bined organic solutions were dried (Na_2SO_4) and evaporated; crystallization of the residue from EtOH afforded the methyl ether **1a** (0.7 g), mp 112–113°. *Anal.* ($C_{21}H_{25}NO_3$) C, H, N.

6,14-*endo*-**Ethanotetrahydrothebaine (2a).** Hydrogenation of 1a in glacial AcOH over 10% Pd/C afforded **2a**, mp 138–140°. *Anal.* ($C_{21}H_{29}NO_3$) C, H, N.

N-Cyano-6,14-*endo*-**ethenotetrahydronorthebaine (1f).** A mixture of 1a (3.2 g) and CNBr (1.3 g) in CH_2Cl_2 (10 ml) was kept at room temperature for 72 hr. The solid which crystallized and the residue from the evaporated solution were washed with EtOH to give a crude product (3.0 g) which was crystallized from EtOH to give 1f, mp 250–253°. *Anal.* ($C_{21}H_{22}N_2O_3$) C, H, N.

6,14-*endo*-**Ethenotetrahydronorthebaine (1c).** The *N*-cyano derivative 1f (2.8 g) was added to a mixture of KOH (3.0 g) and diethylene glycol (20 ml) at 170° under N_2. The mixture was maintained at 170° for 15 min and then poured into ice-H_2O (~150 ml). The solid which separated was crystallized from petroleum ether (bp 60–80°) affording 1c (0.2 g), mp 127–128°. *Anal.* ($C_{20}H_{23}NO_3$) H, N; C: calcd, 73.82; found, 73.34.

The greater bulk of the product (1.3 g) was obtained by extraction into Et_2O from the aqueous liquors.

6,14-*endo*-**Etheno-*N*-propargyltetrahydronorthebaine (1d).** Reaction of 1c (1.4 g) with propargyl bromide (1.54 g) in the general manner described for **3d** afforded after recrystallization from EtOH 1d (1.3 g), mp 168–170°. *Anal.* ($C_{23}H_{25}NO_3$) C, H, N.

N-**Cyclopropylcarbonyl-6,14-*endo*-ethenotetrahydrothebaine.** Cyclopropylcarbonyl chloride (6.9 g) in CH_2Cl_2 (15 ml) was added during 30 min to a stirred mixture of 1c (7.1 g), anhydrous K_2CO_3 (7.0 g), and CH_2Cl_2 (50 ml). The mixture was stirred overnight at room temperature and then poured into H_2O (450 ml). The aqueous phase was further extracted with $CHCl_3$ and the combined organic solution was washed with aqueous $NaHCO_3$ and finally H_2O. It was dried ($MgSO_4$) and evaporated. The residue on treatment with Et_2O and EtOH followed by crystallization from cyclohexane gave the amide, mp 140–150° (150–154° if first melted and resolidified). *Anal.* ($C_{24}H_{27}NO_4$) C, H, N.

N-**Cyclopropylmethyl-6,14-*endo*-ethenotetrahydronorthebaine (1e).** A solution of the above *N*-cyclopropylcarbonyl derivative (2 g) in dry THF (30 ml) was added with stirring to a slurry of $LiAlH_4$ (1.5 g) in dry THF (10 ml). The mixture was heated at reflux for 5 hr and set aside at room temperature overnight. After cautious addition of THF (15 ml) containing H_2O (3 ml) the mixture was again allowed to stand overnight; removal of the salts by filtration and evaporation of the filtrate gave a gum. This material was extracted into dilute AcOH and filtered, and the filtrate was basified (NH_4OH). The product was extracted into Et_2O, washed with H_2O, and dried (Na_2SO_4), and the Et_2O evaporated. The residue was crystallized from aqueous EtOH to give 1e (0.88 g), mp 70–81°. *Anal.* ($C_{24}H_{29}NO_3$) C, H, N.

N-**Cyclopropylcarbonyl-6,14-*endo*-ethanotetrahydronorthebaine.** *N*-Cyclopropylcarbonyl-6,14-*endo*-ethenotetrahydronorthebaine (3 g) in glacial AcOH (25 ml) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (0.3 g); the reduction required about 90 min. Filtration to remove catalyst followed by dilution with H_2O (300 ml) gave a gummy solid; this was extracted into Et_2O, and the extract was washed with aqueous NaOH and then with H_2O, dried (Na_2SO_4), and evaporated. The residue (2.4 g) was crystallized from cyclohexane to give the amide, mp 146–148°. *Anal.* ($C_{24}H_{29}NO_4$) C, H, N.

N-**Cyclopropylmethyl-6,14-*endo*-ethanotetrahydronorthebaine (2e)** was obtained by $LiAlH_4$ reduction of the above amide in a similar manner to that described for 1e. Crystallization from aqueous EtOH afforded **2e**, mp 82–84°. *Anal.* ($C_{24}H_{31}NO_3$) C, H, N.

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Novel Analgetics and Molecular Rearrangements in the Morphine–Thebaine Group. 30.[1] 16-Alkyl-6,14-*endo*-ethenotetrahydrothebaines

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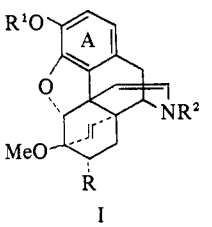
A series of 16-alkyl-6,14-*endo*-ethenotetrahydrothebaines III is described. All the 16-alkyl compounds were less active as analgetics than their 16-H parents.

In derivatives of morphine and related compounds the piperidine ring is of prime importance in determining the pharmacological profile. In particular, certain substituents on the nitrogen atom confer morphine antagonist character. The possibility that similar alterations of analgetic activity could be achieved by substitution in the piperidine ring close to the nitrogen atom led us to investigate the chemistry of 15,16-didehydro derivatives in the 6,14-*endo*-ethenotetrahydrothebaine series.[2] We here report on 16-alkyl (and 16-aryl) derivatives of analgetics from the *endo*-ethenotetrahydrothebaine series.[3] These have been prepared from the dehydro compounds I by reaction of the iminium perchlorates II with Grignard reagents or lithium alkyls.



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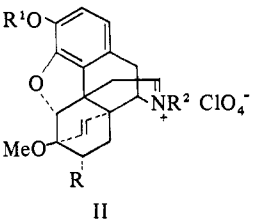
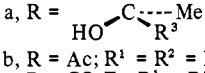


II

a, R = 

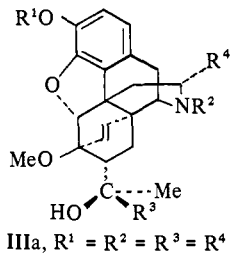
b, R = Ac; $R^1 = R^2 = Me$
c, R = CO_2Et; $R^1 = R^2 = Me$

6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)-16α-methyl-6,7,8,14-tetrahydrothebaine (IIIa) was prepared from the carbinol iminium perchlorate IIa ($R^1 = R^2 = R^3 =$ Me) by reaction with MeMgI or MeLi. Other 16-alkyl carbinols were made in a similar manner. IIIa was also prepared from ketone IIb or the ester IIc by reaction with MeMgI. The configuration of the 16-alkyl group could not be assigned from the nmr spectrum since the splitting of

Table I. 16-Alkyl Compounds of Structure III

No.	R^1	R^2	R^3	R^4	Method	% yield	Mp, °C	Formula	Analyses	Analgesia, ED_{50}, mg/kg[a]
1	Me	Me	Me	Me	A-D	75	140-142	$C_{25}H_{33}NO_4$	C, H, N	16 (11.0-23.2) sc
2	Me	Me	Me	Et	A	65	165-167	$C_{26}H_{35}NO_4$	C, H, N	>100 ip
3	Me	Me	Me	*i*-Pr	A	35	149-152	$C_{27}H_{37}NO_4$	C, H, N	12.5 (8.3-18.8) sc
4	Me	Me	Me	*n*-Bu	A	75	101-102	$C_{28}H_{39}NO_4$	C, H, N	>100 sc
5	Me	Me	Me	*i*-Bu	A	70	157-160	$C_{28}H_{39}NO_4 \cdot 0.5H_2O$	C, H, N	40 (20-80) sc
6	Me	Me	Et	Me	A	75	137-138	$C_{26}H_{35}NO_4$	C, H, N	>100 ip
7	Me	Me	Et	Et	A	70	117-119	$C_{27}H_{37}NO_4$	C, H, N	>100 sc
8	Me	Me	Et	*n*-Bu	A	70	161-163	$C_{29}H_{41}NO_4$	C, H, N	>100 ip
9	Me	Me	*n*-Pr	Me	A	65	143-144	$C_{27}H_{37}NO_4$	C, H, N	1.8 (1.2-2.5) ip
10	Me	Me	*n*-Bu	Me	A	55	118-120	$C_{28}H_{39}NO_4$	C,[b] H, N	27.0 (14.6-49.9) sc
11	Me	Me	*n*-Bu	Et	A	75	135-137	$C_{29}H_{41}NO_4$	C,[c] H, N	11.0 (6.8-17.6) ip
12	Me	Me	*n*-Bu	*n*-Pr	A	50	125	$C_{30}H_{43}NO_4$	C, H, N	20.0 (14.6-27.5) sc
13	Me	Me	*n*-Bu	*n*-Bu	A	70	112-113	$C_{31}H_{45}NO_4$	C, H, N	13.0 (8.1-20.8) sc
14	Me	Me	*n*-Bu	*i*-Bu	A	75	115-116	$C_{31}H_{45}NO_4$	C, H, N	34.0 (19.4-59.5) sc
15	Me	Me	*n*-Pentyl	Me	A	60	124-126	$C_{29}H_{41}NO_4$	C, H, N	7.0 (5.8-8.4) ip
16	Me	Me	*n*-Pentyl	Et	A	50	84-87	$C_{30}H_{43}NO_4$	C, H, N	4.0 (3.1-5.2) ip
17	Me	Me	Cyclohexyl	Me	A	70	182-185	$C_{30}H_{41}NO_4$	C,[d] H, N	11.2 (7.2-17.4) ip
18	Me	Me	Cyclohexyl	Me	A	80	170-171	$C_{30}H_{43}NO_4$[e]	C, H, N	>100 ip
19	Me	Me	Cyclohexyl	Et	A	70	152-153	$C_{31}H_{43}NO_4$	C, H, N	>100 ip
20	Me	Me	Cyclohexyl	*n*-Pr	A	60	99-103	$C_{32}H_{45}NO_4$	C, H, N	27.0 (15.0-48.6) ip
21	Me	Me	Cyclohexyl	Allyl	A	60	154-155	$C_{32}H_{43}NO_4$	C, H, N	>100 sc
22	Me	Me	Cyclohexyl	*n*-Bu	A	75	95-97	$C_{33}H_{47}NO_4$	C,[f] H,[g] N	>100 ip
23	Me	Me	Cyclohexyl	Ph	A	65	160-162[h]	$C_{35}H_{43}NO_4 \cdot HCl$	C, H, N, Cl	>100 ip
24	Me	Me	Cyclohexyl	CH_2Ph	A	65	120-121	$C_{36}H_{45}NO_4$	C, H, N	>100 ip
25	Me	Me	Cyclohexyl	CH_2CH_2Ph	A	60	148-149	$C_{37}H_{47}NO_4$	C, H, N	>100 ip
26	Me	Me	CH_2Ph	Me	A	55	212-213	$C_{31}H_{37}NO_4$	C, H	7.6 (4.9-11.8) sc
27	Me	Me	CH_2Ph	Et	A	50	214-216	$C_{32}H_{39}NO_4$	C, H, N	>100 ip
28	Me	Me	CH_2Ph	*n*-Pr	A	55	150-152	$C_{33}H_{41}NO_4$	C, H, N	5.0 (3.1-8.0) ip
29	Me	Me	CH_2Ph	*n*-Bu	A	60	164-166	$C_{34}H_{43}NO_4$	C, H, N	13.0 (8.4-20.1) sc
30	Me	Me	CH_2Ph	*i*-Bu	A	50	125-126	$C_{34}H_{43}NO_4$	C, H, N	4.2 (3.0-5.9) sc
31	Me	Me	CH_2CH_2Ph	Me	A	75	145-146	$C_{32}H_{39}NO_4$	C,[i] H	0.74 (0.60-0.91) sc
32	Me	CN	Me	Me	F	65	199-201	$C_{25}H_{30}N_2O_4$	C, H, N	>100 sc
33	Me	CN	*n*-Bu	Me	F	90	200-201	$C_{28}H_{36}N_2O_4$	C, H, N	>100 ip
34	Me	CN	*n*-Bu	*n*-Bu	F	85	145-150	$C_{31}H_{42}N_2O_4$	C, H	>100 sc
35	Me	CN	*n*-Pentyl	Me	F	90	184-186	$C_{29}H_{38}N_2O_4$	C, H, N	>100 ip
36	Me	CN	Cyclohexyl	Me	F	80	275-278	$C_{30}H_{38}N_2O_4$	C, H, N	>100 ip
37	Me	H	Me	Me	F	50	>300[h]	$C_{24}H_{31}NO_4HCl \cdot 0.5H_2O$	C, H, N	>100 sc
38	Me	H	*n*-Bu	Me	F	95	67-70	$C_{27}H_{37}NO_4 \cdot 1.5H_2O$	C, H, N	17.5 (10.3-29.8) sc
39	Me	H	Cyclohexyl	Me	F	75	198-199	$C_{29}H_{39}NO_4$	C, H, N	11.2 (7.4-16.8) ip
40	Me	Allyl	Me	Me	F	50	109-111	$C_{27}H_{35}NO_4$	C, H, N	>100 sc
41	Me	Allyl	*n*-Bu	Me	F	55	155-159[h]	$C_{30}H_{41}NO_4 \cdot HCl$	C, H, N, Cl	>100 ip
42	Me	Propargyl	*n*-Bu	Me	F	40	137-139	$C_{30}H_{39}NO_4$	C, H, N	>100 ip
43	Me	CPM[j]	Me	Me	A	55	156-157	$C_{28}H_{37}NO_4 \cdot H_2O$	C, H, N	Not tested
44	Me	CPM	Et	Me	A	50	110	$C_{29}H_{39}NO_4$	C, H, N	Not tested
45	Me	CPM	*n*-Bu	Me	A	50	244-245[h]	$C_{31}H_{43}NO_4 \cdot HCl$	C, H, N, Cl	Not tested
46	H	Me	Me	Me	E	70	235-241	$C_{24}H_{31}NO_4$	C,[k] H	1.3 (0.6-2.9) sc
47	H	Me	Cyclohexyl	Me	A	55	150-153	$C_{29}H_{39}NO_4 \cdot 0.5H_2O$	C, H	0.11 (0.05-0.24) ip
48	H	CPM	Me	Me	E	60	156-157	$C_{27}H_{35}NO_4 \cdot H_2O$	C, H, N	>100 sc
Morphine										1.7 (1.22-2.38) sc 1.3 (0.92-1.79) ip

[a]Measured by the rat tail pressure test (see ref 7). Figures in parentheses are 95% confidence limits. [b]C: calcd, 74.1; found, 74.6. [c]C: calcd, 74.5; found, 75.0. [d]C: calcd, 75.1; found, 74.5. [e]6,14-*endo*-Ethano. [f]C: calcd, 76.0; found, 76.5. [g]H: calcd, 9.1; found, 9.6. [h]Hydrochloride. [i]C: calcd, 76.6; found, 76.1. [j]Cyclopropylmethyl. [k]C: calcd, 72.5; found, 73.1.



IIIa, $R^1 = R^2 = R^3 = R^4 = Me$

the C-16 proton was not observed due to overlapping with other signals. We would expect the Grignard reagent to approach from the less hindered side, which from earlier work[4] has been shown to be the α face (*i.e.*, the ring A side) and the 16-alkyl group has consequently been assigned the α configuration. Grignard reactions were also successful with the phenolic iminium perchlorates IIa (R^1 = H) and with iminium salts containing N substituents other than methyl for which the required dehydro compounds may be prepared.[2] The 16-alkyloripavines III (R^1 = H) were prepared by demethylation of the 3-methyl ethers with alkali. Other N-substituted derivatives of the 16-alkyl carbinols were prepared by alkylation of the 16-alkyl norcarbinols III (R^2 = H). The compounds prepared are listed in Table I.

Structure-Activity Relationships. The analgetic action of morphine has been considered by Beckett and Casy[5] to involve a fit of the drug at three points on the receptor site. These authors postulated that the nitrogen atom interacts with an "anionic center," the aromatic ring lies on a flat hydrophobic site, and C-15 and C-16 fit into a "hole." In order to explain the phenomenal analgetic potency of some members of the 6,14-*endo*-ethenotetrahydrothebaine and

Table II. Analgetic Activity of Carbinols of Structure III (R^1, R^2 = Me)

	Analgetic activity, rat tail pressure, ED_{50}, mg/kg sc				
R^3	R^4 = H	R^4 = Me	R^4 = Et	R^4 = *n*-Pr	R^4 = *n*-Bu
Me	0.45	16	>100[a]		>100
Et	0.15	>100[a]	>100		>100[a]
n-Pr	0.034	1.8[a]			
n-Bu	0.036	27	11	20	13
Cyclohexyl	0.056	20	>100[a]	27[a]	>100[a]
CH_2Ph	0.057	7.6	>100[a]	5[a]	13
Morphine ED_{50} 1.7 mg/kg sc, 1.3 mg/kg ip					

[a]Injected intraperitoneally as a suspension of the base in saline.

oripavine series, it has been suggested†,[6] that the receptor surface is even more extensive and that a C-7 substituent binds with a second lipophilic site. If C-15 and C-16 do indeed fit into a "hole" in the receptor, substitution at one of these centers would be expected to hinder the fit of the drug molecule at the receptor with consequent reduction in analgetic potency. All the 16-alkyl-6,14-*endo*-ethenotetrahydrothebaines are, indeed, far less active as analgetics than the unsubstituted compounds. A comparison of analgetic activities of the 16-alkyl and the 16-H compounds in the tetrahydrothebaine series is given in Table II. The introduction of a 16-methyl group resulted in a marked reduction in analgetic effect although, in general, there was still a small residual activity. A group larger than methyl eliminated analgetic activity completely in the carbinols of lower activity (III, R^3 = Me or Et), but weak activity was still observed in some derivatives of the more potent carbinols (III, R^3 = *n*-Bu or CH_2Ph). The results agree with the suggestion that the C-7 substituent plays a part in attaching these drugs to the receptor. A 16-phenyl, benzyl, or phenethyl group eliminated all analgetic activity.

One of the 16-alkyl compounds **48** showed morphine antagonist action, ED_{50} 0.11 (0.05-0.26) mg/kg sc, when tested by the method of Green and Young[7] in rats.

Three members of this series, compounds **17**, **19**, and **47**, possess interesting antitussive activity[8] when assessed orally in guinea pigs by the method of Winter and Flataker.[9]

†K. W. Bentley and J. W. Lewis, reported to the Committee on Problems of Drug Dependence, Feb 1968.

Experimental Section

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, the results obtained for those elements were within ±0.4% of the theoretical values. The structures of all compounds were assigned on the basis of compatible ir and nmr spectra. The iminium perchlorates II were prepared from the 15,16-didehydro compounds as previously described.[2] In general, the salts were used without purification or characterization.

General Methods for the Preparation of the 16α-Alkyl Carbinols (III). In method A the iminium perchlorate IIa (0.1 mol) was added portionwise to a stirred solution of RMgX (0.3 mol) in Et_2O (500 ml) and the mixture was stirred and boiled for 18 hr. Saturated aqueous NH_4Cl solution was added and the Et_2O layer was separated and evaporated to give the 16α-alkyl compound. Method B used RLi instead of the Grignard reagent. The carbinol IIIa was also prepared by reaction of MeMgI with the 7α-acetyl compound IIb (method C) or the 7α-carbethoxyl compound IIc (method D).

Demethylation of the 3-methyl ethers III (R^1 = Me) with alkali in diethylene glycol at 210° gave[10] the corresponding tetrahydrooripavines III (R^1 = H) (method E). Reaction of the *N*-methyl carbinols III (R^2 = Me) with CNBr and treatment of the cyanamide with alkaline diethylene glycol at 170° gave[10] the nor bases III (R^2 = H). These were alkylated by standard methods[10] to give N-substituted derivatives (method F).

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A Conformational Study of Phenethylamine Receptor Sites. 1. Syntheses of Semirigid Analogs of β-Methylamphetamine

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The syntheses of *dl-threo*- and *dl-erythro*-2-amino-3-phenylbutane (**1** and **2**), *threo*- and *erythro*-2-isopropylamino-3-phenylbutane (**5** and **6**), *dl-cis*- and *dl-trans*-2-phenylcyclohexylamine (**3** and **4**), and *dl-cis*- and *dl-trans*-2-phenylcyclohexylisopropylamine (**7** and **8**) are described. The results of the toxicity and behavioral studies are discussed.

In order to investigate the possibility that amphetamine exists in specific conformations at different receptor surfaces as an explanation for the variety of physiological effects observed when this compound is administered, the phenethylamine nucleus has been incorporated into semirigid and rigid systems. The systems utilized in this study are those previously employed in these laboratories in investigating cholinergic and adrenergic receptor sites.[1-8]

The synthesis and preliminary biological testing of semirigid analogs of β-alkylamphetamines are the subject of this report. The racemic *threo*- and *erythro*-2-amino-3-phenylbutanes (**1** and **2**) and the racemic *cis*- and *trans*-2-phenylcyclohexylamines (**3** and **4**) afford systems which have a certain degree of restriction to rotation about the carbon-carbon single bond to which the phenyl and amino groups are attached. Compounds **1-4** were converted to the

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