mol) of *p*-TosCl in 35 ml of pyridine. Stirring was continued for 0.5 hr after which the solvent was removed by distillation. The residue was partitioned between H_2O and Et_2O. The Et_2O layer crystallized to give 3.8 g of **12**. Evaporation of the mother liquor gave 3.5 g of mixture **13** which was not characterized. Two recrystallizations of **12** from EtOH afforded material which had mp 172–174°. *Anal.* ($C_{22}H_{29}NO_3S$) C, H, N.

***cis*-1,2,3,4,4a,5,10,10a-Octahydro-5,5-dimethyl-1-(*p*-toluenesulfonyl)benzo[*g*]quinoline (14).** **A.**—Compound **12** (2.8 g, 0.07 mol) was cyclized according to the procedure given above for the preparation of **9** and **10**. Crystallization of the crude residue from EtOH gave 2.2 g of **14**. Recrystallization from EtOH gave material, mp 143–145°. *Anal.* ($C_{22}H_{27}NO_2S$) C, H, N.

B.—Residue **13** (0.54 g, 0.0014 mol) was cyclized according to the above procedure to give 0.36 g of **14** identical with that prepared above.

Carbinols for Cyclization Studies.—These derivatives were prepared from the pure isomeric amino alcohols **8b**.[2] Reductive methylation with CH_2O and H_2 over Pd–C gave the NMe derivatives: *cis* isomer m p94–96°, *Anal.* ($C_{17}H_{27}NO$) C, H, N; *trans* isomer mp 78–79°, *Anal.* ($C_{17}H_{27}NO$) C, H, N. Acylation with AcCl or *p*-$O_2NC_6H_4SO_2Cl$ in $CHCl_3$ in the presence of Et_3N gave the corresponding amide: *cis*-*N*-acetyl, mp 138–141°, *Anal.* ($C_{18}H_{27}NO_3$) C, H, N; *trans*-*N*-acetyl, mp 111–113°, *Anal.* ($C_{18}H_{27}NO_3$) C, H, N; *cis*-*N*-*p*-$O_2SC_6H_4NO_2$, mp 182–186°, *Anal.* ($C_{22}H_{28}N_2O_6S$) C, H, N; *trans*-*p*-$O_2SC_6H_4NO_2$, mp 132–134°, *Anal.* ($C_{22}H_{28}N_2O_6S$) C, H, N. The *p*-$C_6H_4NO_2$ derivatives were prepared according to the procedure of Badar, et al.[13] These compounds could not be obtained crystalline, and were characterized only by their ir spectra.

3-Isopropylidene-2-*p*-methoxybenzylpiperidine and Derivatives.—The neutral fraction from the decarbobenzoxylation of 1-benzyloxycarbonyl-2-(*p*-methoxybenzyl)-α,α-dimethyl-3-piperidinemethanol was allowed to stand for 3 months. A 21.7-g sample of this residue was diluted to 200 ml total volume with EtOH and hydrogenated over Pd–C at room temperature and 4 atm. Uptake ceased after 3 hr with the consumption of approximately 1 molar equiv of H_2. The basic fraction was dissolved in dil HCl and cooled to give, after filtration and drying, 9.1 g of crude **23**·HCl. Recrystallization from EtOH–Et_2O gave pure **23**, mp 255–257°, nmr ($CDCl_3$, TMS) 413 (A_2B_2,4) 223 (s, 3), 95 (s, 3), 64 Hz (s, 3). *Anal.* ($C_{16}H_{24}ClNO$) C, H, N.

The NMe and *p*-$SO_2C_6H_4NO_2$ derivatives were prepared by the procedures indicated in the previous section and had the following properties: NMe·HCl, mp 179–183°, *Anal.* ($C_{17}H_{26}ClNO$) C, H, N; *N*-*p*-$SO_2C_6H_4NO_2$, mp 114–116°, *Anal.* ($C_{22}H_{26}N_2O_5S$) C, H, N.

Benzo[*g*]quinoline Derivatives as Nmr References.—The corresponding derivatives of *cis*- and *trans*-1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethyl-7-methoxy-benzo[*g*]quinoline were prepared by the same procedures and the nmr spectra recorded. The compounds not previously reported had the following physical properties (the numbers in parentheses following the melting point are the chemical shifts in Hz of the *gem*-Me_2 groups in the 60 MHz nmr spectra): *cis*-N-*p*-$C_6H_4NO_2$, glass (80,79), *Anal.* ($C_{22}H_{16}N_2O_3$) C, calcd, H, 6.89, N, 7.67; found, H, 7.41, N, 8.60; *trans*-N-*p*-$C_6H_4NO_2$, mp 164–166° (83,70), *Anal.* ($C_{22}H_{26}N_2O_3$) C, H, calcd, N, 7.67; found, 9.04; *cis*-*N*-acetyl, mp 81–85° (80,78), *Anal.* ($C_{18}H_{25}NO_2$) C, H, calcd, N, 4.87; found 5.33; *trans*-*N*-acetyl, mp 157–159° (80,68), *Anal.* ($C_{18}H_{25}NO_2$) C, H, N; *cis*-N-*p*-$SO_2C_6H_4NO_2$, mp 159–161° (81,79), *Anal.* ($C_{22}H_{26}N_2O_5S$) C, H, N, *trans*-N-*p*-$SO_2C_6H_4NO_2$, mp 204–205° (79,59), *Anal.* ($C_{22}H_{26}N_2O_5S$) C, H, N.

Cyclization Procedure.—A solution of 100 ml of AcOH and 20 ml of H_2SO_4 was used for all cyclizations. A 125-mg sample of the carbinol and 1.0 ml of the acid were heated on a steam bath for 5 min, diluted with 25 ml of H_2O, made slightly basic with NH_4OH, and extracted with 25 ml of $CHCl_3$. The extract was dried, filtered, and concentrated and the entire residue used for nmr. The resulting spectrum was compared with that of the two pure products, and the relative amounts of each determined.

Acknowledgments.—The authors wish to thank Mr. K. D. Fleischer for elemental analyses, Dr. R. K. Kullnig for spectral data, and Mr. A. K. Pierson for pharmacological results.

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Novel Analgetics and Molecular Rearrangements in the Morphine–Thebaine Group. XVIII.[1] 3-Deoxy-6,14-*endo*-etheno-6,7,8,14-tetrahydrooripavines

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7-Substituted 3-deoxy-6,14-*endo*-etheno-6,7,8,14-tetrahydrooripavines have been prepared by hydrogenolysis of the oripavine diethylphosphatyl esters. In some cases partial reduction of the etheno bridge also occurs. The deoxy compounds show analgetic potency intermediate between the oripavine and thebaine analogs.

The nature of the C_3 substituent is very important in determining analgetic potency in the morphine series (**1**).[2] Thus heroin (**1c**) is more potent than morphine (**1a**) which is itself considerably more potent than codeine (**1b**). In the related series of analgetics (**3b–6b**) derived from 6,14-*endo*-ethenotetrahydrooripavine the effect of removing the phenolic hydroxyl group by hydrogenolysis with Na in liquid NH_3 of the diethyl phosphate derivatives (**2**)[3] has now been investigated.

The phosphates were prepared by reaction of the oripavine derivatives with diethyl phosphite and CCl_4 and were dissolved in Et_2O for the Na–liquid NH_3 reaction. In most cases the hydrogenolysis reaction went to completion but purification of the products was not always easy. In the case of the 7-dimethylcarbinol (**3c**) a by-product having similar chemical and physical properties was isolated by preparative tlc. This was shown to be identical with the 3-deoxy compound (**8c**) derived from the 6,14-*endo*-ethanooripavine (**8b**). Hydrogenation of the olefinic bond by Na in liquid NH_3 was surprising in view of the fact that **3a** is catalytically hydrogenated only with difficulty,[4] and reduction of disubstituted olefins by metal–amine systems occurs only with the powerful Li–alkylamine reagents.[5] The

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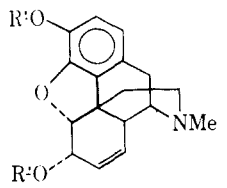
TABLE I

Structure	N substituent	Analgetic potency (tail pressure test), morphine = 1 — 3-H	3-OH	3-OMe
3	Me	6	25	4.2
4	Me	100	1100	16
5	Me	280	2800	40
6	Me	<0.02	20	0.04
7	Me	2000	1600	110
8	Me	13	70	2.8
9	CPM	0.02[a]	100[a]	0.07[a]
10	Allyl	<0.02	2.2[a]	0.02
11	Allyl	1.9	20	0.75
12	CPM	0.11	35[a]	0.4[a]
13	CPM	0.9	70[a]	0.2
14	CPM	5.0	48	3.8
15	Me	1.2	42	0.4

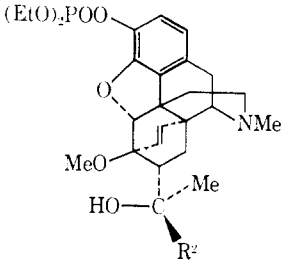
[a] Potency as morphine antagonist in tail pressure test (nalorphine = 1).

phenylmethyl carbinol **6c** also underwent partial hydrogenation of the etheno bridge when the phosphate ester was hydrogenolyzed. Surprisingly the C_7 ethyl derivative **15c** having a more accessible etheno bridge did not suffer partial hydrogenation.

Oripavines **10b–14b** in which the N-substituent is allyl or cyclopropylmethyl were converted into 3-deoxy compounds without affecting the N-substituent but the etheno bridge in **12c** underwent partial hydrogenation.



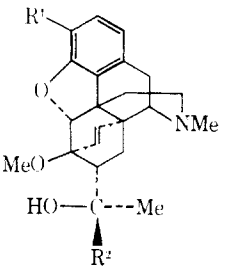
1



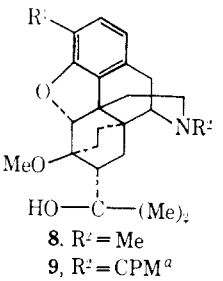
2

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

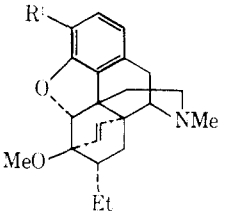
Structure–Activity Relationships.—Table I shows the analgetic and morphine-antagonist potencies of the deoxy compounds compared with the corresponding 3-methoxy and 3-hydroxy analogs. The *N*-methyl deoxy compounds are more potent analgetics than the thebaine analogs (3-OMe) but less potent than the oripavines (3-OH). An exception is the phenethylcarbinol **7c** which is 2000 times more potent than morphine, somewhat greater than the corresponding oripavine **7b**. Where the *N*-allyl and *N*-cyclopropyl-



3, R^2 = Me
4, R^2 = Pr
5, R^2 = *n*-Pentyl
6, R^2 = Ph
7, R^2 = Phenethyl



8, R^2 = Me
9, R^2 = CPM[a]



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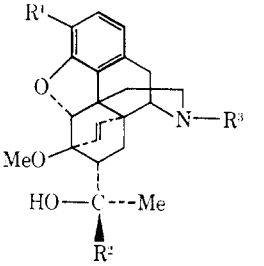

10, R^2 = Me; R^3 = allyl
11, R^2 = *n*-Pr; R^3 = allyl
12, R^2 = Me; R^3 = CPM
13, R^2 = Et; R^3 = CPM
14, R^2 = *iso*-Pentyl; R^3 = CPM

a, R^1 = OMe
b, R^1 = OH
c, R^1 = H

[a] CPM = cyclopropylmethyl

methyl oripavines are morphine antagonists the derived deoxy compounds show much weaker antagonist character and, in most cases, pronounced analgetic activity. On the other hand the potency of the *N*-substituted oripavine analgetics is considerably greater

TABLE II

No.	Crystallization solvent[a]	Mp, °C	Yield, %	Formula	Analyses
3c	A	196–197	42[g]	$C_{23}H_{29}NO_3$	C, H, N
4c	B	207–209	37	$C_{25}H_{33}NO_3$	C,[c] H, N
5c	A	134–135	47	$C_{27}H_{37}NO_3$	C, H, N
6c	B	253–255	26	$C_{28}H_{31}NO_3$	C, H, N
7c	C	157–159	58	$C_{30}H_{35}NO_3$	C,[d] H, N
8c	C	174–176	58	$C_{23}H_{31}NO_3$	C, H, N
9c	D	245–250	43	$C_{26}H_{36}ClNO_3 \cdot 0.5H_2O$[f]	C, H, Cl, N
10c	A	140–141	38	$C_{25}H_{31}NO_3$	C, H, N
11c	B	129–130	25	$C_{27}H_{35}NO_3$	C, H, N
12c	A	135–136	61[h]	$C_{26}H_{35}NO_3$	C,[e] H, N
13c	B	230–235	54	$C_{27}H_{36}ClNO_3$[f]	C, H, Cl, N
14c	B	143–146	37	$C_{30}H_{41}NO_3$	C, H, N
15c	C	125–127	35	$C_{22}H_{27}NO_2$	C, H, N

[a] A, EtOH–H_2O; B, EtOH; C, MeOH; D, Et_2O. [b] Based on oripavine. [c] C: calcd, 75.91; found, 75.3. [d] C: calcd, 78.74; found 78.23. [e] C: calcd, 76.61; found, 76.04. [f] Hydrochloride. [g] Also formed ~10% of **8c**; isolated by preparative tlc on silica–Et_2O. [h] Also formed ~15% of **9c** identified by tlc; **12c** isolated by chromatography on alumina (Grade 1—elution with 5% EtOAc in C_6H_6).

than that of the deoxy derivatives. The corresponding thebaine derivatives have profiles similar to the deoxy compounds but with less analgetic character.

Experimental Section

Melting points were determined on a Kofler hot-plate 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. See Table II for experimental data.

6,14-*endo*-Etheno-7α-ethyltetrahydrooripavine 3*O*-Diethyl Phosphate.—Et_3N (5 ml) was added slowly with vigorous shaking to an ice-cold mixture of 6,14-*endo*-etheno-7α-ethyltetrahydrooripavine[6] (10.8 g), CCl_4 (10 ml), and diethyl phosphite (4.5 ml). The mixture was set aside at room temperature for 18 hr. The mixture was diluted with H_2O and the organic layer separated. The aqueous solution was extracted with $CHCl_3$. The combined organic solutions were washed several times with 1 *N* NaOH and finally H_2O. The dried (Na_2SO_4) extract was evaporated and the residue recrystallized (C_6H_6–petroleum ether) to give 7.0 g (47%) of the phosphate, mp 135–137°. *Anal.* ($C_{26}H_{36}NO_5P$) C, H, N.

(6) K. W. Bentley, D. G. Hardy, J. W. Lewis, M. J. Readhead, and W. I. Rushworth, *J. Chem. Soc. C*, 826 (1969).

The phosphates of the other oripavine derivatives[7] were prepared by analogous procedures and were hydrogenolyzed without purification.

General Procedure for the Hydrogenolysis of the Oripavine Phosphates.—The crude phosphate was dissolved in Et_2O and NH_3 was added (20 ml/g of phosphate); to the mixture Na (2 g-atoms) was added in small pieces, as rapidly as frothing would allow. EtOH (2 mol) was then added and the NH_3 allowed to evaporate. The residue was treated with H_2O and extracted with Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. Crystallization of the residue gave the 3-deoxyoripavine.

Biological Methods.—Analgetic activity was determined subcutaneously in the rat tail pressure test of Green and Young[8] and morphine antagonism by the method of Green, Ruffell, and Walton.[9]

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Central Nervous System Stimulants of the Xanthone Group

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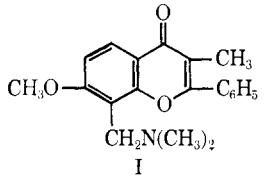
A series of basic derivatives of methoxy-, hydroxy-, and chloroxanthones were synthesized and tested pharmacologically. Some N-disubstituted 4-aminomethyl-3-methoxyxanthones show a powerful CNS stimulating activity. Structure–activity relationships have been examined.

In continuation of our researches[1,2,3] on CNS stimulating drugs of the benzopyrone series, the most significant of which is 3-methyl-7-methoxy-8-dimethylaminomethylflavone (dimefline, I), the xanthone analogs II have now been synthesized.



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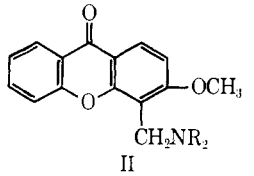

II

This modification of structure I was an outcome of our previous work and was made with the purpose of devising a drug which would reduce some undesirable side effects (such as the excitatory cortical component of the analeptic activity) as well as the toxicity and at the same time improve the clinical safety. The new carrier moiety of the CH_2NR_2 group was to permit a better insight into the structure–activity relationships and to make use of synthetic methods such as addition reactions and partial or total reduction of the CO group, which are more difficult to perform with chromone or flavone analogs.

The present work concerns some N-disubstituted 4-aminomethyl derivatives of 3-methoxyxanthone, selected on the basis of previous results[2] in the benzo-γ-pyrone series, as well as the corresponding derivatives of 3-methoxy-6-chloroxanthone, which were prepared in order to take advantage of the possible widening of the safety margin induced by the introduction of Cl.[4] Furthermore, owing to the symmetry of the xanthone molecule we had the opportunity to prepare the bis(aminomethyl) derivatives of 3,6-dihydroxy- and 3,6-dimethoxyxanthone and so to verify the so-called molecular doubling principle,[5] by which one could expect an inversion of the previously observed activity.

A few papers concerning the same subject (preparation of Mannich bases of hydroxyxanthones and alkylated xanthones) have appeared,[6,7,8] but no biological data have been reported. These compounds however, on the basis of our previous findings,[2] ought to be less active than the MeO analogs.

We also wish to report an attempt to apply the

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