project was completed while one of us (P. N. C.) was associated with Smith, Kline and French Labs.

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Compounds Affecting the Central Nervous System. 3.[1] 3β-Phenyltropan-2-ols

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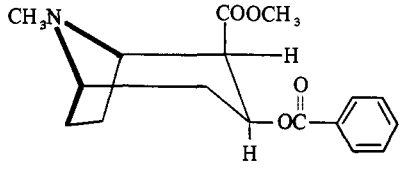
A group of 3β-phenyltropanes bearing both axial and equatorial hydroxyl and acetoxyl groups at C-2 was prepared. The ability of these compounds to prevent and reverse reserpine-induced ptosis in mice and their effects on overt behavior are reported. The modification having a 2β-hydroxyl group appeared to be at least as active as cocaine in the reserpine-induced ptosis screen and a more active stimulant. The optical antipodes of the more interesting compounds were prepared by resolving (±)-3-phenyltropidine. (±)-**8a** appears to be more active than the active enantiomer (−)-**8a** but no explanation is apparent. The ethylene bridge of the tropane structure was found necessary for activity.

The structure of cocaine (**1**) has been modified in a continued effort to obtain a variation of this molecule that would be a useful stimulant or antidepressant. This paper concerns that modification wherein a phenyl group is attached directly to the 3β position of the tropane ring and the 2β-carbomethoxy group is replaced by hydroxyl or acetoxyl in either the α or β configuration.



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Shortly after we prepared the compound with the 2α-hydroxyl configuration (**2a**), Lyle, *et al.*,[2] reported the synthesis of the same compound, but without biological data, by a similar procedure. Treatment of this 2α-hydroxy compound **2a** with ethyl chloroformate followed by saponification of the 2α-carbonate **4** afforded the α-hydroxyurethane **5a**. An alternate approach to **5a** was through the 2α-acetate **3a**,[3] prepared in our hands by the Ac_2O-pyridine method.† The acetate **3a** was converted to the urethane **6a** which was saponified to give the α-hydroxyurethane **5a**. The 2-ketourethane **7a**, obtained by Jones oxidation of **5a**, was reduced with $LiAlH_4$ to afford 3β-phenyltropan-2β-ol (**8a**, 30%), 3β-phenyltropan-2α-ol (**2a**, 31%), and a third 3-phenyltropan-2-ol (9%) which we speculate has the 3α-phenyl structure **9a**. The axial 2β-alcohol **8a** had a band in its ir spectrum at 3455 cm^{-1} that persisted even on dilution to a 0.001 *M* concentration, a characteristic of expected intramolecular hydrogen bonding with nitrogen.[4] Acetylation of **8a** with Ac_2O-pyridine afforded the 3β-acetate **10** (Scheme I).

Similarly **2b** was converted to the 2α-acetate **3b**.† Treatment of **3b** with methyl chloroformate afforded the urethane **6b** which was saponified to give **5b**. Jones oxidation followed by $LiAlH_4$ reduction gave equal amounts of the equatorial 2α-alcohol **2b** and the axial 2β-alcohol **8b**. We did not try to isolate the isomer **9b**. The axial 2β-alcohol **8b** had a band in its ir spectrum at 3450 cm^{-1} that persisted even on dilution to a 0.001 *M* concentration.

In order to gain insight into the role which chirality plays in this biological activity, the optical antipodes of **3a** and **8a** were prepared. 3-Phenyltropidine[5] was resolved by means of its bitartrate salt and the resulting enantiomers were hydroborated using Lyle's[2] method to give (+)- and (−)-**2a**. These alcohols were then converted to (+)- and (−)-**3a** and -**8a** by the procedures described above. *trans*-1-Ethyl-4-phenyl-3-piperidinol acetate (**11**), a nonrigid analog of **3a**, was prepared in order to relate rigidity factors with activity.

Biological Results. The compounds reported were evaluated by means of the reserpine-induced eyelid ptosis screen in mice[6] and by observation of overt behavioral changes (see Table I). Cocaine was included in the study for comparative purposes.

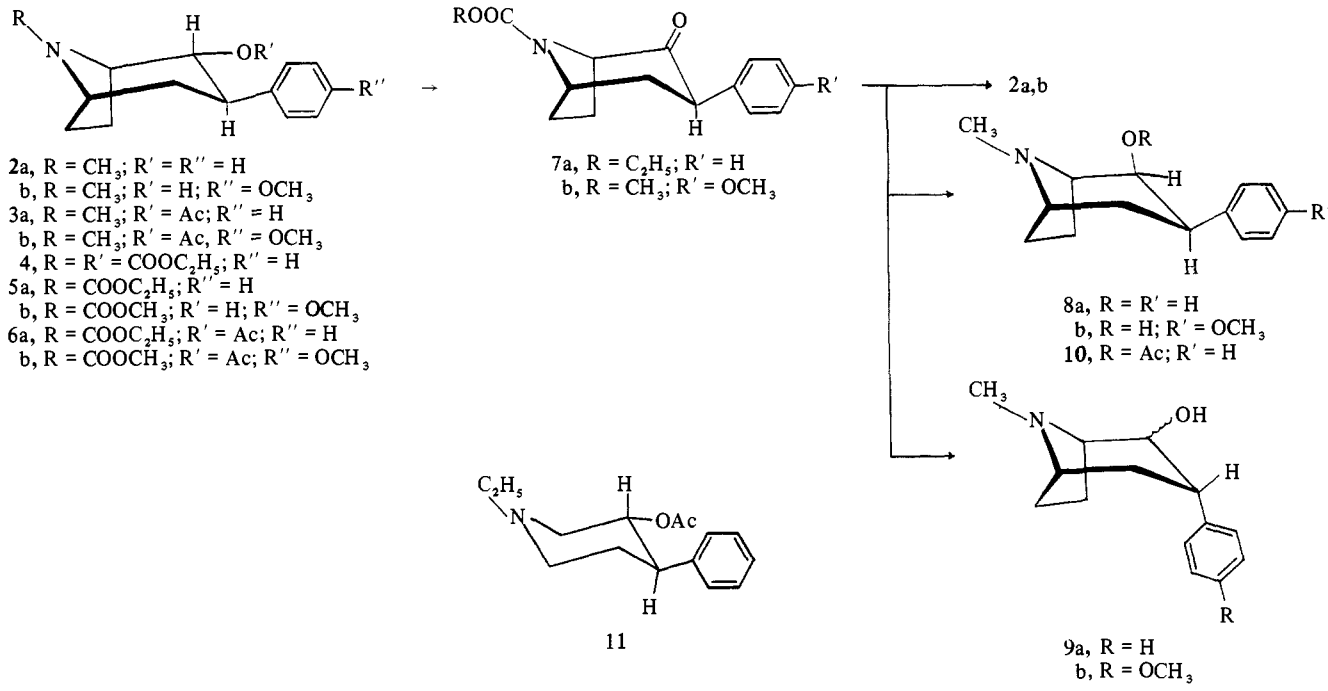
In the ptosis prevention test, only compound (±)-**8a** showed activity, being perhaps slightly more active than cocaine. In the ptosis reversal test, compounds (±)-**8a** and (±)-**3a** were quite active; (±)-**2a** and (±)-**8b** were minimally active. It is interesting that conversion of the 2-equatorial hydroxyl of (±)-**2a** to the axial configuration (±)-**8a** resulted in a substantial increase in activity in the ptosis reversal test. Acetylation of this axial isomer [forming (±)-**10**] produced a drop in this activity. In sharp contrast, acetylation of the equatorial isomer (±)-**2a** caused an increase in ptosis reversal activity. Introduction of a *p*-methoxyl group into the aromatic ring of (±)-**3a** lowered its activity [see (±)-**3b**].

The signs of overt stimulation paralleled the results of the ptosis screen, with indications that stimulation lasted as long as 3 hr with (±)-**8a** and (±)-**10**. (±)-**3a** and (±)-**8a** appear to be more stimulative than cocaine.

Study of the optical antipodes of **3a** and **8a** revealed that only one enantiomer of each was active. These active enantiomers [(+)-**3a** and (−)-**8a**] differ in actual sign of optical rotation but belong to the same absolute configurational

†Ellefson[3] reported failure in the preparation of 2α-acetates **3a** and **3b** using Ac_2O; it required ketene. He reported mp 65–75° (petroleum ether) for **3a**, mp 236.5–239° for **3a** HBr salt, and mp 88–92° for **3b**. We found mp 72–74° (pentane) for **3a**, mp 259–261° for **3a** HBr salt, and mp 100–102° (pentane) for **3b**.

Scheme I



2a, R = CH_3; R′ = R″ = H
b, R = CH_3; R′ = H; R″ = OCH_3
3a, R = CH_3; R′ = Ac; R″ = H
b, R = CH_3; R′ = Ac, R″ = OCH_3
4, R = R′ = $COOC_2H_5$; R″ = H
5a, R = $COOC_2H_5$; R″ = H
b, R = $COOCH_3$; R′ = H; R″ = OCH_3
6a, R = $COOC_2H_5$; R′ = Ac; R″ = H
b, R = $COOCH_3$; R′ = Ac; R″ = OCH_3

7a, R = C_2H_5; R′ = H
b, R = CH_3; R′ = OCH_3

2a,b

8a, R = R′ = H
b, R = H; R′ = OCH_3
10, R = Ac; R′ = H

11

9a, R = H
b, R = OCH_3

series with respect to asymmetric carbons 1 and 5 of the tropane nucleus; both are derived from (+)-phenyltropidine.

It is curious that *rac*-**8a** appears to be more active in both reversal and prevention of ptosis than *l*-**8a**. The presence of inactive *d*-**8a** in the racemate would normally be expected to act merely as a diluent. In order to confirm this observation, a concurrent test was run on (±)-**8a** and its separated optical antipodes, the results of which are shown in Table II. Again the racemic mixture appears to be significantly more active than the levo enantiomer. No explanation for this phenomenon is apparent.

Finally, the high level of activity of (±)-**3a** is somehow related to the presence of the ethylene bridge of the tropane moiety. The unbridged analog, (±)-**11**, is inactive. Whether this dramatic difference in activity is due to limitation of degrees of freedom with attendant differences in active-site complex stability or is simply a matter of steric inhibition at this site has yet to be determined.

Conclusions

(±)-3β-Phenyl-1α*H*,5*H*-tropan-2β-ol [(±)-**8a**] demonstrates about the same activity as does cocaine in the reserpine-induced ptosis test. It appears to be more stimulative than cocaine. This activity appears to reside in only one enantiomer of **8a** but, curiously, the racemate seems to be more active than the active enantiomer alone. The ethylene bridge of the tropane system is required for activity.

Experimental Section‡

Ethyl (±)-2α-Hydroxy-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (5a). Method A. Ethyl chloroformate (148 g, 1.4 mol) was added dropwise over a 40-min period to a stirred solution of 5.92 g (0.27 mol) of (±)-3β-phenyl-1α*H*,5α*H*-tropan-2α-ol (**2a**)§ in 775 ml of refluxing C_6H_6. After being heated under reflux for an additional 3 hr, the reaction mixture remained at room temperature overnight. Et_2O and 6 *N* HCl were added. The organic layer was washed (saturated NaCl), dried ($NaSO_4$), and concentrated by heating *in vacuo* to afford 68.6 g of a straw-colored, viscous oil. The physical data indicated that this oil was a mixture of **4** and **5a**: ir ($CHCl_3$) 3560 (m), 3380 (m), 1740 (ms), 1670 cm^{-1} (vs); nmr δ 1.4 (t, 4 H), 1.5–3.2 (m, 8–9 H), 3.6–4.6 (m, 5 H), 7.3 ppm (m, 5 H). This mixture (61.6 g, 0.19 mol) in 408 ml of H_2O and 950 ml of EtOH containing 61.6 g of $KHCO_3$ was heated under reflux for 24 hr. Et_2O was added, separated, washed (saturated NaCl), dried ($NaSO_4$), and concentrated *in vacuo* to yield 56.5 g of a straw-colored, viscous oil. A short-path distillation of the product at 155–158° (0.01 mm) afforded the analytical sample **5a**. *Anal.* ($C_{16}H_{21}NO_3$) C, H, N.

Method B. Ethyl chloroformate (54.2 g, 0.5 mol) in 100 ml of C_6H_6 was added over a 30-min period to a solution of 33.6 g (0.13 mol) of (±)-3β-phenyl-1α*H*,5α*H*-tropan-2α-ol acetate (**3a**)† in 200 ml of C_6H_6 being heated under reflux. After the mixture was refluxed for 3 hr and left overnight at room temperature, Et_2O and dilute HCl were added. The separated organic layer was washed (saturated NaCl), dried (Na_2SO_4), and concentrated *in vacuo* to yield 42 g of **6a** as a viscous oil: ir (film) 1740 (vs), 1680 cm^{-1} (vs); nmr δ 1.6–2.5 (m, 6 H + 3 H), 3.0 (m, 1 H, *ca.* J = 7, J = 10, and J = 10 Hz), 3.9–4.6 (m, 4 H), 5.1 (q, 1 H, *ca.* J = 3–4 and J = 10.5 Hz), 7.2 ppm (m, 5 H). *Anal.* ($C_{18}H_{23}NO_4$) OEt.

A solution of 40.4 g (0.13 mol) of **6a** (used without further purification) in 250 ml of H_2O and 750 ml of EtOH containing 40 g of $KHCO_3$ was heated under reflux for 24 hr. The work-up was that used in method A and yielded 43.8 g of **5a**.

Ethyl (±)-2-Oxo-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (7a). A solution of 32.8 g (0.10 mol) of **5a** in 250 ml of Me_2CO was treated with 8.7 *N* CrO_3–H_2SO_4 (Jones reagent) until the color remained orange (30 ml). Et_2O and H_2O were added and the Et_2O layer was separated, washed (saturated NaCl), dried (Na_2SO_4), and concentrated by warming *in vacuo* to afford 22.2 g of viscous oil **7a**: $n^{25}D$ 1.5380; ir (film) 1720 (s), 1680 cm^{-1} (s); nmr δ 1.2 (t, 3 H), 1.6–2.5 (m, 6 H), 3.6 (q, 2 H), 4.6 (m, 2 H), 7.2 ppm (m, 5 H). This was used without further purification.

$LiAlH_4$ Reduction of Ethyl (±)-2-Oxo-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (7a). A solution of 18.0 g (0.066 mol) of **7a** in

‡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 an internal standard. Infrared spectra were determined on a Model-21 Perkin-Elmer infrared spectrophotometer or, where dilution studies were done, a Beckmann IR-7 instrument. Spin-decoupling experiments were done with a Varian HA-100 instrument using a Hewlett-Packard audio oscillator 4204A. The mass spectra reported were measured with a Joelco JMS-1-OCS mass spectrograph. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Optical rotations of salts were measured in H_2O, those of bases in $CHCl_3$.

§Lyle, Carle, Ellefson, and Spicer[2] reported **2a** and its *p*-methoxy analog without melting points or purification procedures. In the Ellefson thesis,[3] the unsubstituted 3-phenyl-2α-tropanol **2a** was reported to melt at 120–122° with a footnote that some 3-phenyl-3-tropanol was present in the product. The *p*-methoxy analog **2b** was reported with mp 100–102°. Following chromatographic purification of these substances, we found **2a** to exhibit polymorphism: mp 120–122 and 129–131°; **2b** melted at 124–126°.

Table I. Effect of Compounds on Reserpine-Induced Eyelid Ptosis and the Overt Behavior of Mice

Compd	Dose,[a] mg/kg ip	Ptosis prevention MPS[b]	Ptosis prevention PV[c]	Ptosis reversal MPS[b]	Ptosis reversal PV[c]	Overt behavior[g]
(±)-2a	30	3.5	0.574	3.3	0.574	30 + 50 mg/kg controls, questionable depression
	50	3.1	0.646	2.8	0.038	
	G.T.[d]	3.3		3.5		
(±)-3a[e]	0.6			3.1	0.278	0.6, 6, 18, 30 mg/kg controls, stimulation and
	6			2.0	0.006	running
	18	3.4	0.798	1.9	0.010	
	30	3.1	0.646	1.6	0.004	
	H_2O[h]	3.3		3.4, 3.5		
(+)-3a[f]	0.9			3.1	0.506	9 mg/kg controls, stimulation, running 0.5 hr;
	9			2.5	0.038	26 and 44 mg/kg controls, depression, tremors
	26	2.9	0.328	2.1	0.014	at 0.5 hr, questionable stimulation at 3 hr
	44	3.0	0.506	2.1	0.014	
	H_2O[h]	3.3		3.4		
(−)-3a[f]	26	3.3	0.960	2.8	0.234	26 and 44 mg/kg controls, depression at 0.5 hr
	44	2.9	0.278	2.6	0.130	
	H_2O[h]	3.3		3.3		
(±)-3b	1			3.4	0.720	Drug controls at 10, 30, and 50 mg/kg, stimula-
	10			2.9	0.104	tion, running, gut spasms
	30	2.8	0.104	2.3	0.020	
	50	2.6	0.082	1.8	0.004	
	G.T.[d]	3.4		3.4, 3.5		
(±)-8a	0.1			3.5	1.0	10 mg/kg controls, mild stimulation at 0.5 hr;
	0.5			3.0	0.104	30 mg/kg controls, stimulation, running at 0.5
	1	2.9	0.328	2.8	0.020	hr, and mild stimulation at 3 hr; reversal at 0.5
	10	2.8	0.194	2.5	0.002	hr; 30 + 50 mg/kg stimulation, running and
	30	2.4	0.050	1.8	0.002	jumping when touched
	50	2.1	0.010	1.8	0.002	
	G.T.[d]	3.3, 3.3		3.5, 3.5, 3.5		
(−)-8a[f]	26	3.0	0.720	2.4	0.064	26 and 44 mg/kg controls, mild stimulation,
	44	2.8	0.382	2.3	0.028	biting, squeaking, stimulation after 3 hr
	H_2O[h]	3.3		3.3		
(+)-8a[f]	26	3.1	0.720	3.3	0.328	26 and 44 mg/kg controls, depression, tremors
	44	2.9	0.328	2.9	0.574	at 0.5 hr, questionable stimulation at 3 hr
	H_2O[h]	3.3		3.6		
(±)-8b	30	3.3	1.00	2.8	0.194	Drug controls at 30 and 50 mg/kg, stimulation,
	50	3.1	0.720	2.6	0.082	hyperexcitable, jumping, squeaking
	G.T.[d]	3.3		3.4		
(±)-10[f]	26	2.9	0.234	2.5	0.064	26 mg/kg controls, stimulation, running at 0.5 hr,
	44	2.7	0.190	2.1	0.014	and mild stimulation at 3 hr; 44 mg/kg con-
	H_2O[h]	3.4		3.4		trols, stimulation, running, some atoxia con-
						vulsions at 0.5 hr, and mild stimulation at 3
						hr; reversal at 0.5 hr; 26 and 44 mg/kg stimula-
						tion, some squeaking, prevention 44 mg/kg,
						1/8 dead before reserpine
(±)-11[f]	30	2.9	0.382	3.1	0.506	Inactive
	50	2.6	0.104	3.1	0.506	
	H_2O[h]	3.3		3.4		
Cocaine (1)	1	3.5	0.960	3.4	0.960	50 mg/kg controls, excitement convulsions;
	10	3.4	0.646	2.1	0.010	50-mg reversal, convulsions, complete recovery
	30	2.9	0.160	1.5	0.002	from reserpine, 1/8 dead at 100 mg at 0.5 hr;
	50	2.4	0.010	0.05	0.000	mild stimulation up to 5 hr
	H_2O[h]			3.4		

[a]Doses calculated as free base. [b]MPS, mean ptotic score. [c]PV, probability value, significant if 0.05 or lower. [d]1% gum tragacanth mucilage controls. [e]Tested as cyclohexanesulfamate. [f]Tested as HCl salt. [g]Effect of compound alone unless otherwise specified as "reversal." [h]H_2O control.

300 ml of Et_2O was added dropwise to a suspension of 8 g of $LiAlH_4$ being stirred in 500 ml of Et_2O. After 2 hr of refluxing, 20 ml of H_2O was added with cooling. The salts were separated by filtration and the Et_2O was evaporated to afford 14.3 g of oil that was chromatographed on 750 g of silica gel using Et_2O–pentane–*i*-$PrNH_2$ (25:72:3) for elution. The fractions were combined on the basis of tlc analysis. The combined early fractions afforded 7.7 g of crude **8a** contaminated with **9a**. The later fractions afforded 5.7 g of crude **2a** which, upon recrystallization from Et_2O, yielded 3.7 g of **2a**, mp 119.5–122°.

The crude **8a** combined with 1.7 g of mid-fraction material was chromatographed on 29 silica gel coated plates (Brinkmann PF 254 silica gel, 20 × 40 cm) having a 1-mm coating. The plates were developed with Et_2O–*i*-$PrNH_2$ (97:3). The least polar zone solid (5.5 g) was recrystallized from Et_2O to yield 4.2 g of (±)-3β-phenyl-1α*H*,5α*H*-tropan-2β-ol (**8a**), mp 96–98°. The analytical sample (from Et_2O) had mp 98–100°; ir (CCl_4) 3615, 3455 cm^{-1}; ir (CCl_4, 0.05–0.001 *M*) 3455 cm^{-1}. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

The acetate **10** HCl salt (Ac_2O–pyridine) from acetone exhibited polymorphism, forming a clear melt at 245–246°, resolidifying, and then decomposing at 269°. *Anal.* ($C_{16}H_{21}NO_2 \cdot HCl$) C, H, Cl.

A mid-zone solid (1.7 g) was recrystallized from Et_2O to afford 1.2 g of **9a**, mp 135–137°. The analytical sample (from Et_2O) had mp 136–138°; ir (CCl_4, 0.05–0.001 *M*) 3605 cm^{-1}; nmr δ 1.2–2.2 (m, 7 H), 2.2 (s, 3 H), 3.3 (m, 3 H), 4.3 (m, 1 H), 7.2 ppm (m, 5 H). *Anal.* ($C_{14}H_{19}NO$) C, H, N.

The acetate of **9a** showed poor crystallizing properties but gave only 1 spot by tlc analysis; nmr spin decoupling studies indicated $J_{1,2}$ = *ca.* 7 Hz. The most polar zone solid (1.5 g) was recrystallized from Et_2O to yield another 0.7 g of **2a**, mp 119–121°.

(±)-3β-(*p*-Methoxyphenyl)-1α*H*,5α*H*-tropan-2β-ol (**8b**). (±)-3β-(*p*-Methoxyphenyl)-1α*H*,5α*H*-tropan-2α-ol acetate (**3b**)† was converted to urethane **6b** using methyl chloroformate as the reagent in method B above. *Anal.* ($C_{18}H_{23}NO_5$) C, H, N. Saponification of **6b** by the described method afforded oily **5b**. *Anal.* ($C_{16}H_{21}NO_4$) C, H, N.

Oxidation of alcohol **5b** as described for **5a** afforded the 2-oxo compound **7b** as an oil which was used without purification. Reduction of **7b** (12.3 g, 0.043 mol) with $LiAlH_4$ yielded 2.5 g (24%) of the

Table II. Results of Concurrent Testing of (±)-8a, (+)-8a, and (−)-8a in Reversal of Reserpine-Induced Eyelid Ptosis (Mice)

Compd	Dose[a]	MPS[b]	PV[c]	Overt behavior[d]
(±)-8a	1	3.1	0.506	Controls, 10 and 30, stimulation and running, some biting and squeaking at 0.5 hr
	10	1.9	0.010	
	30	1.8	0.002	
	Control	3.4		
(−)-8a	0.9	3.3	0.720	Controls, 9, ? mild stimulation at 0.5 hr, mild stimulation at 3 hr; controls, 26, mild stimulation and running at 0.5 hr, mild stimulation at 3 hr
	9	2.8	0.194	
	26	2.3	0.014	
	Control	3.4		
(+)-8a	0.9	3.3	0.720	Controls, 26, ? depression at 0.5 hr, ? stimulation at 3 hr
	9	3.0	0.382	
	26	2.8	0.104	
	Control	3.4		

[a]Doses calculated as free base, mg/kg ip. [b]MPS, mean ptotic score. [c]PV, probability value, significant if 0.05 or lower. [d]Effect of compound alone.

β-alcohol **8b**, mp 85.5–87.5°, which on recrystallization from Et_2O melted at 86–87.5°; ir (CCl_4, 0.05–0.001 *M*) 3450 cm^{-1}. *Anal.* ($C_{15}H_{21}NO_2$) C, H, N. Also obtained from the reduction was 2.4 g (23%) of the α-alcohol **2b**,§ mp 124–126° (Et_2O), and an oil in intermediate polarity amounting to 0.3 g which probably contains **9b**.

Resolution of (±)-3-Phenyltropidine. A solution of 92 g (0.61 mol) of (+)-tartaric acid in 240 ml of H_2O was treated with 122.2 g (0.61 mol) of 3-phenyltropidine in 240 ml of Me_2CO. The solution was cooled in an ice bath and the precipitated bitartrate salt was collected. Fractional crystallization from 1:1 H_2O–acetone (6 ml/g) afforded 38.6 g of an apparently hydrated bitartrate: mp 57–60°; $[\alpha]^{25}D$ +23.1°.

The mother liquors were combined and made alkaline with concentrated NH_4OH. Et_2O extraction afforded 97.4 g of basic material which was dissolved in 200 ml of acetone and added to 76 g (0.50 mol) of (−)-tartaric acid in 200 ml of H_2O. The solution was cooled in an ice bath and the precipitated bitartrate salt was collected. Fractional crystallization from 1:1 H_2O–acetone (6 ml/g) afforded 72.5 g of an apparently hydrated bitartrate: mp 56–61°; $[\alpha]^{25}D$ −23.6°.

After recycling the mother liquors, another 64 g of bitartrate, mp 57–59°, $[\alpha]^{25}D$ +21.6°, and 35.8 g of bitartrate, mp 55–62°, $[\alpha]^{25}D$ −21.5°, was obtained.

(+)-3β-Phenyltropidine.# A solution of 103 g of (+)-phenyltropidine (+)-bitartrate·$(H_2O)_x$ in 200 ml of H_2O was made alkaline with concentrated NH_4OH. The Et_2O extract was dried (Na_2SO_4) and concentrated to afford 44.4 g of crude (+)-3β-phenyltropidine. Distillation at 93–101° (0.3–0.7 mm) gave 42.4 g of (+)-3β-phenyltropidine: $n^{25}D$ 1.5785; $[\alpha]^{25}D$ +37.9°. *Anal.* ($C_{14}H_{17}N$) C, H, N.

(−)-3β-Phenyltropidine.# (−)-3β-Phenyltropidine (−)-bitartrate·$(H_2O)_x$ (108.3 g) in a similar fashion afforded 50 g of crude (−)-3β-phenyltropidine. Distillation at 94–110° (0.3–0.4 mm) gave 43.5 g of (−)-3β-phenyltropidine: $n^{25}D$ 1.5781; $[\alpha]^{25}D$ −39.6°. *Anal.* ($C_{14}H_{17}N$) C, H, N.

(+)-3β-Phenyl-1α*H*,5α*H*-tropan-2α-ol [(+)-2a]. A solution of 40.6 g (0.20 mol) of (+)-3β-phenyltropidine in 225 ml of THF was added dropwise to 460 ml of 1 *M* BH_3 in THF with stirring in an ice bath. After being heated for 5 hr under reflux and standing at room temperature ovenight, the solution was carefully treated with 35 ml of H_2O added dropwise followed by 170 ml of 3 *N* NaOH. A 30% solution (65 ml) of H_2O_2 was added dropwise at a rate that maintained reflux. After being heated for an additional 1 hr under reflux, the reaction mixture was cooled. Et_2O was added and the layers were separated. The Et_2O was dried (Na_2SO_4) and evaporated. The residue was taken up in 300 ml of MeOH and was shaken with Raney Ni for 1 hr. Filtration of the catalyst and evaporation afforded 44 g of crude product. Crystallization from Et_2O gave 21.4 g of (+)-2a: mp 147–148°; $[\alpha]^{25}D$ +42.4°. A second crop, recrystallized from Et_2O, gave (±)-2a: mp 120–123°; $[\alpha]^{25}D$ 0°. The analytical sample of (+)-2a** melted at 147.5–148.5°, $[\alpha]^{25}D$ +42.5°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

(+)-3β-Phenyl-1α*H*,5α*H*-tropan-2α-ol acetate [(+)-3a]** melted at 71.5–73.5° (pentane), $[\alpha]^{25}D$ +64.5°. *Anal.* ($C_{16}H_{21}NO_2$) C, H, N.

HCl salt of (+)-3a: mp 263–264° dec (acetone); $[\alpha]^{25}D$ +33.5°. *Anal.* ($C_{16}H_{21}NO_2 \cdot HCl$) C, H, Cl.

(−)-3β-Phenyl-1α*H*,5α*H*-tropan-2α-ol [(−)-2a]. In a similar procedure 42 g of (−)-3β-phenyltropidine afforded 22.1 g of (−)-2a: mp 146.5–148.5°; $[\alpha]^{25}D$ −41.3°. A second crop, recrystallized from Et_2O, gave (±)-2a: mp 119–121°; $[\alpha]^{25}D$ −3.6°. The analytical sampe of (−)-2a** melted at 147.5–148.5°, $[\alpha]^{25}D$ −42.0°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

(−)-3β-Phenyl-1α*H*,5α*H*-tropan-2α-ol acetate [(−)-3a]** melted at 71.5–73° (pentane), $[\alpha]^{25}D$ −63.8°. *Anal.* ($C_{16}H_{21}NO_2$) C, H, N.

HCl salt of (−)-3a: mp 264–265° dec (acetone); $[\alpha]^{25}D$ −34°. *Anal.* ($C_{16}H_{21}NO_2 \cdot HCl$) C, H, Cl.

The following resolved compounds** were prepared by the above described procedures giving ultimately the enantiomers of 8a.

Ethyl 2α-hydroxy-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (optically active 5a) from (+)-2a was characterized spectrally.

Ethyl 2α-hydroxy-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (optically active 5a) from (−)-2a was characterized spectrally.

Ethyl-2-oxo-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (optically active 7a) from (+)-2a was characterized spectrally.

Ethyl 2-oxo-3β-phenyl-1α*H*,5α*H*-nortropane-8-carboxylate (optically active 7a) from (−)-2a was characterized spectrally.

(+)-3β-Phenyl-1α*H*,5α*H*-tropan-2β-ol [(+)-8a] from (−)-2a: mp 122–124° (Et_2O); $[\alpha]^{25}D$ +113.1°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

HCl salt of (+)-8a: mp 297–298° dec (CH_3CN); $[\alpha]^{25}D$ +84.6°. *Anal.* ($C_{14}H_{19}NO \cdot HCl$) C, H, Cl.

(−)-3β-Phenyl-1α*H*,5α*H*-tropan-2β-ol [(−)-8a] from (+)-2a: mp 121–122° (Et_2O); $[\alpha]^{25}D$ −114.7°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

HCl salt of (−)-8a: mp 293–295° dec (CH_3CN); $[\alpha]^{25}D$ −84.0°. *Anal.* ($C_{14}H_{19}NO \cdot HCl$) C, H, Cl

***trans*-(±)-1-Ethyl-4-phenyl-3-piperindol 3-Acetate Hydrochloride (11).** A mixture of 3.0 g of *trans*-(±)-1-ethyl-4-phenyl-3-piperidinol†† in 7.5 ml of Ac_2O and 15 ml of pyridine was heated at 100° for 30 min and left overnight. The oily acetate, isolated in the usual manner, was converted to its HCl salt: heavy needles from acetone; mp 186.5–188°. *Anal.* ($C_{15}H_{21}NO_2 \cdot HCl$) C, H, Cl.

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#This isomer is not quite optically pure. Complete purification was accomplished in the next step.

**Nmr and ir spectra were identical with spectra of unresolved samples.

††The authors thank Dr. W. B. Dickinson of these laboratories for a sample of this unpublished compound. The 1-methyl homolog is described; see ref 7.