9	0.32	

[a]Mean ptosis score. [b]Probability values (PV) were calcd on "2-tailed" probabilities. Values of 0.05 are considered significant. [c]1% gum tragacanth mucilage control. [d]Denotes significantly decreased ptosis score. [e]Effect of compd alone unless otherwise specified.

which, unfortunately, failed to form an acetal under the conditions used for the other acetals in this report. If diol **49** had assumed a boat configuration, the 2 OH groups would have been in close enough proximity for the reaction to occur. Reduction of diol **49** with LAH gave the known *N*-Me diol 50.[9]

Biological Results. The *N*-Me compounds described were evaluated by means of the reserpine-induced eyelid ptosis test in mice.[10] Overt behavioral changes were also noted (see Table III). In the test for prevention of reserpine-induced ptosis, **44** was the most active (10 mg/kg) followed by **26** (50 mg/kg). None of the other compounds was significantly active. In the test for reversal of reserpine-induced ptosis, **44** was again the most active (1 mg/kg). Mixture **28–29** was active at 10 mg/kg followed by **26**, **30**, **36**, and **42–43** which were active at 30 mg/kg. Compounds **34**, **38**, and **40–41** were active at 50 mg/kg. Antireserpine activity was accompanied by overt signs of stimulation such as locomotor activity, squeaking, and biting. Compound **45**, the C-2 epimer of **44**, was the most lethal of all the compounds tested.

Experimental Section‡

Preparation of Benzal Acetals of Ethyl (±)-2β,3β-Dihydroxy-1αH,-5αH-nortropane-8-carboxylate (2). A soln of 27.3 g (0.13 mole) of

‡All melting points are uncorrected. Nmr spectral measurements were made on Varian A-60 or HA-100 spectrophotometers using $CDCl_3$ as solvent unless otherwise indicated. $(CH_3)_4Si$ was used as the internal standard. Ir spectra were detd on a Model-21 Perkin-Elmer infrared spectrophotometer. Brinckmann Instruments silica gel grade PF_{254} was used in 1-mm thickness for prep chromatog. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

diol **2**, 14.0 g (0.13 mole) of PhCHO, and 1.0 g of *p*-TsOH · H_2O in 1.1 l. of C_6H_6 was heated under reflux for 18 hr with a Dean–Stark H_2O sep in the system. Solid $NaHCO_3$ was added followed by H_2O. The layers were sepd and the C_6H_6 was washed with satd NaCl and dried (Na_2SO_4). Evaporation of solvent afforded 41.6 g of a straw-colored liquid. Tlc showed 2 major spots having R_f 0.73 and 0.78 (silica gel, Et_2O–pentane–*i*-$PrNH_2$; 25:24:1). Preparative chromatography on 80 thick-layer plates (20 × 40 cm, 8 passes with Et_2O–pentane–*i*-$PrNH_2$, 25:73:2) afforded 17.0 g (44%) of a less polar compd characterized as ethyl (±)-2β,3β-benzylidenedioxy-1α*H*,5α*H*-nortropane-8-carboxylate (α-Ph isomer) (**8**).

The more polar band eluted from the plates afforded 17.0 g (44%) of ethyl (±)-2β,3β-benzylidenedioxy-1α*H*,5α*H*-nortropane-8-carboxylate (β-Ph isomer) (**9**). See Table I for further data.

Reduction of the *N*-Ethoxycarbonyl Group to *N*-Methyl. Method A. $LiAlH_4$. A soln of 24 g (0.079 mole) of a mixt of ethyl (±)-2β,3β-benzylidenedioxy-1α*H*,5α*H*-nortropane-8-carboxylate α- and β-Ph isomers in anhyd Et_2O was added dropwise to a suspension of 6 g (0.16 mole) of LAH in 1 l. of anhyd Et_2O with stirring at room temp. The reaction mixt was heated under reflux for 15 hr, cooled, and treated with 15 ml of H_2O followed by solid Na_2SO_4. The mixt was filtered and the solvent was removed by warming *in vacuo*. The residue (18.8 g) was distd through a short-path column at 125–140° (0.003 mm) to afford 16.2 g (83% yield) of a mixt of (±)-2β,3β-benzylidenedioxy-1α*H*,5α*H*-tropane α- and β-Ph isomers (**26** and **27**), n^{25}D 1.5478 (See Table II). Tlc analysis (silica gel, Et_2O–pentane–*i*-$PrNH_2$, 25:24:1) showed 2 close spots of almost equal intensity when charred with H_2SO_4. Nmr analysis indicated that this was a 3:2 mixt of α- and β-Ph isomers (ratio of peaks at 6.23 and 5.78 ppm). *Anal.* ($C_{15}H_{19}NO_2$) C, H, N.

Method B. AlH_3. A soln of AlH_3 was prepd by the method of Brown and Yoon[3] using 1.74 g (0.046 mole) of LAH and 2.2 g of concd H_2SO_4 in 55 ml of THF. A mixt of ethyl (±)-2β,3β-(*p*-fluorobenzylidine)-1α*H*,5α*H*-nortropane-8-carboxylate α and β isomers (7.2 g, 0.022 mole) in 5.6 ml of THF was added to the AlH_3 soln with stirring at room temp. After 20 min, the reaction was quenched by the addn of 5 ml of a THF–H_2O mixt (1:1). More H_2O was added and the mixt was extd with Et_2O. The Et_2O was washed (satd NaCl), dried (Na_2SO_4), and evapd to afford 5.4 g of an amber oil. Short-path distn afforded 4.7 g (80% yield) of a mixt of (±)-2β,3β-(*p*-fluorobenzylidenedioxy)-1α*H*,5α*H*-tropane α- and β-aryl isomers (**32** and **33**). See Table II.

(±)-2β,3β-Benzylidenedioxy-1α*H*,5α*H*-nortropane, α- and β-Phenyl Isomer Mixture (42 and 43). A soln of 15 g (0.07 mole) of ethyl (±)-2β,3β-dihydroxy-1α*H*,5α*H*-nortropane-8-carboxylate (**2**) in 250 ml of H_2O and 250 ml of concd HCl was heated on a steam bath for 5 hr. The reaction mixt was cooled and made alkaline with concd NaOH. The soln was concd by heating *in vacuo*. Extn of the residue several times with a mixt of $CHCl_3$–EtOH (2:1) afforded a residue after evapn that was extd with Et_2O to give 6.17 g (62% yield) of a solid, mp 159–161°, that was used directly without further characterization.

The solid was converted to an acetal by reaction with 30 ml of benzaldehyde under condns used in the preparation of *O,O'*-benzylideneecgoninol as described below. Short-path distillation of the crude product afforded 4.5 g (44% yield) of a mixt of **42** and **43** (see Table II for constants).

Mixture of Ethyl (±)-2β,3β-(*p*-Benzyloxybenzylidenedioxy)-1α*H*,5α*H*-nortropane-8-carboxylate (22 and 23). A soln of 9.5 g (0.026 mole) of acetates (**20** and **21**) (6:5 mixt of isomers, α:β) in 250 ml of THF containing 1.42 g (0.026 mole) of NaOMe was heated under reflux for 2 hr. A soln of 4.5 g (0.026 mole) of $PhCH_2Br$ in 10 ml of Et_2O was added and the soln was heated under reflux for another 3 hr in which time a large ppt of NaBr formed. The solid was collected on a filter and the filtrate was concd to afford 8 g of oil. Dil NH_4OH and Et_2O were added to the residue. The Et_2O was sepd, washed (dil NaOH followed by satd NaCl), dried (Na_2SO_4), and evapd to yield 6.3 g of a mixt of **22** and **23**.

This residue partially crystd from Et_2O and filtn gave 1 g of **22**, mp 113–115°. Preparative plate chromatog of the mother liquor [Camag silica gel, 1 pass Et_2O–pentane (1:1) and 4 passes Et_2O] afforded another 0.75 g of **22**, mp 111–112°. A more polar band furnished 2 g of oil **23** which, on the basis of nmr analysis, contd approx 16% of **22** (see Table I).

Preparation of Phenol Derivatives 38, 39, 40, and 41. A soln of 1.65 g (4.1 mmoles) of **22** in 100 ml of anhyd Et_2O was added with stirring to 1 g of LAH in 75 ml of THF. The reaction mixt was heated under reflux for 2 hr. After cooling, 3 ml of H_2O was carefully added. The mixt was filtd and the filtrate was concd by warming *in vacuo* to afford 1.45 g of an oil that was dissolved in 300 ml of 95% EtOH. The soln was shaken with 0.15 g of 10% Pd/C under 3 kg/cm² of H_2 for 2 hr. The catalyst was removed and the solvent was evapd by warming *in vacuo* to afford 0.95 g of a residue that solidified. The residue was recryst from Et_2O to give 0.75 g (75%) of **38**. See Table II for constants.

***O,O'*-Benzylideneecgoninol, Isomer Mixture about Benzylic C (44).** A suspension of 15.0 g (0.072 mole) of ecgoninol · HCl in 100 ml of PhCHO was heated on the steam bath for 6 hr while a slow stream of HCl gas was bubbled into the mixt. The solid dissolved within 10 min. After 1 hr and again after 4 hr the soln was warmed in a rotary evaporator *in vacuo* in order to remove accumulated H_2O. About 5 ml of PhCHO was removed each time.

The soln was cooled and dil with 400 ml each of Et_2O and pentane and the ppt was collected and washed with Et_2O. The ppt was suspended in 400 ml of Et_2O and gaseous NH_3 was added in excess. Removal of pptd NH_4Cl by filtration and concn of the filtrate gave an oil which was distd. A small forerun of PhCHO was followed by the product [16.2 g, bp 150–163° (0.10 mm)] as a viscous oil which solidified. Recryst from 11 ml of cyclohexane afforded 10.4 g (55%) of white spherulites (see Table II). The ir and nmr spectral curves were compatible with the assigned structure. There was no doubling of the NCH_3 or the OCHO signals in the crude or purified product as indication of an isomer mix.

***O,O'*-Benzilidenepseudoecgoninol, Isomer Mixture about Benzylic C (45).** A soln of 14.2 g (0.083 mole) of pseudoecgoninol in 75 ml of PhCHO was treated with gaseous HCl as was done with ecgoninol. One hour elapsed before the pptd pseudoecgoninol · HCl redissolved. Work-up as with ecgoninol gave an oil which solidified without distn. Trituration with pentane afforded 15.1 g (70%) of cryst acetal, mp 80.5–85°. Recryst from 30 ml of hexane gave 14.0 g of massive prisms. See Table II for physical and analytical data. The ir and nmr spectra were compatible with the assigned structure. The presence of an isomer mixt was not evidenced by any doubling of NCH_3 or OCHO signals.

(±)-2β,3β-(*p*-Methoxybenzylidenedioxy)-1α*H*,5α*H*-tropane Methiodide, β-Phenyl Isomer (7). A soln of 30 mg of **22** in 5 ml of Et_2O was treated with 0.5 ml of MeI. After 15 min the pptd solid was collected, dried at 60° (0.7 mm) for 1 hr, and subjected to nmr analysis which supported its assigned structure. Nmr peaks (DMSO-d_6) appeared at 3.14 (s, 3, OCH_3), 3.38 (s, 3, NCH_3), 3.82 (s, 3, NCH_3), and 5.73 ppm (s, 1, benzylic H).

(±)-2β,3β-(*p*-Methoxybenzylidenedioxy)-1α*H*,5α*H*-tropane methiodide, α-phenyl isomer (6), was prepd from **21** as described in the preceding experiment. Nmr peaks (DMSO-d_6) appeared at 3.04 (s, 3, OCH_3), 3.62 (s, 3, NCH_3), 3.71 (s, 3, NCH_3), and 6.24 ppm (s, 1, benzylic H).

Ethyl (±)-3α-Bromo-2β-hydroxy-1α*H*,5α*H*-nortropane-8-carboxylate 2-Benzoate (46). A soln of 3.0 g (10 mmoles) of a mixt of **8** and **9** in 150 ml of CCl_4 was treated with 2.0 g (11 mmoles) of NBS and 5 g (24 mmoles) of $BaCO_3$. The mixt was refluxed for 2.5 hr. The solid (succinimide) was collected on a filter disk and the filtrate was heated *in vacuo* leaving a residue of 4.4 g of crude **46**. Recrystallization from pentane afforded 3.1 g (81%) of **46**, mp 72–75°. The analytical sample from pentane melted at 77–79°; nmr peaks at δ 7.30–8.20 (5 H, m, arom), 5.35 (1 H, s, CHOBz), 4.65 and 4.50 (2 H, m, NCH), 4.30 (1 H, m, CHBr), 3.40–4.40 (2 H, m, OCH_2CH_3), heated to 80° (2 H, q, OCH_2CH_3) and 0.80–3.10 ppm (9 H, m, CH_3 + CH_2), heated to 80° (3 H, t, CH_3 + 6 H, m, CH_2). *Anal.* ($C_{17}H_{20}NO_4Br$) C, H, Br.

Ethyl (±)-2β,3β-Epoxy-1α*H*,5α*H*-nortropane-8-carboxylate (47). A soln of 41.1 g (0.11 mole) of **46** in 660 ml of EtOH was treated with 42.7 g (0.31 mole) of K_2CO_3 in 215 ml of H_2O. After being heated under reflux for 3 hr, the reaction mixt was extd with $CHCl_3$. The H_2O layer was washed again with $CHCl_3$–EtOH (2:1). The combined $CHCl_3$ solns were washed (satd NaCl), dried (Na_2SO_4), and concd *in vacuo* to afford an amber oil. Distn at 110–134° (0.25–0.35 mm) gave 15.6 g of **47** (72%); n^{25}D 1.4930. *Anal.* ($C_{10}H_{15}NO_3$) C, H, N. This oil crystd. Recrystallization from pentane gave colorless crystals, mp 52.5–53.5°. *Anal.* ($C_{10}H_{15}NO_3$) C, H, N.

(±)-1α*H*,5α*H*-Tropan-2β-ol (48). A soln of 0.60 g (3 mmoles) of **47** in 50 ml of Et_2O was heated under reflux for 2 hr with 0.60 g (16 mmoles) of LAH. H_2O (1.5 ml) was added and the salts were removed by filtn. The filtrate was concd *in vacuo* to afford 0.35 g (83%) of **48**; n^{25}D 1.4880; pK_a = 9.4 (reported,[8] n^{25}D 1.4886; pK_a = 9.62). The ir spectrum was identical with that of an authentic sample of **48**.

Ethyl (±)-2β,3α-Dihydroxy-1α*H*,5α*H*-nortropane-8-carboxylate (49). A soln of 12.3 g (0.063 mole) of epoxide **47** in 240 ml of $CHCl_3$ was stirred while 25 ml of CF_3COOH was added quickly. After being stirred at room temp for 1 hr the reaction mixt was added to 200 ml of 0.1 *N* NaOH. Extn with $CHCl_3$–EtOH (2:1), drying (Na_2SO_4), and evapn of the solvent by warming *in vacuo* afforded

13.9 g of an oil. The oily residue was dissolved in 180 ml of EtOH and was stirred together with 180 ml of 2 *N* NH_4OH for 1 hr at room temp. Satd NaCl was added and the soln was extd with $CHCl_3$-EtOH (2:1). Removal of the solvent from the dried (Na_2SO_4) exts by warming *in vacuo* afforded 12.3 g of an oily residue. Chilling of a soln of this residue in 25 ml of Et_2O gave 4 g of **49**, mp 93–98°. The mother liquor was chromatog on 100 g of silica gel. Elution with Et_2O afforded 4.2 g of crude starting material. Elution with 100% THF gave another 3.1 g of **49** (80% yield based on starting material consumed). Recrystallization from Et_2O afforded 4.2 g of **49**, mp 113–115°. *Anal.* ($C_{10}H_{17}NO_4$) C, H, N.

(±)-Tropane-2β,3α-diol (50). A soln of 0.47 g (22 mmoles) of **49** in 6 ml of THF was added to 0.22 g of LAH in 21 ml of THF and the mixt was heated under reflux for 6.5 hr. A 1:1 mixt (4 ml) of H_2O and THF was added, then more H_2O and the mixt was extd with $CHCl_3$-EtOH (2:1). The ext was dried (Na_2SO_4) and concd by heating *in vacuo* to afford 0.41 g of an oil that partially crystd. Recrystallization from C_6H_6 afforded 0.15 g of rhombic crystals of **50**,[9] mp 100–101°, ir ($CHCl_3$) 3438 and 3628 cm^{-1} (bonded and nonbonded OH bands).

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Diazirines. 3.[1] Synthesis of a Series of Diazirine-Containing Molecules and Their Pharmacological Evaluation

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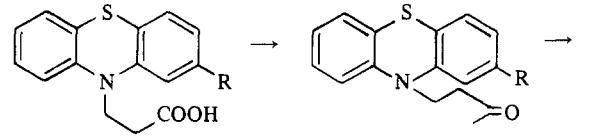
Several diazirine-containing congeners of biologically active molecules were synthesized. In addition, as a result of observations of biological activity for some small diazirine-containing molecules not related to compounds with established biological activity, a series of simple diazirines were prepared.

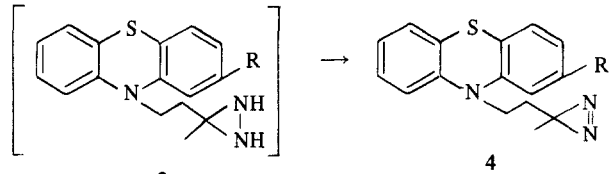
In an earlier report[2] we described the synthesis of several steroids containing the diazirine group and noted the favorable effect on the anabolic to androgenic ratio of certain of these derivatives. Since there were only a few other reports[3] concerning the biological properties of diaziridine and diazirine-containing molecules, we were encouraged to investigate the biological effects of this novel group.

Our initial approach was aimed at the preparation of diazirines congeneric with substances of established utility. Thus, we prepared the phenothiazine diazirine **4a** from phenothiazine acid **1a**[4] *via* ketone **2a**.† However, repeated attempts to effect the transformation of 2-chloro-*N*-(3-ketobutyl)phenothiazine **2b**, prepared from the corresponding acid **1b**, to the more interesting diazirine **4b** were unsuccessful. Although the reason for this failure is not known, this result, as well as the meager yield (15%) obtained in the preparation of **4a** from **2a**, further illustrates the less-than-satisfactory nature, in many instances, of the ketone-to-diazirine transformation.‡

The unreliable nature of this transformation with more complex molecules persuaded us to shift our approach and base our syntheses on the utilization of relatively simple, otherwise functionalized, diazirine-containing substances. Toward this end we prepared, among others, the acids **5** (n = 2–4), the alcohols **6** (n = 1–3), the acetals **7** (n = 0–2), and the amines **8** (n = 1 and 2). The preparation and properties of these useful simple molecules, as well as selected



1 **2**



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a series, R = H
b series, R = Cl

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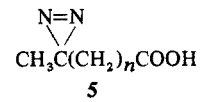
derivatives, are described in detail in an earlier paper.[1,§]

By unexceptional procedures, the following diazirine-



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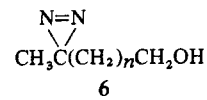

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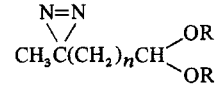

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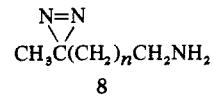

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containing analogs of clinically useful pharmaceutical agents were obtained: amides **9** and **10**, respectively, of psychic stimulants tranylcypramine and amphetamine, the phenyl-

†It should be noted that all attempts to isolate the diaziridine **3a**, a more pertinent analog of the aminoalkylphenothiazines, were unsuccessful.

‡For additional examples see ref 1 and 2.

§The use of these compounds for the preparation of cephalosporins containing the diazirine group has been reported; see ref 5.