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Novel Analgetics and Molecular Rearrangements in the Morphine–Thebaine Group. 28.[1] Derivatives of 6,14-*endo*-Etheno-7-oxo-6,7,8,14-tetrahydrothebaine and 6,14-*endo*-Etheno-6,7,8,14-tetrahydrothebaine

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6,14-*endo*-Ethenotetrahydrothebaine (**1a**) obtained *via* the 7-oxo derivative **3a** is equipotent with morphine as an analgetic; the derived oripavine **1b** is 40 times more potent. The *N*-cyclopropylmethyl derivatives **1e** and **2e** are morphine antagonists more potent than nalorphine.

The chemistry of derivatives of 6,14-*endo*-ethenotetrahydrothebaine has been extensively studied as has the relationship between structure and analgetic activity in this series.[2] However, all the derivatives so far described have had a C-7 substituent. We here report the synthesis of the parent 6,14-*endo*-ethenotetrahydrothebaine (**1a**), the corresponding oripavine **1b**, and some related compounds.

Chemistry. The oripavine **1b** was obtained by Huang-Minlon reduction of 6,14-*endo*-etheno-7-oxotetrahydrothebaine (**3a**) which was prepared from either the thebaine-2-chloroacrylonitrile adduct **5a**[3] or the thebaine-ethyl 2-acetoxyacrylate adduct **5b**.[3]

The C-7 epimeric chloronitriles **5a** undergo a variety of reactions with basic reagents.[4] Both epimers in boiling aqueous alcoholic NaOH gave the 7-oxo derivative **3a**. The ketone was also obtained from **5b** either by reduction with $LiAlH_4$ to give diol **5c** followed by HIO_4 cleavage or by Curtius degradation *via* **5d** and **5e**.

The chloronitrile hydrolysis product contained a C-4 phenolic γ lactone **7** in addition to ketone **3a**. This phenol was also obtained from **3a** by reaction with NaOH in boiling aqueous 2-ethoxyethanol. Its formation involves a benzilic acid type rearrangement of **3a** to **6** followed by lactonization when the reaction mixture is neutralized (Scheme I). Treatment of **7** with cold HCl gave **8** while with boiling EtOH–HCl, **7** gave keto ester **9** in which transetherification of the 3-*O*-methyl group had occurred in addition to opening of the lactone.

Demethylation of the 3-*O*-methyl group of **3a** was achieved by treatment of the dimethyl ketal with NaOH in diethylene glycol at 210°. The ethanotetrahydrooripavine **4c** was similarly obtained from the hydrogenated 7-oxo compound **4a**.

N-Demethylation of **3a** by the azodicarboxylate route[5] followed by reaction of the nor ketone **3b** with appropriate halides afforded the *N*-allyl **3d**, *N*-propargyl **3e**, and *N*-2-methylallyl **3f** analogs. Similar procedures applied to the ethano ketone **4a** gave **4d-f** (Table I). The *N*-cyclopropylmethyl etheno ketone **3g** was obtained directly from the *N*-cyclopropylmethylchloronitrile **5a** (*N*-CPM replaces *N*-Me) by reaction with NaOH–EtOH; the *N*-CPM lactone **7** (*N*-CPM replaces *N*-Me) was also isolated from the reaction mixture.

Huang-Minlon reduction of **3a** gave 6,14-*endo*-etheno-tetrahydrooripavine (**1b**) which was converted to the corresponding tetrahydrothebaine **1a** with methyl iodide. A similar reduction of the ethano ketone **4a** produced 6,14-*endo*-ethanotetrahydrooripavine (**2b**); the corresponding tetrahydrothebaine **2a** was in this case made by hydrogenation of 6,14-*endo*-ethenotetrahydrothebaine (**1a**). The

Scheme I

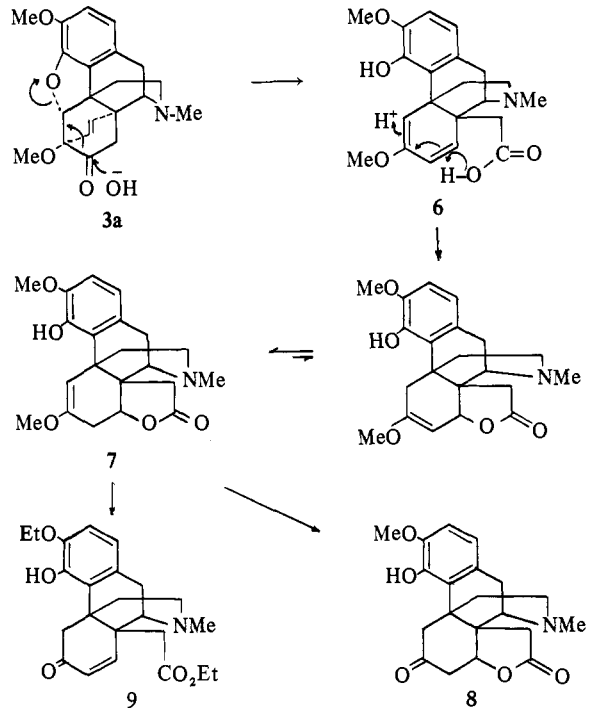
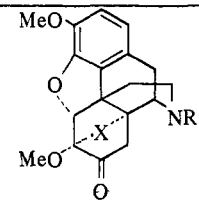


Table I



No.	R	X	Mp, °C	Formula[a]
3d	$CH_2CH=CH_2$	C_2H_2	152–155	$C_{23}H_{25}NO_4$
3e	$CH_2C\equiv CH$	C_2H_2	197–198	$C_{23}H_{23}NO_4$[b]
3f	$CH_2C(Me)=CH_2$	C_2H_2	158–161	$C_{24}H_{27}NO_4$
4d	$CH_2CH=CH_2$	C_2H_4	110–111	$C_{23}H_{27}NO_4$
4e	$CH_2C\equiv CH$	C_2H_4	145–147	$C_{23}H_{25}NO_4$
4f	$CH_2C(Me)=CH_2$	C_2H_4	171–173	$C_{24}H_{29}NO_4$

[a] All compounds were analyzed for C, H, N and are within ±0.4% of the theoretical values except where indicated. [b] C: calcd, 73.19; found, 72.60.

Table II

No.	N substituent	C_3 substituent	Analgetic activity,[a] ED_{50}, mg/kg sc[f]	No.	N substituent	C_3 substituent	Morphine antagonism,[a] ED_{50}, mg/kg sc[f]	Phenylquinone antiwrithing, ED_{50}, mg/kg sc[f]
1a	Me	OMe	1.6 (1.15–2.24)	1e	CPM	OMe	0.62 (0.40–0.94)	11.5 (5.8–23.0)
1b	Me	OH	0.056 (0.037–0.084)	2e	CPM	OMe	0.27 (0.15–0.45)	72 (–)
1d	Propargyl	OMe	29 (19.3–45.3)	3d	Allyl	OMe	*b*	*b*
2a	Me	OMe	1.7 (1.13–2.55)	3e	Propargyl	OMe	*b*	*b*
2b	Me	OH	0.034 (0.018–0.065)	3f	Methallyl	OMe	*b*	NT[e]
3a	Me	OMe	*b*	3g	CPM	OMe	8.8 (4.0–19.4)	5.3 (2.5–11.1)
3b	H	OMe	*b*	4d	Allyl	OMe	30 (17.6–51)	25 (–) ip
3c	Me	OH	1.1[c] (0.73–1.7)	4e	Propargyl	OMe	*b*	36 (16.3–79.2)
4a	Me	OMe	3.5[c] (0.70–12.5)	4f	Methallyl	OMe	*b*	NT[e]
4c	Me	OH	0.42 (0.27–0.62)	Nalorphine			1.6 (0.93–2.72)	2.1 (1.05–4.2)
11a	Me	OH	*d*	Pentazocine			60 (18.2–127.5)	3.0 (0.71–12.6)
11b	Me	OMe	3.8 (1.9–7.6)					
5g	Me	OMe	*b*					
5h	Me	OMe	26.0 (10.0–67.6)					
5j	Me	OMe	1.1 (0.49–2.42)					
5k	Me	OMe	5.2 (2.73–9.88)					
11c	Morphine		1.7 (1.22–2.38)					
	Pentazocine		15.5 (5.1–32.0)					

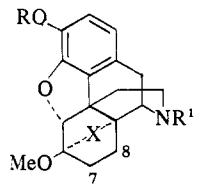
[a] Rat tail pressure. [b] Inactive at 100 mg/kg. [c] Intraperitoneally. [d] See ref 8. [e] NT, not tested. [f] Figures in parentheses are 95% confidence limits.

etheno nor base **1c** was prepared from **1a** *via* the *N*-cyano nor compound **1f** and N-substituted analogs **1d,e** of 6,14-*endo*-ethenotetrahydrothebaine were then accessible by the usual methods. The *N*-cyclopropylcarbonyl intermediate was hydrogenated to provide its ethano analog and, hence, by $LiAlH_4$ reduction, *N*-cyclopropylmethyl-6,14-*endo*-ethanotetrahydronorthebaine (**2e**).

Structure–Activity Relationships. Analgetic activity was determined subcutaneously or intraperitoneally by the rat tail pressure test of Green and Young[6] and morphine antagonism by the method of Green, Ruffell, and Walton.[7] These results are listed in Table II.

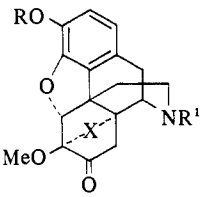
6,14-*endo*-Ethenotetrahydrothebaine (**1a**) is equipotent with morphine while the corresponding oripavine **1b** is 30–40 times more potent; hydrogenation of the etheno group has very little effect on activity. Comparison of this data with that for morphine (5x morphine, see ref 8) and codeine 6-methyl ethers **11a,b** shows that in the bridged ring compounds, C-7 and C-8 are responsible for a significant increase in analgetic activity. This result is surprising in view of the low activity of B/C *trans*-morphine **12** in comparison with the natural cis compound **11c**.[9] In **1b**, C_7 and C_8 are equivalent to the same-numbered atoms in *trans*-morphine while C_{17} and C_{18} correspond to C_7 and C_8 of *cis*-morphine. It may be that in the trans series C_7 and C_8 need to be tetrahedral for satisfactory analgetic activity. In the *endo*-etheno series substituted at C_7, the tetrahedral configuration at this carbon atom is associated with considerably higher activity than the trigonal configuration. Thus, the methylene **5g** and ethylidene **5h** derivatives[10] have little or no activity, whereas the 7α-methyl and 7α-ethyl compounds **5j** and **5k**[10] are, respectively, equipotent and three times less potent than morphine (Table II). The *N*-cyclopropylmethyl bases **1e** and **2e** are morphine antagonists significantly more potent than nalorphine with weak antinociceptive activity; the *N*-propargyl derivative **1d** is a weak analgetic.

The etheno ketone **3a** is inactive at 100 mg/kg as an analgetic, but the corresponding ethano compound **4a** has about one-half of morphine's potency. The 7-oxooripavines **3c** and **4c** are respectively two and five times more potent than morphine. The only N-substituted derivative of the ketone **3a** to show morphine antagonist action is the *N*-cyclopropylmethyl compound **3g** which has about one-tenth of the activity of nalorphine. It is about half as potent as pentazocine in the antiwrithing test.



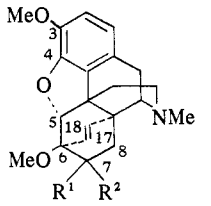
1, X = C_2H_2
2, X = C_2H_4

a, R = R^1 = Me
b, R = H; R^1 = Me
c, R = Me; R^1 = H
d, R = Me; R^1 = $CH_2C{\equiv}CH$
e, R = Me; R^1 = CH_2-c-Pr
f, R = Me; R^1 = CN

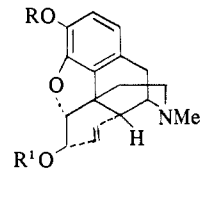


3, X = C_2H_2
4, X = C_2H_4

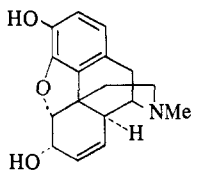
a, R = R^1 = Me
b, R = Me; R^1 = H
c, R = H; R^1 = Me
d, R = Me; R^1 = $CH_2CH{=}CH_2$
e, R = Me; R^1 = $CH_2C{\equiv}CH$
f, R = Me; R^1 = $CH_2CMe{=}CH_2$
g, R = Me; R^1 = CH_2-c-Pr



5a, R^1 = Cl; R^2 = CN
b, R^1 = OAc; R^2 = CO_2Et
c, R^1 = OH; R^2 = CH_2OH
d, R^1 = OH; R^2 = $CONHNH_2$
e, R^1 = OH; R^2 = CON_3
f, R^1 = R^2 = OMe
g, R^1,R^2 = $=CH_2$
h, R^1,R^2 = =CHMe
j, R^1 = H; R^2 = Me
k, R^1 = H; R^2 = Et



11a, R = H; R^1 = Me
b, R = R^1 = Me
c, R = R^1 = H



12

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.

6,14-*endo*-Etheno-7-oxotetrahydrothebaine (3a). (i) 7α-

Chloro-7β-cyano-6,14-*endo*-ethenotetrahydrothebaine[3] (3 g) was dissolved in hot EtOH (70 ml) and aqueous NaOH (1 *N*, 50 ml) was added until a turbidity appeared. The mixture was heated under reflux for 16 hr. After removal of the EtOH by distillation, the ketone **3a** (0.8 g), mp 190–192° (from MeOH), was obtained. *Anal.* ($C_{21}H_{23}NO_4$) C, H, N.

The material remaining after the isolation of **3a** was extracted from inorganic residues ($CHCl_3$). Tlc showed that the major component of this material was **7** by comparison with a purified sample prepared as described below.

7β-Chloro-7α-cyano-6,14-*endo*-ethenotetrahydrothebaine (3 g) in a similar reaction gave the same ketone (1.8 g), mp 189–192°.

(ii) A solution of 7-acetoxy-6,14-*endo*-etheno-7-ethoxycarbonyltetrahydrothebaine[3] (mixed epimers, 15.0 g) in THF (40 ml) was added slowly to a cooled, stirred slurry of $LiAlH_4$ (6.5 g) in THF (60 ml); the mixture was then boiled for 3.5 hr and kept at room temperature overnight. Saturated aqueous Rochelle salt (500 ml) was added and the mixture was repeatedly extracted with C_6H_6; the organic extract was washed with H_2O, dried (Na_2SO_4), and evaporated. The residual gum was dissolved in hot MeOH (40 ml) and filtered; the filtrate was treated with H_2O (400 ml) and cooled when the glycol **5c** (5.6 g) separated.

The above glycol (1.25 g) was dissolved in 5% aqueous AcOH (7.5 ml), the solution was diluted with H_2O (2.5 ml) and treated at room temperature with $NaIO_4$ (0.73 g), and the mixt was stirred for 4 hr and then kept overnight. Dilution with H_2O to 30 ml, filtration, and basification of the filtrate with NaOH gave ketone **3a** (0.94 g), mp 194–197°.

(iii) 7-Acetoxy-6,14-*endo*-etheno-7-ethoxycarbonyltetrahydrothebaine (20 g) was treated with $N_2H_4 \cdot H_2O$ (99–100%, 124 g) in boiling 2-ethoxyethanol (100 ml) for 16.5 hr. The cooled mixture was poured into H_2O (500 ml) and kept in an ice bath for 2 hr. The precipitate was collected and recrystallized from EtOH to give the hydrazide **5d** (5.2 g), mp 231–233°. *Anal.* ($C_{22}H_{27}N_3O_5 \cdot H_2O$) C, H, N.

A solution of the above hydrazide (2.8 g) in 1 *N* HCl (17.5 ml) was treated with $NaNO_2$ (0.7 g) in H_2O (7 ml) at 0–10° over a period of 30 min; the mixture was kept at 0–10° for a further 2 hr and treated with NH_4OH when the azide **5e** (1.7 g) was precipitated.

The above azide (1.7 g) was treated with $C_6H_5CH_2OH$ (5 ml) at 90–100° for several hours and the cooled mixture was diluted with Et_2O and extracted with dilute aqueous AcOH. Basification (aqueous NaOH) of the aqueous phase precipitated the ketone **3a** (1 g), mp 190–194°, identical (ir and tlc) with authentic material.

2′,3′,4′,5′,7,8-Hexahydro-5′-oxofurano[2′,3′:3,14]thebainone Δ⁵-Enol Methyl Ether (7). Aqueous NaOH (2.5 *N*, 150 ml) at 95° was added to a solution of **3a** (30 g) in 2-ethoxyethanol (300 ml) also at 95°. The solution was boiled for 35 min and poured into H_2O (100 ml), and the mixture was cooled in an ice bath for 1.5 hr. The solution was filtered to remove a small amount of precipitate and the filtrate treated with saturated aqueous NH_4Cl. The mixture was set aside at room temperature for 1 hr; the precipitated solid was collected and recrystallized from EtOH to give the lactone **7** (9.8 g), mp 209–213°. *Anal.* ($C_{21}H_{25}NO_5$) C, H, N.

The 4-*O*-methyl ether prepared by treatment of **7** with MeI and K_2CO_3 had mp 197–198° (from EtOH). *Anal.* ($C_{22}H_{27}NO_5$) C, H N.

2′,3′,4′,5′,7,8-Hexahydro-5′-oxofurano[2′,3′:8,14]thebainone Hydrochloride (8). The enol ether **7** (3.5 g) was dissolved in 5 *N* HCl (10 ml). Within a few minutes the HCl salt of the product precipitated. Recrystallization from MeOH afforded the hydrochloride **8** (3.3 g), mp 234–236°. *Anal.* ($C_{20}H_{23}NO_5 \cdot HCl$) C, H, N, Cl.

The free base, precipitated from an aqueous solution of the HCl salt with $NaHCO_3$, had mp 110–116°.

14-(Ethoxycarbonylmethyl)-3-*O*-ethyloripavinone A (9). Enol ether **7** (5 g) was heated in boiling ethanolic HCl (*ca.* 1 *N*, 50 ml) for 6 hr. The mixture was kept at room temperature overnight and evaporated, and the residue was dissolved in hot 5 *N* HCl (50 ml). Cooling gave crystals which were treated with NH_4OH; filtration and recrystallization from aqueous EtOH afforded **9** (1.2 g), mp 123–126°. *Anal.* ($C_{23}H_{29}NO_5$) C, H, N.

The 4-*O*-methyl ether prepared by treatment of **9** with MeI and K_2CO_3 had mp 125–128° (from EtOH). *Anal.* ($C_{24}H_{31}NO_5$) C, H, N.

6,14-*endo*-Ethano-7-oxotetrahydrothebaine (4a). A solution of **3a** (4.8 g) in glacial AcOH (30 ml) was hydrogenated at atmospheric pressure and room temperature in the presence of 5% Pd/C (1 g). After 4 hr the mixture was diluted with H_2O (100 ml) and filtered, and the filtrate was basified using concentrated NH_4OH. The precipitated material was recrystallized from EtOH to give ketone **4a** (3.6 g), mp 215–216°. *Anal.* ($C_{21}H_{25}NO_4$) C, H, N.

6,14-*endo*-Etheno-7,7-dimethoxytetrahydrothebaine (5f). $HClO_4$ (1 ml, 72% w/w) was added to a stirred solution of **3a** (1 g) in MeOH (20 ml) at room temperature. Trimethyl orthoformate (4 ml) was added and the mixture kept at 24° for 48 hr. After the addition of pyridine (2 ml) the mixture was poured into aqueous $NaHCO_3$, the precipitated solid was recrystallized from MeOH to give the dimethyl ketal (0.9 g), mp 172–173°. *Anal.* ($C_{23}H_{29}NO_5$) C, H, N.

6,14-*endo*-Etheno-7,7-dimethoxytetrahydrooripavine. 6,14-*endo*-Etheno-7,7-dimethoxytetrahydrothebaine (5 g) was added with stirring to a solution of KOH (15 g) in diethylene glycol (80 ml) at 210° under N_2. The mixture was kept at 210° for 1 hr, poured into cold H_2O (250 ml), and filtered after 1 hr. Treatment of the filtrate with hot saturated aqueous NH_4Cl (~250 ml), filtration, and recrystallization from MeOH afforded the phenol (2.5 g), mp 222–226°. *Anal.* ($C_{22}H_{27}NO_5$) C, H, N.

6,14-*endo*-Etheno-7-oxotetrahydrooripavine (3c). A solution of the oripavine ketal (2 g) in 1 *N* HCl (20 ml) was heated at 100° After 10 min the mixture was cooled and basified with concentrated NH_4OH. NH_4Cl was added and the mixture extracted with $CHCl_3$. Evaporation and recrystallization of the residue from MeOH afforded the ketone **3c** (0.8 g), mp 220–225°. *Anal.* ($C_{20}H_{21}NO_4$) C, H, N.

6,14-*endo*-Ethano-7-oxotetrahydrooripavine (4c), mp 193–195° [*Anal.* ($C_{20}H_{23}NO_4$) C, H, N], was obtained by an analogous procedure from **4a** *via* the intermediate ketal, mp 121–122°. *Anal.* ($C_{23}H_{31}NO_5$) C, H, N.

6,14-*endo*-Etheno-7-oxotetrahydronorthebaine (3b). A mixture of **3a** (5.3 g), diethyl azodicarboxylate (2.9 g), and Me_2CO (60 ml) was boiled under reflux for 3 hr. The solvent was removed and the residue heated at 100° for 30 min. The residue was dissolved in hot 1 *N* HCl (40 ml) and filtered and the filtrate was cooled. The precipitate was collected and crystallized from EtOH to give the HCl salt of **3b** (3.3 g), mp 310° dec. The base had mp 188–192°. *Anal.* ($C_{20}H_{21}NO_4$) C, H, N.

6,14-*endo*-Ethano-7-oxotetrahydronorthebaine hydrochloride (4b), mp 300° [*Anal.* ($C_{20}H_{23}NO_4 \cdot HCl$) C, H, N, Cl], was obtained similarly from **4a.**

N-Alkylation of Nor Bases. General Procedure (See Table I). ***N*-Allyl-6,14-*endo*-etheno-7-oxotetrahydronorthebaine (3d).** A stirred mixture of nor base **3b** (2.5 g), allyl bromide (2.7 g), and anhydrous K_2CO_3 (3.0 g) in EtOH (30 ml) was heated under reflux overnight. The hot mixture was filtered and the filtrate evaporated; the residue was extracted into C_6H_6. Evaporation of the extract and recrystallization of the residue from EtOH afforded the *N*-allyl derivative **3d** (2.1 g), mp 152–155°. *Anal.* ($C_{23}H_{25}NO_4$) C, H, N.

Reaction of *N*-Cyclopropylmethyl-7-chloro-7-cyano-6,14-*endo*-ethenotetrahydronorthebaine with NaOH. To *N*-cyclopropylmethyl-7-chloro-7-cyano-6,14-*endo*-ethenotetrahydronorthebaine[3] (10 g, mixture of epimers) in warm 2-ethoxyethanol (100 ml) was added 2 *N* aqueous NaOH (75 ml). This mixture was boiled under reflux for 25 min, cooled, and poured into ice–H_2O. Crystallization of the precipitate from EtOH afforded the *N*-cyclopropylmethyl derivative **3g** (1.6 g), mp 138–139°. *Anal.* ($C_{24}H_{27}NO_4$) C, H, N.

The mother liquors from above were treated with a saturated solution of NH_4Cl when a precipitate slowly formed which was collected and recrystallized from EtOH to give **7** (*N*-CPM replaces *N*-Me) (2.5 g), mp 188–190°. *Anal.* ($C_{24}H_{29}NO_5$) C, H, N.

6,14-*endo*-Ethenotetrahydrooripavine (1b). $N_2H_4 \cdot H_2O$ (8 ml) was added to a solution of **3a** (8 g) in hot diethylene glycol (70 ml) and the mixture was heated at 180° with stirring for 45 min. KOH (24 g) was added and the mixture was distilled until the temperature rose to 210°. This temperature was maintained for 5 hr after which time the mixture was poured into ice–H_2O (300 ml) containing a small amount of $Na_2S_2O_4$. The solution was filtered and the filtrate treated with hot saturated aqueous NH_4Cl (300 ml). The filtrate was kept at room temperature overnight and the precipitate (3.1 g) was collected. This solid was extracted with Et_2O (2 × 75 ml) and the solid (1.5 g) obtained after removal of the solvent recrystallized from EtOH to give **1b** (0.9 g), mp 208–210°, with softening. *Anal.* ($C_{20}H_{23}NO_3$) C, H, N.

A larger amount of the same product was isolated from the aqueous NH_4Cl liquors by extraction with Et_2O; the washed extract on evaporation gave material (~3 g) which was recrystallized from EtOH to give a sample (1.9 g), mp 210–211°.

6,14-*endo*-Ethanotetrahydrooripavine (2b) was obtained by a similar reduction of ketone **4a;** it had mp 206–209°. *Anal.* ($C_{20}H_{25}NO_3$) C, H, N.

6,14-*endo*-Ethenotetrahydrothebaine (1a). Oripavine **1b** (2.8 g) was heated in boiling EtOH (30 ml) in the presence of MeI (5 g) and anhydrous K_2CO_3 (3.5 g) for 20 hr. The filtered mixture was evaporated and the residue extracted with C_6H_6 (50 ml). The com-

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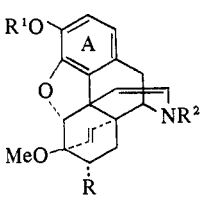
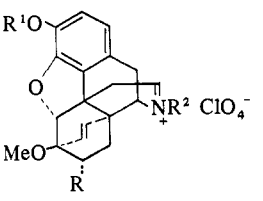
A series of 16-alkyl-6,14-*endo*-ethenotetrahydrothebaines III is described. All the 16-alkyl compounds were less active as analgetics than their 16-H parents.

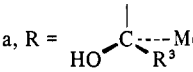
In derivatives of morphine and related compounds the piperidine ring is of prime importance in determining the pharmacological profile. In particular, certain substituents on the nitrogen atom confer morphine antagonist character. The possibility that similar alterations of analgetic activity could be 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.



I



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