

rated, combined with the filtrate from the second crystallization, and recrystallized from EtOAc giving 0.22 g of yellow crystals, mp 237–239°. This was found by ir, nmr, and uv spectra to have the structure 15. The principal spectral bands are: ir (Nujol mull) 1725, 1685 (C=O) and 1620, 1590, 1580 cm^{-1} (C=N; C=O); uv (EtOH) 220 $\text{m}\mu$ (ϵ 32,050), 265 (13,250), 374 (5150); nmr (CDCl_3) δ 3.22 and 3.24 (2 s, 6, NCH_3), 6.42 (s, 1, 5=CH), and between 6.75 and 7.55 (m's, 7, arom H's).

Column fractions 10–17 were evaporated giving 0.2 g of nearly white solid. This was recrystallized from *i*-PrOH yielding 0.18 g of white needles, mp 226–228.5°. Ir, nmr, and analysis showed this to have the structure 16. The principal spectral bands are: ir (Nujol mull) 1740, 1675 (C=O) and 1610, 1590, 1570 cm^{-1} (C=N; C=C); nmr (CDCl_3) δ 1.8 (d, 3, 5- CH_3), 3.39 (s, 3, NCH_3), 4.14 (q, 1, 5-CH), and between 7.05 and 7.65 (m's, 7, arom H's).

7-(*o*-Chlorophenyl)-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,5*H*)-dione 2-Methoxyethanol Solvate (17). This was prepared from 5.39 g (0.02 mol) of 24 essentially as described for 13 using diethylene glycol-dimethyl ether as a solvent for the first step. The intermediate 1-carboxy-3-[5-*o*-chlorophenyl]-3*H*-1,4-benzodiazepin-2-yl]urea failed to crystallize but tlc (SiO_2 , 5% MeOH in CHCl_3) showed mostly one spot. It was used in the second step without purification. Crude 17 crystallized from the xylene solution during reflux. It was collected and recrystallized first from MeOH and then from 2-methoxyethanol and dried at 100° (0.02 mm) for 6 hr giving 2.95 g of solid, mp 225–232°. This was found by nmr to contain one molecule of 2-methoxyethanol. The principal spectral bands are: ir (Nujol mull) 3250, 3060 (NH/OH), 1705 (C=O), and 1615, 1595, 1570 cm^{-1} (C=N; C=C); nmr ($\text{DMSO}-d_6$) δ 3.25 (s, 3, OCH_3), between 3.0 and 3.8 (m's, 5, $\text{OCH}_2\text{CH}_2\text{OH}$), ab centered at 4.3 and 4.8 (2, $J = -11$ Hz, 5- CH_2), and between 6.8 and 7.8 (m's, 8, arom H's).

1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-2-imidazolidinone (18). To a solution of 7.5 g (0.02 mol) of 8 in 100 ml of THF under N_2 was added portionwise with stirring 3.0 g (0.07 mol) of 56% NaH in mineral oil. After stirring at room temperature for 18 hr the mixture was concentrated *in vacuo*, mixed with water and pentane, and neutralized with AcOH. The solid was collected, washed (H_2O and pentane), and dried giving 6.66 g of crystalline solid, mp 217–227° dec. Recrystallization from *i*-PrOH yielded 4.45 g (65.5%) of white crystals, mp 245–247.5°. The principal spectral bands are: ir (Nujol mull) 3220, 3120 (NH), 1710 (C=O), and 1605, 1580 cm^{-1} (C=N; C=C); nmr (CDCl_3) δ 3.46 (t, 2, CH_2), 4.05 (t, 2, CH_2), 3- CH_2 too broad to locate, 6.23 (broad s, 1, NH), and between 7.1 and 7.7 (m's, 8, arom H's); mass spectrum $M^+ \cdot$ 338 (1 Cl).

1-[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]-2-imidazolidinone (19). This was prepared as described for 18 from 4.1 g (0.01 mol) of 10. The crude product was dissolved in EtOAc, treated with decolorizing charcoal, filtered, concentrated, and diluted with Et_2O giving 1.16 g (31%) of white crystals, mp 197–199°. The principal spectral bands are: ir (Nujol mull) 3270, 3120 (NH), 1725 (C=O), and 1605, 1580 cm^{-1} (C=N; C=C); nmr (CDCl_3) δ 3.45 (t, 2, CH_2), 4.07 (t, 2, CH_2), 4.8 (broad s, 2, 3- CH_2), 6.5 (broad s, 1, NH), and between 7.0 and 7.6 (m's, 7, arom H's).

1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-methyl-

midazolidin-2-one (20). To a solution of 2.7 g (0.008 mol) of 18 in 50 ml of DMF, under N_2 , was slowly added with stirring 0.602 ml (2.0 g, 0.008 mol) of TlOEt. After stirring for 15 min 0.62 ml (0.01 mol) of MeI was added dropwise. After stirring at room temperature for 18 hr the mixture was filtered and the solid TlI was extracted with DMF. The DMF solution was concentrated *in vacuo* and diluted with water. The resulting solid was collected, washed (H_2O), and dried giving 2.58 g of cream-colored solid showing only one spot on tlc (SiO_2 , 5% MeOH in CHCl_3 or 60% EtOAc in cyclohexane). Recrystallization from *i*-PrOH yielded 2.32 g (82%) of light yellow crystals, mp 212–215° (after scintering at 195.5–199°). The principal spectral bands are: ir (Nujol mull) 1720 (C=O) and 1605, 1595, 1580 cm^{-1} (C=N; C=C); nmr (CDCl_3) δ 2.9 (s, 3, NCH_3), 3.38 (t, 2, CH_2), 3.95 (t, 2, CH_2), 3- CH_2 too broad to locate, and between 7.22 and 7.7 (m's, arom H's).

1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-[2-(dimethylamino)ethyl]-2-imidazolidinone (21). To a solution of 1.7 g (0.005 mol) of 18 in 25 ml of DMF, under N_2 , was added with stirring 0.362 ml (0.005 mol) of TlOEt. A solid separated and 1.3 ml (0.65 g, 0.006 mol) of 4.6 *M* 2-(dimethylamino)ethyl chloride in xylene was added. After stirring at room temperature for 18 hr tlc (SiO_2 , 20% MeOH in PhH) indicated the reaction was not complete so 1.3 ml more of the 2-(dimethylamino)ethyl chloride solution was added and stirring was continued for 4 days. The mixture was filtered, concentrated, diluted with H_2O , and extracted with CHCl_3 . The extracts were washed ($\text{H}_2\text{O} + \text{NaCl}$ solution) and dried (Na_2SO_4). Evaporation of the solution gave light brown gum which was crystallized from cyclohexane-pentane and recrystallized from cyclohexane yielding 1.07 g (52%) of fluffy white needles, mp 129–130.5°. The principal spectral bands are: ir (Nujol mull) 1710 (C=O) and 1600, 1580 cm^{-1} (C=N; C=C); nmr (CDCl_3) δ 2.22 [s, 6, $\text{N}(\text{CH}_3)_2$], 2.45 (t, 2, CH_2), 3.42 (t, 2, CH_2), 3.5 (t, 2, CH_2), 3.95 (t, 2, CH_2), 3- CH_2 too broad to locate, and between 7.1 and 7.7 (m's, arom H's); mass spectrum $M^+ \cdot$ 409 (1 Cl).

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Compounds Affecting the Central Nervous System. 4. 3 β -Phenyltropane-2-carboxylic Esters and Analogs

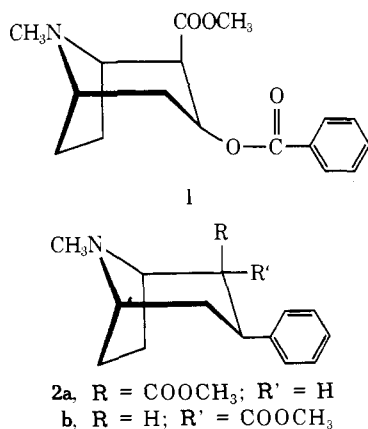
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Modification of the structure of cocaine (1) by attachment of the aromatic ring directly to the 3 position of the tropane ring has resulted in a five- to sixtyfold increase in several biological parameters accompanied by a tenfold drop in local anesthetic activity and a fourfold lowering of intravenous toxicity.

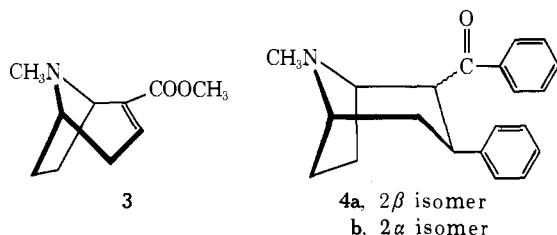
Cocaine (1) has a variety of pharmacological actions, primary among them being strong CNS stimulation and local anesthetic action. These effects are accompanied by

high toxicity and dependence liability. It was of considerable interest to see if modification of this molecule could result in a useful stimulant or antidepressant.



The present paper describes modification **2a** and analogs. Formally, the phenyl group of cocaine has been attached directly to the tropane ring. The most active of these compounds are powerful stimulants which inhibit norepinephrine uptake in both heart and brain, reverse and prevent reserpine-induced eyelid ptosis, and produce only mild local anesthesia. The enantiomers of these compounds are devoid of stimulative activity.

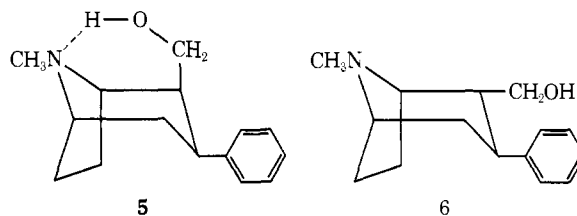
Compound **2a** was prepared along with **2b** (1:3 ratio) by the reaction of phenylmagnesium bromide with (–)-anhydroecgonine methyl ester (**3**) at –20°. The 2-benzoyl derivatives **4a** and **4b** were formed in small quantity through reaction with a second molecule of Grignard reagent; the 2 α configuration predominated. At room temperature, **4a** and **4b** were the principal products.¹ When 1 equiv of Cu₂Br₂ was used, only highly insoluble complexes resulted. A 5 mol % of cuprous salt produced troublesome complexes. Phenyllithium could not be substituted for the Grignard reagent owing to 1–2 addition with carbinol formation.¹ Most of the esters reported were prepared before optimum conditions were defined, and the low yields also reflect the early struggles with isomer separation.



Normally the 2-axial and 2-equatorial esters **2a** and **2b** were separated by column or plate chromatography. When it developed that the axial form **2a** was the epimer of interest, the equatorial epimer was removed from the reaction mixture by selective quaternization† with ethyl iodide at room temperature.

Configurational assignments for **2a** and **2b** were made on the basis of nmr and ir data.^{3,4} The more polar (silica tlc) of the epimers showed an nmr coupling constant for the C-2 and C-3 hydrogens which indicated that they were in a trans-diaxial relationship. Therefore, it was the 3 β -phenyl-2 α -carboxylate **2b**. The nmr spectrum of the less polar of the epimers showed the C-2 and C-3 hydrogens to have a cis relationship. The functional groups at these positions then had to be β,β (as in **2a**) or α,α . This final distinction was made by reducing the epimer with LiAlH₄. The resulting alcohol **5** of necessity had the 2 β configura-

tion since its ir spectrum showed intramolecular hydrogen bonding. The less polar epimer is then properly represented by structure **2a**. As a confirmatory experiment, **2b** was reduced to **6** which showed only the expected intermolecular hydrogen bonding; it disappeared at high dilution. The acetates of **5** and **6** were also prepared, primarily for biological evaluation.

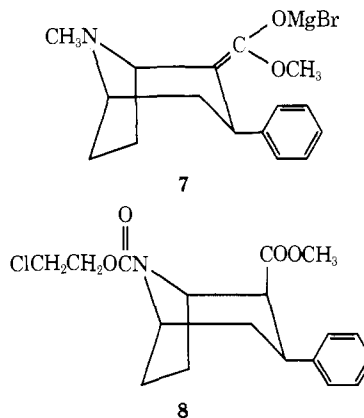


Nmr spectroscopy furnishes a convenient means for configurational assignment to these esters which are epimeric at C-2. The ester moiety in the axial (2 β) position has a shielding effect on the NCH₃, producing a shift of 0.12–0.20 ppm upfield from that of the C-2 equatorial ester.† There is a minor and unpredictable difference (± 0.03 or less) in the COOCH₃ positions of these epimers.

Optical rotatory data are of questionable usefulness for configurational assignments to pairs of these C-2 epimeric compounds. Thus, cocaine (axial 2-COOCH₃) has a molar rotation value which is 17,570° more negative than that of pseudococaine (equatorial 2-COOCH₃). In the parallel case of ecgonine *vs.* pseudococaine, the difference is minus 12,580°. The difference for **2a** and **2b** is only minus 2670°. The 2-axial benzoyl compound **4a** is 31,110° more positive than equatorial compound **4b**.

There is indication that the equatorial configuration is the more stable at C-2. In experiments followed by tlc, NaOCH₃ in CH₃OH converted **2a** into **2b**, but accompanying decomposition destroyed the latter. Under the same conditions **2b** never produced any **2a** spot. On one sample of **2a**, heating for 30 min at 150° caused 10% conversion to **2b**; 30 min at 200° caused 50% conversion (followed by tlc). Subsequent samples were stable for 2 hr at 200° and began to decompose in a complex manner at 250°.

Attempts to influence the ratio of **2a** to **2b** in their initial formation were focused on the proton source for the hydrolysis of the Grignard adduct **7**. In order to increase the amount of the axial isomer **2a**, it appeared necessary to increase the amount of protonation at C-2 from the



under or more hindered side of the molecule. The usual hydrolytic procedure of adding ice, followed by 2 N HCl, was varied by adding acetic acid in ether at both 0 and –50°, HCl gas, phenol in ether, BF₃·Et₂O, NH₄Cl, meth-

† Based on an observation of selective tropane quaternization by Weisz, *et al.*² Methyl iodide can be used where an isopropyl ester is present at C-2.

1NCH₃ peak positions (ppm): **2a**, 2.22, 15, 2.31, and 18, 2.25 (2 β -COOCH₃); **2b**, 2.42, 16, 2.43, and 19, 2.39 (2 α -COOCH₃).

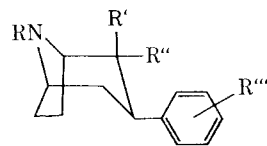


Table I

Compd	R	R'	R''	R'''	Mp, °C (base)	Mp, °C (salt)	Yield, %	Formula	Analyses ^a	$[\alpha]_D^{25}$, deg
2a	CH ₃	COOCH ₃	H	H	62-64 ^{b,c}		16	C ₁₆ H ₂₁ NO ₂	C, H, N	-5.3 ^{c,d}
2b	CH ₃	H	COOCH ₃	H	70-72 ^{e,f}	197-198 ^{g,h,i}	46	C ₁₆ H ₂₁ NO ₂ ·HCl	Cl, OCH ₃	+31.4 ^{g,h,i}
4a	CH ₃	COC ₆ H ₅	H	H	179-180 ⁱ		<1	C ₂₁ H ₂₃ NO	C, H, N	+44.1 ^c
4b	CH ₃	H	COC ₆ H ₅	H	129-130 ^j		<1	C ₂₁ H ₂₃ NO	C, H, N	-57.9 ^c
5	CH ₃	CH ₂ OH	H	H	95-97 ^{k,l}		92	C ₁₅ H ₂₁ NO	C, H, N	-73.4 ^c
6	CH ₃	H	CH ₂ OH	H	181-183 ^{m,n}	259-260 ^{m,b}	92 ^d	C ₁₅ H ₂₁ NO·HCl	C, H, Cl	+25.0 ^{g,h}
11	CH ₃	CH ₂ OAc	H	H		236.5-238.5 ^{h,m}		C ₁₇ H ₂₃ NO ₂ ·HCl	C, H, Cl	-73.2 ^h
12	CH ₃	H	CH ₂ OAc	H		227.5-230 ^{m,n}		(C ₁₇ H ₂₃ NO ₂) ₂ C ₁₀ H ₈ S ₂ O ₆	N, S	+31.1 ^h
13	CH ₃	COOCH ₃	H	F ^r	93-94 ⁵	288-290 dec ^m	5 ^{g,r}	(C ₁₆ H ₂₀ FNO ₂) ₂ C ₁₀ H ₈ S ₂ O ₆ ^g	C, H, S	-83.9 ^{g,h}
14	CH ₃	H	COOCH ₃	F ^r	70.5-73 ^r	85-93 ^{h,h}		C ₁₆ H ₂₀ FNO ₂ ·HCl·H ₂ O	C, H, Cl	+23.7 ^{g,h,r}
15	CH ₃	COOCH ₃	H	OCH ₃ ^r		288 dec ^{c,m}	1.2	(C ₁₇ H ₂₃ NO ₂) ₂ C ₁₀ H ₈ S ₂ O ₆ ^g	C, H, S	-92.0 ^g
16	CH ₃	H	COOCH ₃	OCH ₃ ^r	74.5-75.5 ^r		4	C ₁₇ H ₂₃ NO ₂	C, H, N	+9.3 ^r
17	CH ₃	H	COC ₆ H ₅	OCH ₃ ^r	122-123 ⁱ		5	C ₂₃ H ₂₇ NO ₂	C, H, N	-82.7 ^c
18	CH ₃	COOCH ₃	H	OCH ₃ ^r		Oil	4.5 ^d	C ₁₇ H ₂₃ NO ₂	dd	
19	CH ₃	H	COOCH ₃	OCH ₃ ^r	81-82 ^{l,m}			C ₁₇ H ₂₃ NO ₂	C, H, N	+4.5 ^c
20	CH ₃	COOCH ₃	H	OH ^s	Oil	311 dec ^{k,r}	38 ^g	C ₁₆ H ₂₁ NO ₂ ·HCl	C, H, Cl	-111.3 ^h
21 ^a	CH ₃	COO- <i>i</i> -Pr	H	H		244-245 dec ^{u,v,w}	20	C ₁₈ H ₂₃ NO ₂ ·HCl	C, H, N	-105.4 ^h
22 ^v	CH ₃	COO- <i>i</i> -Pr	H	F ^r	110-112 ^v	224 dec ^h	6 ^{h,p}	C ₁₈ H ₂₃ FNO ₂ ·HCl	C, H, Cl	-97.3 ^{g,h}
23 ^u	H	COOCH ₃	H	H		79-80 ^{s,u}		C ₁₅ H ₁₉ NO ₂ ·HCl·H ₂ O	C, H, Cl	-110.0 ^h
24 ^c	CH ₃	COOCH ₃	H	H	Oil	272-274 dec ^{i,k}	14 ^d	C ₁₆ H ₂₁ NO ₂ ·C ₁₀ H ₈ O ₆ S ₂	C, H, S	+85.2 ^h
25 ^u	CH ₃	COOCH ₃	H	F ^r	94-96 ^u	292-294 dec ^{m,w}	9.5	(C ₁₆ H ₂₀ FNO ₂) ₂ C ₁₀ H ₈ S ₂ O ₆ ^c	C, H, S	+84.5 ^{g,h}
26 ^c	CH ₃	H	COOCH ₃	F ^r	71.5-73.5 ^{v,w}		25	C ₁₆ H ₂₀ FNO ₂	C, H, F	-1.2 ^l
27 ^{d2}	CH ₃	COOH	H	F ^r		272-274 ⁿ	63	C ₁₅ H ₁₉ FNO ₂ ·HCl	C, H, Cl	-105.3 ^h
28 ^{d4}	CH ₃	COOH	H	H		273-274 dec ^h	84	C ₁₅ H ₁₉ NO ₂ ·HCl	C, H, N, Cl	

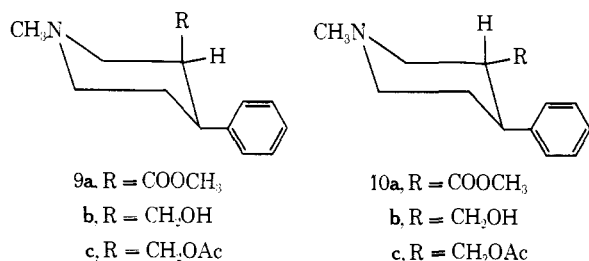
^a Analytical results for indicated elements are within $\pm 0.4\%$ of the theoretical values. ^b Plates. ^c 1% in CHCl₃. ^d Free base. ^e From pentane. ^f Prisms. ^g Salt. ^h 1% in H₂O. ⁱ From ether. ^j From EtOH. ^k Heavy needles. ^l From hexane. ^m From CH₃CN. ⁿ From acetone. ^o Spherulites. ^p Poor reaction work-up. ^q Naphthalene-1,5-disulfonate salt. ^r $[\alpha]_D^{25} +1.1^\circ$ (5% in CHCl₃) for free base. ^s From moist MeOH with ether added. ^t 5% in CHCl₃. ^u From MeOH with ether added. ^v Starting material described in Experimental Section. ^w Prepared from the *N*-(2-chloroethoxycarbonyl) derivative. See Experimental Section. ^x Para position. ^y Meta position. ^z $[\alpha]_D^{25} +4.6^\circ$ (2% in CHCl₃) for the free base. ^{aa} Fine needles. ^{bb} From EtOAc-Et₂O-H₂O mixture. ^{cc} 24, 25, and 26 are enantiomers of 2a, 13, and 14, respectively. ^{dd} See Experimental Section. ^{ee} From MeOH.

anol, and trimethylamine. Dilute HCl was then added in each case. These variations had no effect on the ratio of isomers formed.

The absolute configuration of cocaine is known.⁵ Since tropane ester **2a** was prepared from (-)-anhydroecgonine methyl ester derived from cocaine, it has the 1R,2S,3S,5S configuration. All other compounds reported here are related to this configuration with the exception of enantiomers **24-26** and piperidines **9** and **10**.

Table I summarizes the tropanes which were prepared in the course of defining the relationship between structure and CNS activity. The sole 8-nortropane, compound **23**, was prepared by treatment of **2a** with ClCH₂CH₂O-COCl⁶ to form **8** which was then cleaved to the HN< compound **23** by treatment with chromous perchlorate.⁷ Compounds **27** and **28** were prepared by simple acid hydrolysis of **13** and **2a**, respectively. Compounds **24-26** are enantiomeric with **2a**, **13**, and **14**, respectively. They were prepared from methyl (±)-3-oxo-1αH,5αH-tropane-2α-carboxylate which was resolved according to the method of Findlay⁸ with slight modification. The bitartrate salt of the unnatural (-) isomer was reduced (Pt, HOAc) to give methyl (+)-3α-hydroxy-1αH,5H-tropane-2α-carboxylate which was dehydrated with POCl₃ to form (+)-anhydroecgonine methyl ester. This enantiomer of natural (-)-anhydroecgonine methyl ester (**3**) was then converted to **24-26** by the standard procedure.

It was of particular interest to determine if high rigidity in the molecule was a requirement for CNS activity. The unbridged (nonrigid) analog of **2a** is the cis ester **9a**. It and the trans isomer **10a** have been reported by Plati, *et al.*,⁹ without configurational assignment. Reduction (LiAlH₄) of **9a** and **10a** has afforded alcohols **9b** and **10b**,[§] only one of which (**9b**, cis) showed intramolecular H bonding at high dilution. It was, therefore, possible to assign the cis and trans configurations respectively to the β and α compounds of Plati and coworkers. The corresponding acetate esters **9c** and **10c** were made for biological evaluation.



Biological Studies. Table II summarizes the overt behavioral effects produced by these 3β-aryltropane-2-carboxylates. The values reported are the lowest oral doses which produced an increase in locomotor activity. The most active compounds of the series are **13** and **23** which are some 64 times as active as cocaine. With a 4 mg/kg dose of **13**, stimulation was still evident at the end of 5 hr. Compound **25**, the enantiomer of **13**, is a mild depressant. Comparison of **2a** with **2b** and **13** with **14** shows that the 2-COOR group must have an axial configuration in order to be stimulative. Substitution of a 4-fluorine on the aromatic ring enhances activity (**13** vs. **2a**), whereas insertion of a 4-methoxy group reduces it (**15** vs. **2a**).

Reduction of the axial ester function on carbon 2 to a hydroxymethyl group (compound **5**) and acetylation of the resulting alcohol (compound **11**) did not lower the stimu-

[§]Plati, *et al.*,⁹ isolated a 1-methyl-4-phenylpiperidine-3-methanol of mp 107-109° by reduction of 5-carbomethoxy-4-phenyl-2-pyridone with copper chromite catalyst. It probably is the trans isomer **10b** (our mp 111-113° as opposed to mp 99-100° of the cis isomer).

Table II. Effect of 3β-Aryltropanecarboxylate Esters on Locomotor Activity in Mice

Compd	Min stimulative dose, mg/kg of base po	Compd	Min stimulative dose, mg/kg of base po
Cocaine	64	12^b	>256
2a^a	4	13^b	1
2b^b	>256	14^b	>256
5^a	4	15^b	64
6^b	>256	16^a	>256
9a^a	>256	17^a	>256
9c^b	256	21^b	4
10c^b	<256	22^b	4
11^b	4	23^b	1
		25^b	64 ^c

^a The free base was administered. ^b The salt of the compound shown in Table I was administered. ^c Slight depressant.

lative activity appreciably (compare with **2a**). However, removal of rigidity through removal of the ethylene bridge (compound **9a**) destroyed activity. Compound **9c**, the nonrigid analog of compound **11**, was only very weakly active. For all active compounds, the peak effect occurred at about 1 hr following medication. Further observations on stimulation are recorded in the ptosis study described below.

Like cocaine,¹⁰ the presently reported stimulants prevent as well as reverse reserpine-induced eyelid ptosis.¹¹ The most active compound, **13**, is more than five times as active as cocaine in the preventive test and 20 times as active in the reversal test. Table III summarizes the results. Again the enantiomer of **13** is inactive.

The local anesthetic action of these compounds was evaluated in parallel with cocaine using an intradermal anesthetic test in guinea pigs.¹² Compound **13** showed only about 15% of the local anesthetic activity produced by cocaine (after making allowance for the different salts involved). The activity of equatorial esters **2b** and **14** and the enantiomer **25** was not greatly different from that of compound **13**. Table IV summarizes these results.

Cocaine is known to inhibit the uptake of tritiated norepinephrine (NE-³H) by heart, brain, and other adrenergically innervated tissues. For determination of this type of inhibition in heart tissue by some of the presently reported compounds, these compounds were injected subcutaneously into mice. After 15 min, 1 μCi of NE-³H was injected into the tail vein. After 2 hr the animals were sacrificed, their hearts were incinerated, and the amount of NE-³H therein was compared with that found in controls. Figure 1 shows the inhibitory effects of compounds **2a** and **15** and how they compare with cocaine and desmethylinipramine (DMI). Compound **2a** and DMI are about equiactive and some 15 times more active than cocaine.

The role which various substances play in influencing the normal action of norepinephrine in rat brain can be studied by introducing tritiated norepinephrine (NE-³H) directly into the lateral ventricle of the brain.¹³ This procedure circumvents the blood-brain barrier to norepinephrine and allows the tritiated material to equilibrate with endogenous stores. Thus, when a compound like cocaine inhibits the absorption of norepinephrine by the neuron, administration of the compound prior to the administration of the tritiated norepinephrine results in significantly lower levels of radioactivity in the brain tissue as compared to unmedicated controls.

Table III. Effect of 3 β -Aryltropanecarboxylate Esters on Reserpine-Induced Ptosis in Mice

Compd	Dose, mg/kg ip	Prevention test		Reversal test		Overt behavior
		MPS ^a	PV ^b	MPS ^a	PV ^b	
2a	0.1			3.0	NS ^d	0.5 and 1 mg/kg controls questionable stim, 0.5 hr; 10, 30, and 50 mg/kg controls stim, running, jumping, biting, squeaking, hyperexcitable at 0.5 and 3 hr; mild stim at 5 hr; reversal 10, 30, and 50 mg/kg stim, running, biting, squeaking, vasodilation, some salivation at 0.5 hr
	0.5			2.9	NS	
	1	2.6	NS	2.4	0.038	
	10	2.1	0.038	1.8	0.002	
	30	1.4	0.000	1.3	0.000	
	50	0.75	0.000	1.1	0.000	
	G.T. ^e	3.1, 3.1		3.5, 3.4, 3.3		
2b	30	3.4	NS	2.6	NS	30 and 50 mg/kg controls mild stim, some biting, squeaking; reversal, 30 and 50 mg/kg, moving about at 0.5 hr
	50	2.6	NS	2.5	0.038	
	H ₂ O ^f	3.1		3.4		
5	1	3.4	NS	3.3	NS	10, 30, and 50 mg/kg stim, running, jumping, biting, squeaking, tearing, salivation, hyperexcitable at 0.5 hr; moderate stim at 3 hr; reversal, 10, 30, and 50 mg/kg, stim, running, biting, squeaking at 0.5 hr; prevention, 1/8 dead at 30 and 2/8 dead at 50 mg/kg before reserpine
	10	2.5	NS	1.8	0.002	
	30	2.3	0.054	1.8	0.002	
	50	1.6	0.018	1.8	0.002	
	G.T. ^e	3.3, 3.3		3.3, 3.4		
6	30	3.1	NS	3.0	NS	
	50	2.9	NS	2.8	NS	
	H ₂ O ^f	3.4		3.4		
11	0.1			3.4	NS	10, 30, and 50 mg/kg controls stim, running, jumping, biting, squeaking, hyperexcitable at 0.5 and 3 hr; mild stim at 5 hr; 0.5 and 1 mg/kg control questionable mild stim at 0.5 hr
	0.5			2.6	0.064	
	1			2.1	0.006	
	10			1.1	0.000	
	30	2.6	0.064	1.3	0.002	
	50	2.2	0.030	1.6	0.000	
	H ₂ O ^f	3.4		3.4, 3.5, 3.3		
12	30	3.4	NS	2.8	0.038	
	50	3.4	NS	2.8	0.064	
	H ₂ O ^f	3.4		3.5		
13	0.1			3.1	NS	0.5 and 1 mg/kg controls stim, running, jumping; 10, 30, and 50 mg/kg stim, running, jumping, biting, squeaking, some salivation, still stimulated at 3 and 5 hr; reversal, 10, 30, and 50 mg/kg stim, running, jumping, vasodilation, mild stimulation at 3 hr; prevention, 30 and 50 mg/kg, vasodilation
	0.5			2.4	0.010	
	1	2.5	0.064	2.4	0.004	
	10	2.1	0.006	1.1	0.000	
	30	1.4	0.000	1.8	0.002	
	H ₂ O ^f	3.4, 3.1		3.6, 3.3, 3.5		
23	1	3.0	NS	2.4	0.050	Stim, running, jumping, biting, squeaking at 10, 30, and 50 mg/kg; still stimulated at 3 and 5 hr
	10	1.8	0.006	1.5	0.002	
	30	0.9	0.000	1.3	0.000	
	50	0.9	0.000	1.0	0.000	
	H ₂ O ^f	3.3, 3.1		3.3, 3.4		
25	30	3.1	NS	2.8	NS	No changes obsd at 30 and 50 mg/kg
	50	3.0	NS	3.0	NS	
	H ₂ O ^f	3.4		3.5		
27	30	3.5	NS	3.1	NS	
	50	3.1	NS	3.1	NS	
	H ₂ O ^f	3.3		3.4		
Cocaine	1	3.5	NS	2.4	NS	50 and 100 mg/kg controls excitement, convulsions; reversal, 50 and 100 mg/kg, convulsions, complete recovery from reserpine; at 100 mg/kg 1/8 dead at 0.5 hr
	10	3.4	NS	2.1	0.010	
	30	2.9	NS	1.5	0.002	
	50	2.4	0.010	0.5	0.000	
	H ₂ O ^f	3.6		3.4		

^a Mean ptosis score. ^b Probability values (PV) were calculated on "two-tailed" probabilities. Values of 0.05 are considered significant. ^c Effect of compound alone unless otherwise specified as "reversal" or "prevention" test. ^d NS denotes "not significant." ^e 1% gum tragacanth mucilage controls. ^f H₂O control.

Table V shows the results of such a study wherein graded doses of compound 13 were administered subcutaneously. Cocaine was run in parallel for comparison, but higher doses of the latter were not practical owing to toxicity. 13 appears to be about 22 times more active than cocaine and apparently crosses the blood-brain barrier easily. Whereas 13 and DMI are about equiactive in the mouse heart, 13 is about 20 times more active than DMI in rat brain. This comparison is based on a report by Schildkraut, *et al.*,¹⁴ that 25 mg/kg of DMI caused a 30 \pm 3% drop in NE-³H concentration in rat brain.

Toxicity studies on compounds 2a and 13 in mice gave 24-hr LD₅₀ values of 63 (48-73) and 71 (64-78) mg/kg iv. re-

spectively, compared with 18 (17-19) mg/kg for cocaine. Both of these 3-aryltropanes showed about the same oral toxicity as that of cocaine, the values being in the 200-400 mg/kg range. Further indications of toxicity are contained in the notes on overt behavior in Table III.

Conclusions

Attachment of the benzene ring of cocaine directly to carbon 3 of the tropane moiety produced strongly enhanced stimulant activity. Using structure 2a as a point of reference, replacement of the *N*-methyl group by a hydrogen atom (23) or substitution of a fluorine for hydrogen in the para position of the benzene ring (13) enhanced

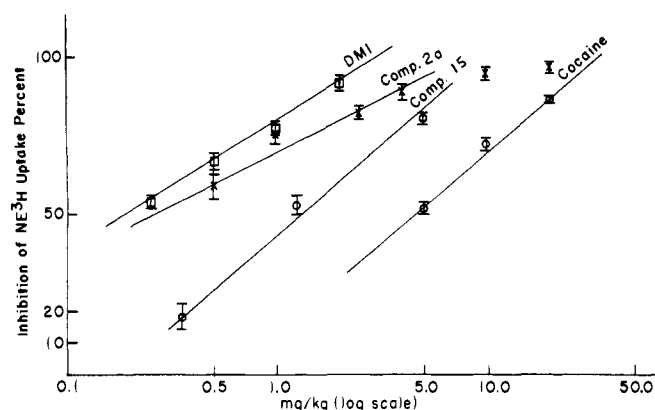
Figure 1. Inhibition of NE-³H uptake in mouse heart.

Table IV. Local Anesthetic Activity in Guinea Pigs

Drug ^a	Concn, ^b %	No. posi- tive/no. tested	Mean anes- thetic score	TAC ₅₀ , % (g/ml)	Ac- tivity ratio ^c
Cocaine	0.125	4/4	32	0.033	0.13
	0.06	4/4	14		
	0.03	4/4	5		
2a	1	4/4	27	0.25	0.13
	0.5	4/4	11		
	0.25	4/4	7		
Cocaine	0.125	4/4	24	0.035	0.2
	0.06	4/4	17		
	0.03	2/4	1.5		
2b	1	4/4	19	0.16	0.2
	0.5	4/4	13		
	0.25	4/4	9		
Cocaine	0.125	4/4	35	0.03	0.11
	0.06	4/4	21		
	0.03	3/4	5		
13	1	4/4	27	0.27	0.11
	0.5	4/4	18		
	0.25	2/4	2		
Cocaine	0.125	4/4	27	0.031	0.10
	0.06	4/4	14		
	0.03	3/4	5		
14	1	4/4	23	0.30	0.10
	0.5	4/4	15		
	0.25	2/4	1		
Cocaine	0.125	4/4	31	0.03	0.2
	0.06	4/4	25		
	0.03	7/8	3		
21	1	4/4	21	0.15	0.2
	0.5	4/4	19		
	0.25	4/4	11		
Cocaine	0.125	4/4	29	0.034	0.11
	0.06	4/4	14.5		
	0.03	3/4	4		
25	1	4/4	22	0.3	0.11
	0.5	4/4	11		
	0.25	2/4	3		

^a The free base **2a** was dissolved in dilute lactic acid for test. The remainder of the compounds were tested in the form of salts as listed in Table I. Cocaine was tested as its HCl salt. ^b The concentrations shown are those of salts used except for that of base **2a**. ^c Activity of cocaine = 1.

stimulant action even further. Other modifications of **2a** tended to diminish this activity. The enantiomer of **13** was not a stimulant. Removal of the ethylene bridge (**9a**) also destroyed activity. Moving the 2-carbomethoxy group from an axial to an equatorial configuration gave a compound (**2b**) which was inactive in the locomotor screen

Table V. Effect of Compound **13** and Cocaine on NE-³H Concentrations in Rat Brain

Compd	Dose, mg/kg (base)	nCi/g of brain ± S.E.	% reduc- tion of NE- ³ H
13	21	5.3 ± 0.5	61
13	5.3	5.7 ± 0.3	59
13	1.3	9.2 ± 0.7	33
Cocaine	28.5	10.3 ± 1.2	25
Control		13.7 ± 0.5	

(>256 mg/kg) but appeared to produce slight stimulation as judged by the operator of the ptosis test.

The general activity profile of these 3β-phenyltropane-2β-carboxylic esters appeared to parallel that of cocaine. Compound **13**, the most broadly studied member of the series, was about five times more active than cocaine in preventing reserpine-induced ptosis and some 20 times more effective in reversing it. Concurrently, the level of local anesthetic activity dropped to about 15% of that of cocaine. Finally, the inhibitory action of cocaine on uptake of norepinephrine in adrenergically innervated tissues was observed with **2a** and **13** in mouse heart and rat brain, these 3-phenyltropanes being some 15–20 times more active than cocaine.

Experimental Section**

General Method for 3β-Aryltropanecarboxylic Esters. The best method for preparing these compounds became apparent near the end of this work and is given in general terms here. Specific details follow under the appropriate compound heading with additional data in Table I. To an efficiently stirred solution of 1.0 mol of the Grignard reagent in 1.0 l. of Et₂O under N₂ and maintained at -20° (±3°) was added a solution of 0.5 mol of (-)-anhydroecgonine methyl ester in 300 ml of Et₂O. Stirring was continued at this temperature for 1 hr and then the mixture was poured onto 500 g of ice. This mixture was acidified with 2 N HCl to dissolve all solid and the Et₂O layer was then separated and discarded. The H₂O layer was made basic with concentrated NH₄OH and saturated with NaCl. Three extractions with Et₂O separated the product which was then distilled (0.4 mm). A minor amount of unchanged anhydroecgonine ester distilled first, followed by an unseparable mixture of the 2α- and 2β-carboalkoxy isomers. The 2-benzoyl-3-phenyltropane by-products, exemplified by **4a** and **4b**, remained in the still pot.

If isolation of both the 2α and 2β epimers was desired, the mixture of these isomers was chromatographed on silica gel (40 g/g of compound) using *i*-PrNH₂-Et₂O-pentane (3:30:67) for elution. The 2β epimer was eluted first. If only the biologically interesting 2β epimer was wanted, the mixture was heated under reflux for 5 hr with 4 vol of acetone and 1.1 equiv of EtI. Removal of acetone and excess EtI *in vacuo* and partition of the residue between Et₂O and H₂O gave the pure β epimer in the Et₂O layer and the quaternary salt of the α epimer in the H₂O.

Chromatography of the still pot residue above on silica gel afforded the 2β-aryl-3-aryltropane (such as **4a**) as a quickly eluted material and the 2α-aryl isomer (such as **4b**) as a more polar component.

Compounds 2a and 2b were formed in 75% yield, bp 128–134° (0.4 mm). Epimers were separated by chromatography. **2a** showed M⁺ 259; λ_{max} (oil) 5.72 and 5.82 μ; λ_{max} (KBr) 5.70 μ; nmr on HCl salt (10% in DMSO-*d*₆) J_{2,3} = 6.5 Hz. **2b** showed λ_{max} (oil) 5.76 μ; nmr on HCl salt (10% in DMSO-*d*₆) J_{2,3} = 11–12 Hz, J_{3,4} = 5.5, 12 Hz.

Compound 4a: ε_{254 nm} (EtOH) 11,200; λ_{max} (KBr) 5.93 μ; nmr J_{1,2} and J_{2,3} ca. 1.5 and 3 Hz but unassigned (axial benzoyl).

Compound 4b: ε_{246 nm} (EtOH) 13,800; λ_{max} (KBr) 5.97 μ; nmr J_{2,3} = 11 Hz, J_{1,2} = 2 Hz (equatorial 2-benzoyl).

3β-Phenyl-1αH,5αH-tropane-2β-methanol (5). A solution of 2.96 g (11.4 mmol) of **2a** in 15 ml of Et₂O was added dropwise

** All melting points are uncorrected. Nmr spectra were measured in CDCl₃ unless otherwise noted using TMS as an internal standard. Where water was used, the TMS was external. Brinckmann Instruments silica gel grade PF₂₅₄ was used in 1-mm thickness for preparative plate chromatography. Analytical results for indicated elements are within ±0.4% of the theoretical values.

with stirring to 0.47 g (12.4 mmol) of LiAlH_4 in 25 ml of Et_2O . The mixture was stirred at room temperature for 2 hr, treated with 1.1 ml of H_2O , and filtered. Concentration of the filtrate and recrystallization of the residue from pentane gave 2.43 g (92%) of needles, mp 94–96.5°. A further recrystallization from hexane gave 2.10 g of compound 5 of Table I: ir (CCl_4) broad OH band at 3231 cm^{-1} not diluted out in 0.001 M solution.

The acetate ester of 5 (Ac_2O -pyridine, 1 hr, 100°) was an oil whose crystalline hydrochloride salt is compound 11 of Table I.

3 β -Phenyl-1 α H,5 α H-tropane-2 α -methanol (6). This alcohol was prepared from 2b and LiAlH_4 in the manner described immediately above except that the cake resulting from hydrolysis had to be extracted thoroughly with CHCl_3 . The basic product was recrystallized to give compound 6 of Table I: ir (CCl_4) single sharp peak at 3648 cm^{-1} in 0.001 M solution.

The HCl salt of 6 is described in Table I. The acetate ester of 6 (Ac_2O -pyridine, 2.5 hr, 100°) was an oil whose crystalline naphthalene-1,5-disulfonate salt is compound 12 of Table I.

Compounds 13 and 14. Cu_2Cl_2 (7 mol %) was used in this preparation. The reaction was run at -10° . On a small scale they were separated by thick-layer plate chromatography (silica gel). On a large scale, epimer 13 was separated from 14 by selective quaternization of the latter with EtI.

Compounds 15 and 16. The unsaturated ester was added at 0° but the reaction was allowed to warm to 25° during the stirring period. Epimers were distilled together and then separated on silica preparative plates. The still pot residue crystallized and yielded compound 17. A repeat run at -20° with quenching at that temperature gave a 43.5% yield of the distilled mixture of esters 15 and 16, bp 164–179° (0.8–1.5 mm).

Compounds 18 and 19. The standard procedure gave 38% recovery of starting material and 34% of the 18–19 mixture, bp 150–170° (0.5 mm). Nmr indicated a 3:1 ratio of 2 α :2 β esters. Reflux of this mixture with 2 equiv of benzyl chloride in CH_3CN for 27 hr left most of the 2 β epimer 18 unchanged (4.5%). It was purified finally by plate chromatography (nmr compatible, NCH_3 2.25 ppm; $\epsilon_{273 \text{ nm}}$ 1980, $\epsilon_{280 \text{ nm}}$ 1810) and the oily base was used in the preparation of 20 without further characterization.

The benzyl quaternary of the 2 α epimer was debenzylated (Pd/C catalyst plus 1 equiv of HCl in 95% EtOH with H_2 under 3.5 kg/cm^2) to give the crystalline 2 α epimer. Preparative plate chromatography gave the analytical sample, compound 19 of Table I: nmr NCH_3 2.39 ppm; $\epsilon_{273 \text{ nm}}$ 2070, $\epsilon_{280 \text{ nm}}$ 1900.

Compound 20. A solution of 5.2 g of methoxy ester 18 in 25 ml of 48% HBr was refluxed for 1 hr and chilled, and the crystalline 3 β -(*m*-hydroxyphenyl)-1 α H,5 α H-tropane-2 β -carboxylic acid hydrobromide was collected (3.62 g, 66%). It was mixed with 80 ml of MeOH and gaseous HCl was bubbled in to saturation. The resulting solution was refluxed gently for 6 hr with a slow stream of HCl passing through. The solvent was removed, concentrated NH_4OH was added, and the basic ester product was extracted with ether. Conversion of the oily base to its HCl salt gave compound 20 of Table I.

Isopropyl esters 21 and 22 were prepared from the isopropyl ester of (–)-anhydroecgonine which is described immediately below.

(–)-Anhydroecgonine Isopropyl Ester. A mixture of 50 g of natural ecgonine hydrochloride and 100 ml of POCl_3 was refluxed for 1 hr and the excess POCl_3 was removed by warming *in vacuo*. The residue was treated with 350 ml of *i*-PrOH and let stand for 65 hr. Removal of the solvent, basification with 35% NaOH, and fourfold extraction with Et_2O gave 45.8 g of oil. Distillation gave 42 g (90%) of product, bp 87–96° (0.8 mm). A center cut furnished the analytical sample: $[\alpha]^{25\text{D}} -33.1^\circ$ (1% in CHCl_3); $n^{25\text{D}}$ 1.4860; $\epsilon_{218 \text{ nm}}$ (EtOH) 9217; ir and nmr spectra compatible with structure. Anal. ($\text{C}_{12}\text{H}_{19}\text{NO}_2$) C, H, N.

Methyl 8-(2-Chloroethoxycarbonyl)-3 β -phenyl-1 α H,5 α H-nortropane-2 β -carboxylate (8). A mixture of 5.40 g (2.08 mmol) of the 2-axial ester 2a and 4.3 ml (5.9 g, 4.16 mmol) of 2-chloroethyl chloroformate was heated at 100° for 1.25 hr. Gas evolution ceased after 40 min. The excess chloroformate was removed by warming *in vacuo* and the residual oil in Et_2O was percolated through 200 g of silica gel. The 4.8 g (65%) of oil in the first 400 ml of eluate showed a single spot by tlc and its spectra (ir and nmr) were completely compatible with the structure for the expected product. This material was used without further treatment.

Methyl 3 β -Phenyl-1 α H,5 α H-nortropane-2 β -carboxylate (23). All solutions and the apparatus were flushed with argon. A stirred solution of 10 ml of $(\text{CH}_2\text{NH}_2)_2$ in 800 ml of DMF was treated with 100 ml (83 mequiv) of 0.83 N $\text{Cr}(\text{ClO}_4)_2$.⁶ The temperature rose to 42°. It was brought back to 25° and 4.80 g (1.36

mmol) of the chloroethylurethane 8 in 20 ml of DMF was added. This mixture was stirred for 2 hr, allowed to stand overnight, and then poured into ice-water. $(\text{NH}_4)_2\text{CO}_3$ (10 g) was added and the weakly basic mixture was extracted three times with CHCl_3 -EtOH (2:1). The extracts were treated with an excess of 2 N HCl and concentrated to a pasty residue by warming *in vacuo*.

The pasty residue was treated with excess cold 2 N NaOH and the product was extracted with Et_2O . The oil obtained from the extracts was chromatographed on eight 20 × 40 cm preparative silica chromatoplates with development by *i*-PrNH₂- Et_2O (3:97). The crystalline solid (2.05 g) from the principal product band was converted to its HCl salt, compound 23 of Table I.

3 β -(*p*-Fluorophenyl)-1 α H,5 α H-tropane-2 β -carboxylic Acid (27). A solution of 1.23 g (4.4 mmol) of ester 13 in 60 ml of 2 N HCl was heated under reflux for 24 hr and concentrated to give a crystalline residue. Two recrystallizations from acetone furnished 0.83 g of compound 27 of Table I.

3 β -Phenyl-1 α H,5 α H-tropane-2 β -carboxylic Acid (28). A solution of 4.6 g (0.018 mol) of ester 2a in 75 ml of 2 N HCl was refluxed for 20 hr and concentrated to a residual oil by warming *in vacuo*. Trituration with acetone produced a solid which was recrystallized to give compound 28 of Table I. Nmr (5% in D_2O) showed the C-3 hydrogen at 3.5 ppm with a pattern ($J_{3,4} = 12$ Hz, $J_{3,4}$ and $J_{2,3} = 6$ and 6.5 Hz) supportive of the structure assigned.

Resolution of Methyl (±)-3-Oxo-1 α H,5 α H-tropane-2 α -carboxylate. The method of Findlay⁸ was used on his crude keto ester which, incidentally, crystallized quickly and completely upon addition of 2 equiv of H_2O . In the original precipitation of bitartrate salt only 1.2 ml of H_2O was used for each gram of keto ester dihydrate and the warm, homogeneous mixture was treated with charcoal before allowing the salt to crystallize. Slow cooling and proper seeding gave an easily filterable mass of needles. One recrystallization from an equal weight of H_2O then gave adequately pure bitartrate dihydrate $[\alpha]^{25\text{D}} +16.4^\circ$, mp 100–103° (lit.⁸ $[\alpha]^{25\text{D}} +15.4^\circ$, mp 91–94°) in 66% yield (11% reported⁸).

Following isolation of roughly an equal quantity of the enantiomer from the processed mother liquors using (–)-tartaric acid, the filtrates were brought to pH 8 and the remaining basic material was extracted with CHCl_3 . Short-path distillation of this basic residue at 0.2 mm using steam heat afforded substantial recovery of white, crystalline, unresolved keto ester which could be reprocessed.

(+)-Methyl 3 α -Hydroxy-1 α H,5 α H-tropane-2 α -carboxylate [(+)-Pseudoalloeconine Methyl Ester]. A solution of 7.00 g (0.0183 mol) of methyl 1-(1-3-oxo-1 α H,5 α H-tropane-2 α -carboxylate (–)-bitartrate dihydrate in 100 ml of H_2O was diluted with 200 ml of HOAc.†† 1.0 g of PtO_2 was added, and the mixture was hydrogenated at room temperature under 4.2 kg/cm^2 for 19 hr. The catalyst and solvent were removed and the residual oil was treated with CHCl_3 and an excess of cold 35% NaOH. The aqueous layer was extracted twice with CHCl_3 and the combined CHCl_3 layers were concentrated to give an oil. This oil was dissolved in 100 ml of Et_2O , the solution was filtered to remove a powdery impurity, and the solvent was evaporated to give an oil which solidified (3.05 g, 82.5%).

This (+)-pseudoalloeconine methyl ester was recrystallized twice from hexane (small amount of insoluble brown powder)‡‡ to give massive prisms: mp 82.5–84.5°; $[\alpha]^{25\text{D}} +38.2^\circ$ (1% in CHCl_3); ir curve superimposable on that of its enantiomer; nmr peaks appeared in expected positions³ but the coupling constants, $J_{2,3} = 3$ –4 Hz and $J_{3,4} = 3$ –4, 1 Hz, are lower in value than those reported by Sinnema, *et al.*³ Supple, *et al.*,⁴ attribute this to a flattening of the piperidine ring caused by the 3 α -OH group. Anal. ($\text{C}_{16}\text{H}_{17}\text{NO}_3$) C, H, N.

(+)-Anhydroecgonine Methyl Ester (Unnatural). A mixture of 15.7 g (0.079 mol) of (+)-allopseudoecgonine methyl ester and 50 ml of POCl_3 was refluxed for 2.5 hr and concentrated to a residual oil by warming *in vacuo*. The oil was poured onto ice and the mixture made basic with 35% NaOH. The product was extracted with two portions of Et_2O and four portions of CHCl_3 and distilled, practically all (8.72 g, 61%) boiling at 67–74° (0.1 mm). A center cut showed $n^{26\text{D}}$ 1.5011; $[\alpha]^{25\text{D}} +38.3^\circ$ (1% in CHCl_3); ir λ_{max} 1712 ($\text{C}=\text{O}$) and 1633 cm^{-1} ($\text{C}=\text{C}$). Anal. ($\text{C}_{10}\text{H}_{15}\text{NO}_2$) C, H, N.

†† When the keto ester was dissolved in an H_2O -HOAc mixture using heat to aid dissolution, considerable enol acetate was formed.

‡‡ Recrystallization requires about 12 ml of hexane/g but considerably more hexane is necessary to extract all the product from the brown powder.

Compound 24. The standard procedure using phenylmagnesium bromide and (+)-anhydroecgonine methyl ester (3) and no Cu salt gave a mixture isomeric at C-2: 42.6 g (72%); bp 129–135° (0.5–0.6 mm); isomer ratio 18:82 2β:2α (by vpc, 160° isothermal, OV-17). Reflux of the mixture (0.16 mol) with 0.20 mol of benzyl chloride in 100 ml of CH₃CN for 5 hr, addition of Et₂O, and filtration separated most of the quaternary salt of the 2α-ester. The filtrate was extracted with 2 N HCl and the extracts were made basic with concentrated NH₄OH. Extraction with Et₂O gave 8.2 g (14%) of the 2β-ester whose 1,5-naphthalenedisulfonate salt is compound 24 of Table I.

Compounds 25 and 26. Cu₂Cl₂ (6 mol %) was used in this reaction. The temperature was held at 0 to –5° during addition of (+)-anhydroecgonine methyl ester and subsequent stirring. The epimers were separated on a silica gel column (50:1 ratio) using *i*-PrNH₂–Et₂O–pentane (0.5:69.5:30) for elution.

cis-1-Methyl-4-phenylpiperidine-3-methanol (9b). Plati, *et al.*,⁹ report a mixture of *cis*- and *trans*-methyl (±)-1-methyl-4-phenylpiperidine-3-carboxylates from which they removed most of what is shown here to be the *trans* isomer as the HBr salt. The enriched *cis* isomer (Plati's β isomer) (10.6 g, 0.046 mol) was reduced with LiAlH₄ in the manner described for the preparation of 5 above. The crude product was recrystallized twice from EtOAc to give 6.12 g of massive prisms: mp 99–100°; ir (CCl₄) broad OH band at 3322 cm⁻¹ not diluted out in 0.001 M solution. *Anal.* (C₁₃H₁₉NO) C, H, neut equiv.

The acetate ester of 9b (Ac₂O–pyridine, 3 hr, 100°) was an oil, the HCl salt of which formed long prisms, mp 191–194° (CH₃CN). *Anal.* (C₁₅H₂₁NO₂·HCl) C, H, Cl.

trans-1-Methyl-4-phenylpiperidine-3-methanol (10b). The α isomer of methyl (±)-1-methyl-4-phenylpiperidine-3-carboxylate reported by Plati, *et al.*,⁹ (5.4 g) was reduced with LiAlH₄ in the manner described for the preparation of 5 above. Recrystallization of the product from EtOAc gave 3.9 g of prism clusters, mp 109–111°, which probably is the same material as that isomer of unknown configuration reported by Plati, *et al.*,⁹ with mp 107–109°. The present material showed a single sharp ir peak at 3647 cm⁻¹ (nonbonded OH) in 0.005 M solution (CCl₄). The ir and nmr spectra were compatible with the expected structure.

The acetate ester 10c of 10b (Ac₂O–pyridine, 2 hr, 100°) was an oil, the HCl salt of which formed needles, mp 213.5–215° (CH₃CN). *Anal.* (C₁₅H₂₁NO₂·HCl) C, H, Cl.

Biological. The studies on locomotor activity (Table II), ptosis reversal and prevention (Table III), norepinephrine uptake inhibition in mouse heart (Figure 1), and acute toxicity were done using male Swiss-Webster mice (20 ± 2 g). The norepinephrine uptake inhibition experiments on brain tissue were done with male Sprague-Dawley strain rats (220 ± 20 g) and the local anesthetic determinations were made on Hartley strain guinea pigs (250–370 g). When compounds were administered as suspensions in 1% gum tragacanth, a volume of 0.1 ml was given per 10 g of animal body weight.

For the locomotor activity determinations the compounds were administered orally as suspensions in 1% gum tragacanth. The lowest doses which produced an increase in locomotor activity were gauged by visual observation of a group of six mice at the various dose levels beginning 30 min after medication. The results were confirmed with the aid of actophotometers.¹⁵

The ptosis prevention and reversal tests were done as described by Aceto and Harris.¹¹ In Table III where the controls are recorded as G.T. (1% gum tragacanth), the compounds in free base form were given as suspensions in that vehicle. Otherwise, the compounds were administered in salt form in aqueous solution.

Each value for a mean ptosis score (MPS) represents observation of eight mice. The doses reported are in terms of the salts when used.

The local anesthetic activity was measured by the intradermal method of Bülbring and Wajda using guinea pigs. The average threshold anesthetic concentration (TAC₅) was obtained from the dose-effect curve (semilogarithmic plot of duration in minutes *vs.* dosage) as described by Luduena and Hoppe.¹⁶

In the mouse heart norepinephrine uptake inhibition experiments, aqueous solutions of DMI and cocaine hydrochlorides were used, as was an aqueous solution of compound 15-1,5-naphthalenedisulfonate. Compound 2a was dissolved in lactic acid. The dosage plotted is that of the salt used except for 2a which was a free base. Each point in Figure 1 represents the mean ± S.E. obtained from six individual mouse hearts.

In the rat brain norepinephrine uptake inhibition studies, aqueous solutions of compound 13-1,5-naphthalenedisulfonate and cocaine-HCl were used. The compounds were administered sc 45 min before intraventricular injection of 1 μCi of NE-³H in a weakly acidic and buffered solution of 0.01-ml volume. The rats were sacrificed 2 hr after the NE-³H injection. Each value in Table V represents the mean from six individual rat brains. Doses have been recalculated to a free amine basis.

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