data were as follows: for **3c**, λ_{max} 271 nm (log ϵ 4.15), 279 (4.16), 303 (3.90); for **3d**, λ_{max} 270 nm (log ϵ 4.13), 280 (4.15), 303 (3.86); for **3e**, λ_{max} 270 nm (log ϵ, 4.14), 279 (4.15), 301 (3.90).

***N*-(2-Bromoallyl)-2,10,11-trihydroxynoraporphine Hydrochloride (3f).** A mixture of *N*-propargylnormorphothebaine (5e; 0.30 g, 0.93 mol) in 10 mL of 48% (w/v) HBr was heated and evaporated in the same manner as described for the preparation of **3c–e**, to give a dry solid (0.35 g). Further purification of the product was carried out through the preparation of its triacetoxy derivative, followed by subsequent hydrolysis as follows: the residue was diluted with 10 mL of CF_3CO_2H, and 4.0 mL of acetyl bromide was added dropwise. After the initial exothermic reaction subsided, the reaction mixture was heated at 90 °C under nitrogen for 2 h and evaporated. The residue was taken up with 50 mL of $CHCl_3$, washed with 30 mL of 3% (w/v) $NaHCO_3$ in brine, dried, and concentrated to approximately 2 mL of a solution, which was then chromatographed on silica gel packed and eluted with $CHCl_3/Et_2O$ (1:1) to give a pure product with an R_f of 0.32 (in $CHCl_3$) on TLC. The triacetoxy derivative underwent alcoholysis after being treated with a mixture of 25 mL of absolute methanol and 12.5 mL of ethereal HCl for 16 h. The reaction mixture was evaporated to a residue, which was recrystallized from a methanol and ethyl ether mixture to give an off-white solid: yield 120 mg (38%); mp 180–184 °C; TLC R_f 0.40 ($CH_3OH/CHCl_3$, 1:6); NMR (CD_3OD) δ 2.77–4.40 (broad signals, H at C-4, C-5, C-6a, C-7, NCH_2), 6.43–7.10 (m, 5, H at C-3, C-8, C-9, C=CH_2), 7.9–8.0 (d, 1, H at C-1); UV (EtOH) λ_{max} 271 nm (log ϵ 4.11), 279 (4.12), 303 (3.86); MS, *m/e* 388 (M^+). Anal. ($C_{19}H_{18}NO_3Br\cdot HCl\cdot 0.5H_2O$) C, H, N.

***N*-Propargyl-2,10,11-trihydroxynoraporphine (3g).** A mixture of normorphothebaine hydrochloride (6; 1.5 g, 4.7 mol) in 48% (w/v) HBr was heated at 130 °C under nitrogen for 3 h and evaporated in vacuo. The residue was taken up with a minimal amount of absolute methanol, and the solution was added dropwise to 200 mL of ethyl ether to give a precipitate. Filtration of the mixture yielded the intermediate 2,10,11-trihydroxynoraporphine (**3a**; 1.55 g). A mixture of **3a**, propargyl bromide (0.54 g, 4.5 mol), $NaHCO_3$ (0.92 g, 11 mol), and 0.3 g of potassium iodide in 75 mL of acetonitrile was heated at reflux under nitrogen for 18 h, cooled, and filtered. The filtrate was evaporated to a residue, which was taken up with 5 mL of a chloroform and methanol mixture (1:1), and the solution was added dropwise to 100 mL of ethyl ether to result in precipitation. The supernatant was decanted and evaporated to give the crude desired product (0.45 g, 32%). Further purification of the product was carried out through the preparation of its triacetoxy derivative, followed by column chromatography and acid hydrolysis in the same manner as the preparation of **3f** to give pure **3g** as hydrochloride salt: yield 275 mg (17%); mp 178–181 °C; NMR ($CDCl_3/CD_3OD$) δ 2.8–4.4 (broad signals, H at C-4, C-5, C-6a, C-7, NCH_2, C≡CH), 6.4–6.7 (m, 3 H at C-3, C-8, C-9), 7.8 (d, 1, H at C-1); UV (EtOH) λ_{max} 238 nm (log ϵ 4.40), 259 (4.40), 280 (4.14), 306 (4.03), 358 (3.62), 376 (3.61); MS, *m/e* 307 (M^+). Anal. ($C_{19}H_{17}NO_3\cdot HCl\cdot H_2O$) C, H, N.

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Analgesic Narcotic Antagonists. 8.[1] 7α-Alkyl-4,5α-epoxymorphinan-6-ones

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The preparation of a series of 7α-alkylated dihydrocodeinones is described. *N*-(Cyclopropylmethyl) (P series) or *N*-(cyclobutylmethyl) (B series) 7α-methyl (a series) or 7α,8β-dimethyl (b series) substituted dihydronorcodeinones (**7**) were prepared from the appropriately substituted *N*-(cycloalkylmethyl)-4-hydroxymorphinan-6-ones (**5**) by dibromination, 4,5-epoxy ring closure, and catalytic debromination. Treatment of **7** with BBr_3 gave low yields of the corresponding 3-phenols **8**. Alternatively, reaction of dihydrocodeinone (**10**) with dimethylformamide dimethyl acetal gave the 7-[(dimethylamino)methylene] adduct **11**, which was hydrogenated to 7α-methyl- (**12**) or 7α-(hydroxymethyl)dihydrocodeinone (**13**). Treatment of **11** with lithium reagents, followed by hydrogenation, gave a mixture of 7α-alkyl (**15c–f**) compounds and the corresponding 4,5-epoxy-cleaved products **16**. Reaction of **11** with α-ethoxyvinyllithium gave intermediate **17**, which on hydrolysis and hydrogenation yielded the 6,7-furyl (**18**) or pyrroyl (**19**) derivative. *N*-(Cycloalkylmethyl)-14-hydroxydihydronorcodeinones **23P,B** reacted with dimethylformamide dimethyl acetal to give **25P,B**, which were hydrogenated to the 7α-methyl compounds **26P,B** and O-demethylated to give **27P,B**. The 7α-methyl-*N*-methyl compounds were about equipotent with dihydrocodeinone. Derivatives with larger alkyl groups were less potent. Corresponding *N*-(cycloalkylmethyl) compounds did not show strong mixed agonist–narcotic antagonist activity.

We recently reported[2] that reaction of thebaine with lithium dimethylcuprate yields 7β-methyldihydrothebaine-φ (**1**). The facile preparation of this 4,5α-epoxy-cleaved 7-alkylated product allowed entry into a series of 7-methyl-8-alkylmorphinan-6-ones and -isomorphinan-6-ones with potent analgesic activity.[3] These compounds were converted to their corresponding *N*-(cycloalkylmethyl) derivatives, several of which had interesting mixed agonist–narcotic antagonist properties. In view of the modification in the pharmacological profile of opiate derivatives by the incorporation of alkyl groups in the C ring,[3,4] we have now extended our work to the preparation of the 4,5α-epoxy counterparts of these previously reported

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(2) Leland, D. L.; Polazzi, J. O.; Kotick, M. P. *J. Org. Chem.* **1980**, *45*, 4026.
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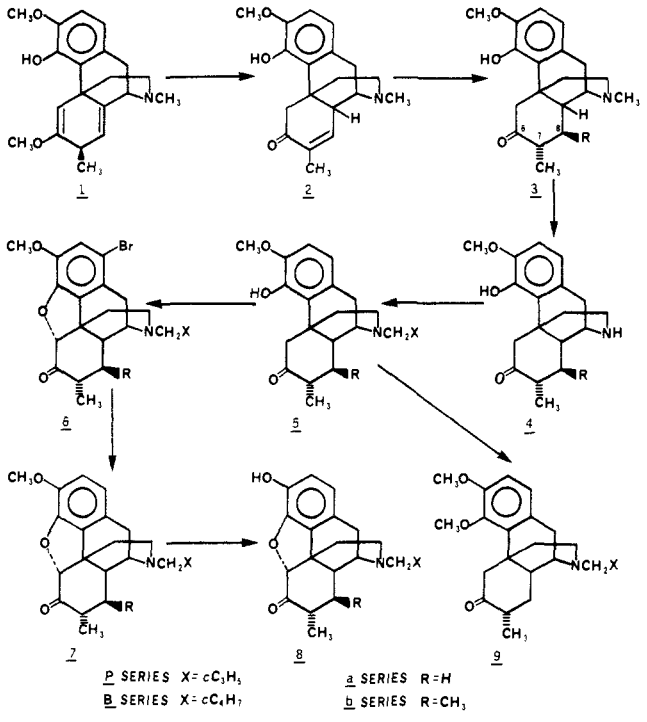
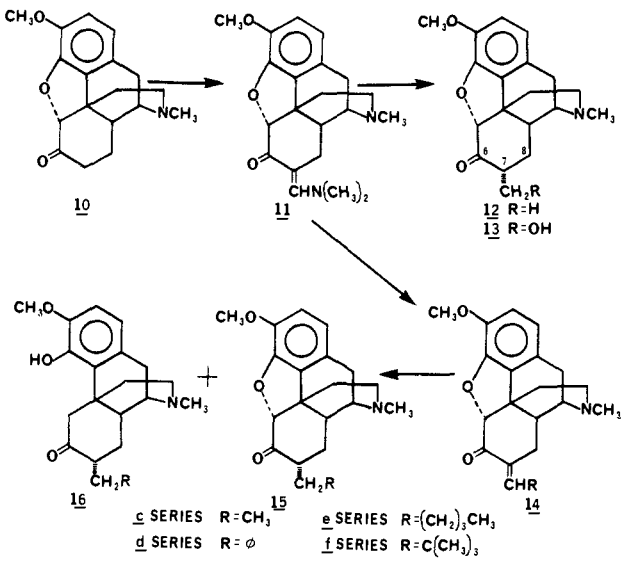
Scheme I



Scheme II



7-methyl compounds. In addition, we report a novel useful method for the introduction of other alkyl groups into the 7α position of the dihydrocodeinone molecule.

Chemistry. Reaction of 14-hydroxydihydrocodeinone with methyl iodide and sodamide in liquid ammonia–THF has been reported to yield a 7-methyl derivative.[5] Our attempts to reproduce this reaction, both with dihydrocodeinone or the 14-hydroxy compound, were unsuccessful. Several other attempts at direct monoalkylation of the C7 position were likewise not fruitful. We therefore investigated 4,5-epoxy ring closure of our previously reported 4-hydroxy-7α-methyl-*B*/*C*-*cis*-morphinan-6-ones.

Closure of the oxide bridge has had great impact on the field of morphine alkaloid chemistry. This reaction was utilized some years ago in the preparation of metopon (5-methyldihydromorphinone).[6,7] A minor product obtained in this sequence was 7-methyldihydrothebainone (**3a**), which was ring closed to yield 7-methyldihydrocodeinone (**12**). The structure of these compounds was not definitively proven until some years later.[8] Oxide ring closure has most recently been investigated by Weller and Rapoport.[9] These authors report a facile, high-yielding conversion of dihydrothebainone to dihydrocodeinone via the sequence: 1,7-dibromination, ring closure under mild base conditions, and 1-debromination by catalytic hydrogenation.[9] The ease of this reaction sequence attracted our attention.[10]

Preliminary work in our laboratory revealed that, in contrast to dihydrocodeinone and 7,7-dimethyldihydrocodeinone,[11] 7α-methyldihydrocodeinone (**12**) was unstable to acid conditions.[12] Refluxing a solution of **12** in 2 N HCl rapidly gave rise to an equilibrium mixture containing epoxy-cleaved products, which underwent further slow degradation. Since aqueous acid hydrolysis of *N*-cyano groups comprises the second step of our N-demethylation sequence,[4] removal of the *N*-methyl group and subsequent cycloalkylmethylation were performed at the onset of our synthetic sequence, prior to oxide ring closure.

The cis isomer **2** was hydrogenated to **3a** as previously reported[2] or treated with an excess of Me_2CuLi to give **3b** (Scheme I). The assignment of stereochemistry to the methyl groups in the C ring as 7α,8β (diequatorial) follows from our previous work.[2-4] Conversion to the nor-derivative **4** was carried out with cyanogen bromide, followed by acid hydrolysis of the intermediate *N*-cyano compound. Cycloalkylmethylation of **4** gave N-substituted compounds **5** in good yield. Treatment of **5** with bromine in glacial acetic acid, followed by ring closure with aqueous base, gave about a 50% yield of the 1-bromo-4,5α-epoxy derivatives **6**. Hydrogenation in acetate buffer to suppress epoxy bond cleavage[9] proceeded smoothly to give **7** in excellent yields. Treatment of 3-methoxy compounds **7** with boron tribromide[15] gave low yields of 3-hydroxy compounds **8**, which were purified by chromatography. The presence of a considerable amount of an epoxy-cleaved product, which was not isolated and purified, accounted for the poor yield in this reaction. In view of the high analgesic activity reported for 3,4-dimethoxymorphinans,[16] compound **9Pa** was prepared by reaction of the sodium salt of **5Pa** with methyl *p*-toluenesulfonate.

The major drawback associated with the synthetic sequence outlined in Scheme I, aside from the length and the need for pure cis isomer **2**, was that the method is not generally applicable to the preparation of other 7-alkylated derivatives. This caused us to search still further for alternative methods to prepare the desired compounds by a method which maintains the integrity of the 4,5-epoxy bond of dihydrocodeinone.

The Mannich reaction on dihydrocodeinone was reported some years ago to yield dimeric material.[17] Rep-

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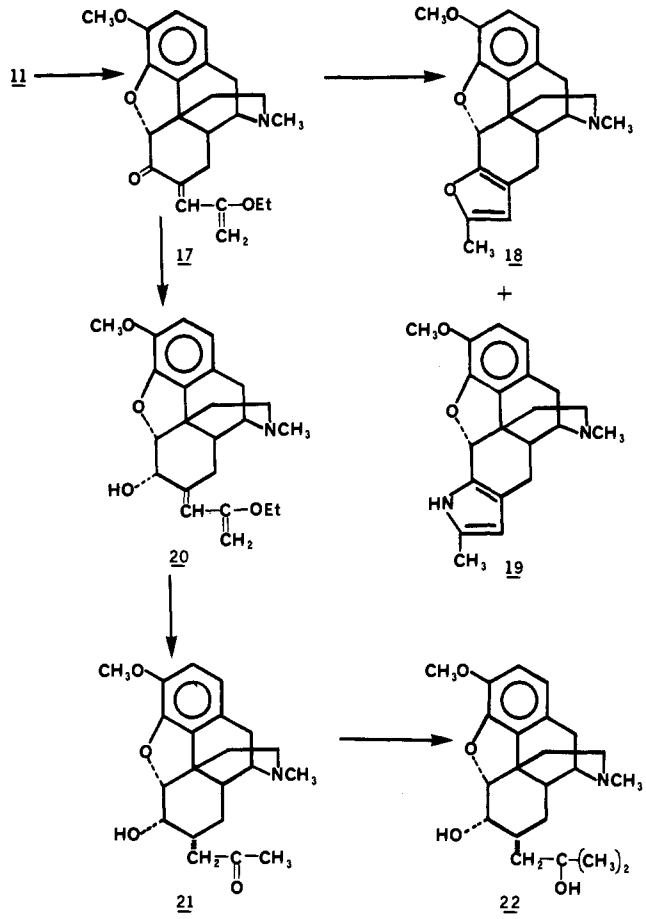
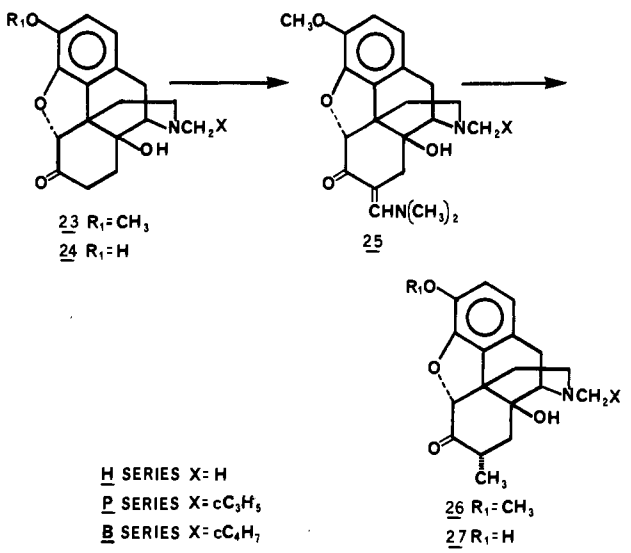
(6) Small, L.; Fitch, H. M.; Smith, W. C. *J. Am. Chem. Soc.* **1936**, *58*, 1457.
(7) Small, L.; Turnbull, S. G.; Fitch, H. M. *J. Org. Chem.* **1938**, *3*, 204.
(8) Stork, G.; Bauer, L. *J. Am. Chem. Soc.* **1953**, *75*, 4373.
(9) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171.
(10) This sequence has recently been utilized as part of an elegant total short synthesis of racemic dihydrocodeinone and related compounds by K. C. Rice (*J. Org. Chem.* **1980**, *45*, 3135).
(11) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1981**, *24*, 717.
(12) The acid-catalyzed opening of the ether bridge in 7-oxomorphine derivatives has been reported. See ref 13 and 14.
(13) Iijma, I.; Minamikawa, J.; Rice, K. C.; Jacobson, A. E. *J. Med. Chem.* **1978**, *21*, 1321.
(14) Fleischhacker, W.; Leitner, E. *Monatsh. Chem.* **1979**, *110*, 97.
(15) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.
(16) Rahman, M. F.; Brossi, A. *Heterocycles* **1977**, *6*, 881.

Scheme III



Scheme IV



etition of this reaction utilizing tetramethylmethanediamine–acetic anhydride[18] also gave a dimeric product.[19] Surprisingly, reaction of dihydrocodeinone (**10**) with dimethylformamide dimethyl acetal (DMF-DMA)[20] gave a good yield of a yellow, crystalline, monomeric product. This product was identified as the 7-[(dimethylamino)-methylene] adduct **11** (Scheme II). Hydrogenation of **11** in 95% EtOH gave a 46% yield of the *N*-methyl-7α-methyl compound **12**. Substantial amounts of **3a** from 4,5-epoxy cleavage were also obtained. Alternatively, **11** could be transformed into the hydroxymethyl derivative **13** by hydrogenation in acetate buffer. Reaction of **11** with several organolithium reagents, in a manner analogous to that reported,[20] yielded unstable α,β-unsaturated ketones **14**. These intermediates were hydrogenated in EtOH to give a mixture of the desired 7α-substituted 4,5α-epoxy-6-oxo compounds (**15**) and the corresponding products of epoxy ring cleavage (**16**). Thus, we were able to obtain various 7α-alkyldihydrocodeinones by a simple, albeit not high yielding, synthetic sequence.

The original concept which led us to explore substitution in the C ring of the morphine alkaloids was that the extremely potent analgesic activity observed with the *endo*-ethanotetrahydrooripavines is due to the presence of both alkyl and tertiary alcohol functions in this region of the molecule.[21] Thus, methods were sought to introduce similar functionality into **10**. Reaction of **11** with α-ethoxyvinyllithium to give **17**, followed by concomitant hydrolysis of the protecting group and hydrogenation, gave two products (Scheme III). These products were identified by mass spectral and NMR analyses as the 6,7-fused furan and pyrrole derivatives **18** and **19**. Isolation of these products indicate that the desired 1,4-diketone was formed but underwent base-catalyzed internal condensation to give **18** or further reaction with ammonia during workup to yield **19**. To circumvent this further reaction, **17** was reduced with $NaBH_4$ to give mainly the 6α alcohol **20**, which was hydrolyzed and hydrogenated to give **21**. Treatment of **21** with MeLi afforded a moderate yield of tertiary alcohol **22**, which gave a multitude of products on attempted oxidation to the C6 ketone.

Having already obtained the desired *N*-(cycloalkylmethyl)dihydronorcodeinone derivatives **7** and **8** by the circuitous route outlined in Scheme I, we applied our new preparation of 7α-methyl compounds to the 14-hydroxydihydrocodeinone series. Treatment of *N*-(cyclopropylmethyl) and *N*-(cyclobutylmethyl) compounds **23**[22] with DMF-DMA gave intermediates **25**, which were hydrogenated to give **26** (Scheme IV). Cleavage of the 3-methoxy groups in **26** to give **27** was effected by BBr_3. Direct reaction of the 3-hydroxy compounds **24** with DMF-DMA was attempted but resulted in O-alkylation as has been reported[23] with reagents of this type.

Results and Discussion

The *N*-methyl compounds were tested for antinociceptive activity in the acetic acid mouse writhing[24] and heat stimulus rat tail-flick[25] assays. The results of these assays are presented in Table I. These data indicate that the introduction of a methyl group into the 7α position in *N*-methyl compounds does not significantly change the antinociceptive activity when comparison is made to the

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(19) Polazzi, J. O. *J. Org. Chem.*, in press.
(20) Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248.
(21) Lewis, J. W.; Bentley, K. W.; Cowan, A. *Annu. Rev. Pharmacol.* **1971**, *11*, 241. See ref 4 for additional references and discussion.
(22) Compound **24P** is naltrexone. See *Drugs Future* **1977**, *2*, 45. For the synthesis and pharmacology of **24P** and **24B**, see Blumberg, H.; Dayton, H. B. *Adv. Biochem. Psychopharmacol.* **1973**, *8*, 33. Compounds **23** and **24** were prepared in our laboratory from 14-hydroxydihydronorcodeinone by alkylation followed by O-demethylation and were obtained in analytically pure form.
(23) Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 211. See also Leimgruber, W.; Mohacsi, E. U.S. Patent 3920746, 1975.
(24) Whittle, B. A. *Br. J. Pharmacol.* **1964**, *22*, 246.
(25) Harris, L. S.; Pierson, A. K. *J. Pharmacol. Exp. Ther.* **1964**, *143*, 141.

Table I. Agonist Activity

compd (salt)	ED_{50}, μmol/kg sc (95% CL) mouse writhing	rat tail flick
11	11.0 (1.6-76)	IA [c] 28
12 [a]	2.7 (1.9-3.9)	4.2 (2.5-7.1)
13	9.1 (0.08-104)	IA 30
15c (tartrate)	4.6 (2.9-7.4)	IA 21
15d	>25	IA 25
15e (HCl)	20.7 (14-31)	
15f [b]	IA 23	IA 23
18	12.3 (1.5-25)	IA 30
19	>29	IA 29
21	>28	IA 28
22 (tartrate)	IA 18	>18
26H	2.2 (1.2-3.9)	2.1 (0.8-5.5)
codeine [d]	10.3 (2.7-40)	75 (19-293)
morphine [d]	2.1 (1.1-4.0)	19 (9.2-41)
dihydrocodeinone [d]	2.4 (1.6-3.6)	5.2 (3.6-7.5)
dihydromorphinone [d]	0.3 (0.1-0.4)	1.3 (1.2-1.5)
5-methyldihydromorphinone [e]	0.8 (0.3-1.9)	2.5 (1.8-3.6)
14-hydroxydihydrocodeinone [f]	1.5 (0.9-2.4)	2.9 (0.8-5.5)

[a] Corresponding 3-hydroxy compound; ED_{50} = 0.2 (0.1-0.5) and 1.0 (0.5-2.0) in mouse writhing and rat tail flick, respectively. [b] Corresponding 3-hydroxy compound; ED_{50} = 3.0 and >28. [c] Inactive at dose indicated. [d] Data from ref 4. [e] Metopon; new data. [f] Oxycodone; new data.

Table II. Agonist and Narcotic Antagonist Activity

compd (salt)	ED_{50}, μmol/kg sc (95% CL) agonist: mouse writhing	antagonist: rat tail flick
5aP	9.7 (1.6-57)	>28
5bP (HCl)	>25	>25
5bB (HCl)	14.0 (7.6-25)	>22
7P [a] (HBr)	39.6 (25-61)	7.9 (2.5-25)
7Pa (HCl)	IA 25	4.1
7Pb (HCl)	>25	2.4 (1.2-4.8)
7B [a] (HBr)	20.3 (11-39)	IA [b] 7
7Ba (HCl)	>25	>25
7Bb	>26	>26
8P [a]	4.1 (0.8-20)	0.6 (0.3-1.1)
8Pa	1.1 (0.8-16)	4.4 (3.1-6.3)
8Pb (HCl)	IA 26	1.5 (1.2-1.7)
8B [a]	0.2 (03-1.8)	5.0 (1.0-24)
8Ba (HCl)	0.8 (0.2-3.4)	33.1 (14-80)
8Bb	15.0 (6.6-35)	6.5 (0.8-50)
9Pa (HCl)	9.1 (2.9-29)	~25
23P	IA 28	0.7 (0.5-1.2)
23B (tartrate)	16.2 (6.9-38)	>18
24P	>28	0.2 (0.1-0.3)
24B	9.7 (7.5-52)	1.1 (0.3-5.1)
26P	18.7 (4.6-78)	25.4 (14-48)
26B (tartrate)	1.2 (0.7-22)	IA 18
27P	IA 26	0.09 (0.05-0.18)
27B	3.5 (1.4-8.7)	14.6 (10-21)
butorphanol [c]	0.3 (0.1-0.9)	2.0 (1.0-9.4)
cyclazocine [c]	0.4 (0.1-1.7)	0.8 (0.5-1.4)
pentazocine [c]	13.0 (8.4-19)	36.4 (14-100)
nalorphine [c]	3.5 (0.6-21)	2.5 (0.5-13)

[a] 7,8-Unsubstituted compound. Data from ref 4. [b] Inactive at dose shown. [c] Data from ref 4.

corresponding unsubstituted dihydrocodeinones. Increasing the size of the group in the 7α position to larger than methyl causes a drop in potency, as does the incorporation of a ketone or tertiary alcohol function or ring formation between positions 6 and 7.

The results obtained with the *N*-(cycloalkylmethyl) compounds for agonist and narcotic antagonist activity are indicated in Table II. The 4-hydroxy compounds **5**, as well as the 3,4-dimethoxy derivative **9Pa**, are weak agonists devoid of antagonist properties. In the *N*-(cycloalkylmethyl)-4,5-epoxy compounds **7**, methyl substitution at the 7 or 7,8 positions does not restore significant antinociceptive activity when compared with the 7,8-dihydro reference compounds but does decrease antagonist potency in the P series. The 7-methyl group in the **8P** series enhances agonist potency but decreases antagonist potency. The addition of the 8-methyl group causes a loss of analgesic activity but restores antagonism. Restoration of antagonist potency, with diminution of analgesic potency, is evident for the **8B** series. In the 14-hydroxy compounds, no discernible trend is evident in the activity observed.

The major conclusion which can be drawn from these data is that the introduction of a 7α-methyl group into the dihydro-*N*-(cycloalkylmethyl) compounds does not result in agents which have potent mixed agonist–narcotic antagonist activity. Our studies aimed at clarifying the effect of ring C modifications in opiate derivatives are continuing.

Experimental Section

Methods have previously been described.[4] For pharmacological testing, compounds which were prepared as salts were administered in distilled H_2O; free bases were dissolved by the addition of 1 N HCl and then further diluted. For both agonist and antagonist assays, at least five animals per dose and at least three doses of each drug were utilized in determination of the ED_{50} or AD_{50} values. Processing in the usual manner implies that the combined organic phases were washed with dilute NH_4OH, dried ($MgSO_4$), and evaporated at a 40 °C bath temperature. The residue was further dried at 50–60 °C bath temperature under high vacuum. Column chromatography was carried out over silica gel 60 G (E. Merck) using a loading factor of 1 g of material to 100 g of gel. Elution was with $CHCl_3$–MeOH mixtures (30:1 to 4:1, v/v) containing concentrated NH_4OH (0.2–2%). NMR were determined in $CDCl_3$ unless otherwise noted. Only certain characteristic NMR data are presented. The presence of solvent of crystallization was usually verified by NMR in an appropriate solvent. Where analysis is indicated only by symbols of elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

4-Hydroxy-3-methoxy-7α,8β,17-trimethylmorphinan-6-one (3b). Compound **2** (20.0 g, 64 mmol) in CH_2Cl_2 (400 mL) was added to a solution of $(Me)_2CuLi$ (165 mmol) prepared in Et_2O (800 mL) with cooling in an ice–salt bath under an argon atmosphere. The mixture was stirred in the cold for 1 h, after which it was poured into saturated NH_4Cl solution (1.0 L). After concentrated NH_4OH was added to pH ~12 and the solution was stirred for 30 min, the organic phase was separated and washed twice with dilute NH_4OH. The aqueous phase was extracted with additional CH_2Cl_2, and the combined organic phases were dried and evaporated to give a quantitative yield of **3b** as a thick syrup: NMR δ 6.63 (s, 2 H, aromatic), 4.25 (d, 1 H, H-5α, J = 13 Hz), 3.80 (OCH_3), 2.43 (NCH_3), 1.08 (unsymmetrical d, 3 H, 8β-CH_3, J = 6 Hz), 0.90 (symmetrical d, 3 H, 7α-CH_3, J = 6 Hz). A portion of this material was crystallized from EtOAc to give pure **3b**, mp 154–155.5 °C. Anal. ($C_{20}H_{27}NO_3$) C, H, N.

4-Hydroxy-3-methoxy-7α-methyl- or -7α,8β-dimethylmorphinan-6-ones (4). To a rapidly stirred solution of **3a** (13.0 g, 41.2 mmol) in $CHCl_3$ (150 mL) containing powdered, anhydrous K_2CO_3 (8.5 g, 61.8 mmol) was added dropwise a solution of BrCN (5.5 g, 51.9 mmol) in $CHCl_3$ (100 mL). The mixture was stirred for 30 min at room temperature and then refluxed for 2 h. The cooled mixture was filtered from insoluble material, and the filtrate was evaporated to give a foam, which was azeotroped several times with EtOH. The foam was refluxed with 2 N HCl (250 mL) for 8 h. The cooled solution was made basic with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were processed to give 13.6 g of a foam, which was chromatographed. Elution of unchanged **3a** was followed by elution of 7.3 g (59%) of **4a**, which was obtained as a foam. 17-Cyano-7α,8β-dimethyl-4-hydroxy-3-methoxymorphinan-6-one was prepared in a similar manner and

obtained as crystals, mp 206–209 °C, in 44% yield. Hydrolysis with 2 N HCl as above gave a quantitative yield of **4b** as a foam, homogeneous by TLC. Both **4a** and **4b** were used in alkylation reactions without further purification.

17-(Cycloalkylmethyl)-4-hydroxy-3-methoxy-7α-methyl- or -7α,8β-dimethylmorphinan-6-ones (5). A mixture of **4a** (5.00 g, 16.6 mmol), $NaHCO_3$ (2.90 g, 34.6 mmol), and cyclopropylmethyl bromide (2.80 g, 20.8 mmol) in DMF (50 mL) was heated at 100 °C (oil bath) under argon for 2 h. The mixture was cooled and filtered from insoluble material, and the filtrate was evaporated under high vacuum. The residue was dissolved in dilute NH_4OH and extracted with toluene. The toluene extract was evaporated to give 4.89 g (83%) of crystalline **5Pa**. Two recrystallizations from EtOH gave pure **5Pa**: mp 176.5–178 °C; NMR δ 6.65, 6.17 (exchangeable), 4.23 (d, 1 H, H-5α, J = 12.5 Hz), 3.78, 0.87 (d, 7α-CH_3). Anal. ($C_{22}H_{29}NO_3$) C, H, N. **5Pb** was obtained in the same manner as a foam in quantitative yield. The foam was converted to the HCl salt, which crystallized from acetone to give 90% of **5Pb** as the hemiacetone solvate, mp 194–195 °C. Anal. ($C_{22}H_{31}NO_3$·HCl·0.5C_3H_6O) C, H, N. **5Ba** was obtained as a foam in 99% yield as reported above utilizing cyclobutylmethyl bromide and with a reaction time of 8 h. **5Bb** was obtained after an 8-h reaction period in 85% yield as a foam. The HCl salt crystallized from acetone to give the hemiacetone solvate of **5Bb**, mp 184–187 °C. Anal. ($C_{24}H_{33}NO_3$·HCl·0.5C_3H_6O) C, H, N.

1-Bromo-17-(cycloalkylmethyl)-4,5α-epoxy-3-methoxy-7α-methyl- or -7α,8β-dimethylmorphinan-6-ones (6). A solution of Br_2 (1.0 mL, 20 mmol) in glacial HOAc (10 mL) was added to a stirred solution of **5Pa** (3.59 g, 10 mmol) in glacial HOAc (70 mL) at room temperature over 45 min. Stirring was continued for 1.5 h, after which the mixture was concentrated at 45–50 °C to a thick syrup. The syrup was dissolved in $CHCl_3$ and added to 1 N NaOH (100 mL) stirred in an ice bath. The mixture was adjusted to pH ~14 by the use of 50% NaOH solution and then stirred in the cold for 10 min. The $CHCl_3$ layer was separated, the aqueous phase was washed several times with $CHCl_3$, and the organic extracts were backwashed with dilute NH_4OH. The dried organic phase was evaporated to give 4.98 g of a foam, which was chromatographed. Homogeneous fractions were pooled to give 2.43 g (56%) of **6Pa** as a foam: NMR δ 6.92 (s, 1 H, H-1), 4.68 (s, 1 H, H-5), 3.93 (OCH_3), 3.16 (1 H, broad), 0.96 (d, 7α-CH_3). The following were obtained in a similar manner as homogeneous foams: **6Pb** (58% yield), **6Ba** (54% yield), and **6Bb** (33% yield).

17-(Cycloalkylmethyl)-4,5α-epoxy-3-methoxy-7α-methyl- and -7α,8β-dimethylmorphinan-6-ones (7). Compound **6Pa** (1.90 g, 4.4 mmol) was hydrogenated in a mixture of EtOH (50 mL) and 2 N HOAc–1.5 N NaOAc buffer (150 mL) over 10% Pd/C (0.4 g) at an initial pressure of 50 psi for 2 h. After the catalyst was removed by filtration, the filtrate was made basic by the addition of concentrated NH_4OH. This mixture was processed with $CHCl_3$ in the usual fashion to give 1.55 g (100%) of **7Pa** as a foam, homogeneous by TLC: NMR δ 6.60 (d, 2 H, aromatic, J = 1 Hz), 4.65 (s, 1 H, H-5). This material was converted to the HCl salt, which was crystallized from aqueous acetone to give the hemihydrate of **7Pa**, mp 214–216 °C. Anal. ($C_{22}H_{27}NO_3$·HCl·0.5H_2O) C, H, N. Similarly obtained was **7Pb** in 93% yield as the free base. The HCl salt, **7Pb**·HCl, mp 256–258 °C, crystallized from EtOH. Anal. ($C_{23}H_{29}NO_3$·HCl) C, H, N. **7Ba** was obtained in 93% yield as a foam. The HCl salt of **7Ba** was crystallized and recrystallized from MeOH–EtOAc. This hygroscopic salt (**7Ba**·HCl), mp foams above 150 °C, analyzed as the hemihydrate. Anal. ($C_{23}H_{29}NO_3$·HCl·0.5H_2O) C, H, N. The free base **7Bb** was obtained in quantitative yield but could not be obtained in crystalline form as the free base or HCl salt: mass spectrum, m/e 381 (M^+, 9), 326 (-c-C_4H_7, 100). Anal. ($C_{24}H_{31}NO_3$) H, N; C: calcd, 75.56; found, 74.71.

17-(Cycloalkylmethyl)-4,5α-epoxy-3-hydroxy-7α-methyl- and -7α,8β-dimethylmorphinan-6-ones (8). A solution of **7Pa**·HCl·0.5H_2O (1.00 g, 2.5 mmol) in $CHCl_3$ (30 mL) was added rapidly to a solution of BBr_3 (4.26 g, 17 mmol) in $CHCl_3$ (40 mL) under an argon atmosphere, while maintaining the temperature at 20 °C by cooling in ice. The suspension was stirred at room temperature for 15 min and then poured into an ice–concentrated NH_4OH (20 mL) slurry. After stirring for 10 min, the organic phase was separated and the aqueous phase was extracted with additional portions of $CHCl_3$. Evaporation of the extracts gave 680 mg of a foam which contained, in addition to **8Pa**, starting material **7Pa** and a 4,5-epoxy-cleaved product. Chromatography gave 250 mg (30%) of **8Pa** as a foam. Crystallization from *i*-PrOH gave crystalline **8Pa**, mp 209–211 °C, as the hemi-2-propanol solvate. Anal. ($C_{21}H_{25}NO_3$·0.5C_3H_8O) C, H, N. The free base of **8Pb** was obtained in 66% yield as a foam. The HCl salt, melts slowly above 200 °C, was precipitated from acetone with Et_2O: mass spectrum, m/e 353 (M^+, 100), 337 (CH_3, 8), 312 (-c-C_3H_5, 56).

Compound **8Ba** was obtained in 56% yield after chromatography. This was converted to the HCl salt, obtained as a foam on evaporation, which analyzed as the hemihydrate. Anal. ($C_{22}H_{27}NO_3$·HCl·0.5H_2O) C, H, N. **8Bb** was obtained as a foam in 62% yield after chromatography, which best analyzed as the monohydrate: mass spectrum, m/e 367 (M^+, 9), 312 (c-C_4H_7, 100). Anal. ($C_{23}H_{29}NO_3$·H_2O) H, N; C: calcd, 71.66; found, 72.62.

17-(Cyclopropylmethyl)-3,4-dimethoxy-7α-methylmorphinan-6-one (9Pa). A solution of **5Pa** (1.24 g, 3.5 mmol) in DMF (10 mL) was added to a suspension of NaH (0.10 g, 4.2 mmol) in DMF (10 mL) under argon. After stirring for 10 min, the mixture was cooled in an ice bath and a solution of methyl *p*-toluenesulfonate (0.65 g, 3.9 mmol) in DMF (3 mL) was added dropwise. The mixture was stirred for 30 min in the ice bath and then at room temperature for 1.5 h. The mixture was cooled, the excess NaH was quenched by the addition of ice, and the mixture then evaporated under high vacuum. The residue was dissolved in water and processed by extraction with toluene in the usual manner. Evaporation gave 1.28 g of a foam, which was chromatographed to yield 1.01 g (79%) of **9Pa** as an oil. This oil was converted to **9Pa**·HCl, which was obtained in crystalline form, mp >260 °C, from MeOH–EtOAc. Anal. ($C_{23}H_{31}NO_3$·HCl) C, H, N.

7-[(Dimethylamino)methylene]dihydrocodeinone (11). A mixture of **10** (6.00 g, 20 mmol) and DMF-DMA (2.86 g, 24 mmol) in toluene was refluxed for 12 h. Light yellow crystals (4.97 g, 70%) of **2**, mp 212–215 °C, were collected after cooling. Recrystallization of a portion of this material from EtOAc gave pure **11**: mp 213–215 °C; NMR δ 7.47 (s, 1 H, =CHN), 6.64 (d, 2 H, aromatic, J < 1 Hz), 4.54 (s, 1 H, H-5), 3.87 (OCH_3), 3.04 [s, $N(CH_3)_2$], 2.43 (NCH_3). Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

7α-Methyldihydrocodeinone (12). A solution of **11** (3.00 g, 8.46 mmol) in 95% EtOH (150 mL) was hydrogenated over 10% Pd/C (0.6 g) at an initial pressure of 50 psi for 2 h. After the catalyst was removed by filtration, the filtrate was evaporated to give 2.83 g of a foam, which was chromatographed. The faster migrating component **12** (1.28 g, 46%) was obtained as a foam, which crystallized from EtOH as fine needles: mp 141–143 °C (lit.[6] mp 144–145 °C); NMR δ 6.72 (s, 2 H, aromatic), 4.72 (s, H-5), 0.98 (d, 3 H, 7α-CH_3, J = 6 Hz). Anal. ($C_{19}H_{23}NO_3$) C, H, N. Continued elution gave 0.61 g (22%) of **3a**.

7α-(Hydroxymethyl)dihydrocodeinone (13). A solution of **11** (5.0 g, 14.1 mmol) in 2 N HOAc–1.5 N NaOAc buffer (125 mL) was hydrogenated at 50 psi over 10% Pd/C (1.0 g) for 1.5 h. The catalyst was removed by filtration, and the filtrate made basic with concentrated NH_4OH. Extraction with $CHCl_3$ and processing in the usual fashion gave a foam, which crystallized from EtOH to give 2.8 g (60%) of **13**, mp 169–171 °C, contaminated with traces of the corresponding 4,5-epoxy-cleaved product. An analytical sample of **13**, mp 177–178 °C, was prepared by chromatography, followed by crystallization from EtOH. Anal. ($C_{19}H_{23}NO_4$) C, H, N.

7α-Alkyldihydrocodeinones (15c–f). A solution of **11** (5.3 g, 15 mmol) in THF (300 mL) was cooled to −30 °C under argon, and the appropriate alkyllithium reagent (1.2 equiv) was added dropwise. After stirring for 30 min at this temperature, the mixture was allowed to warm to 0 °C and quenched with H_2O. The mixture was evaporated, and the residue was partitioned between H_2O and $CHCl_3$. Processing of the organic extracts gave a foam, which was dissolved in 95% EtOH. Sufficient HCl was added to render the mixture slightly acidic, and the solution was hydrogenated as above. Workup gave residues, which were purified by chromatography. The desired product **15** eluted before the epoxy-cleaved product **16**, which was not isolated.

Compound **15c** was isolated as a foam in 24% yield. This formed a *d*-tartrate salt, mp 85–92 °C, which was recrystallized from MeOH–EtOAc to give **15c**·tartrate, mp 105–110 °C, as the

hemihydrate. Anal. ($C_{20}H_{25}NO_3 \cdot C_4H_6O_6 \cdot 0.5H_2O$) C, H, N.

Intermediate **14d** was obtained in 50% yield after chromatography. Hydrogenation yielded a foam, which gave 1.4 g (88%) of crystalline **15d**, mp 195–198 °C, on trituration with EtOH. Recrystallization from EtOH gave pure **15d**, mp 210–213 °C. Anal. ($C_{25}H_{27}NO_3$) C, H, N.

Intermediate **14e** was obtained in 44% yield after chromatography. Hydrogenation of crude material containing **14e** gave a 36% yield of **15e**. The HCl salt was obtained in crystalline form, mp 77–80 °C, from EtOH. After drying under high vacuum at room temperature overnight, **15e**·HCl gave a mp of 105–115 °C. Anal. ($C_{23}H_{31}NO_3 \cdot HCl$) C, H, N.

Intermediate **14f** was not purified but directly reduced to **15f**, which was obtained in 50% yield after chromatography. The HCl salt, mp 191–195 °C, was obtained as the EtOH solvate from EtOH–Et_2O. Analysis, after drying at 80 °C under high vacuum, of **15f**·HCl indicated the presence of 0.7 mol of EtOH: mass spectrum, m/e 369 (M^+, 81), 312 (C_4H_9, 100). Anal. ($C_{23}H_{31}NO_3 \cdot HCl \cdot 0.7C_2H_6O$) C, H, N.

7-(2-Ethoxypropenylidene)dihydrocodeinone (17). α-Ethoxyvinyllithium was prepared under argon by the dropwise addition of *t*-BuLi (18 mmol) to ethyl vinyl ether (2.34 g, 32.4 mmol) in THF (25 mL) at −55 °C. The mixture was warmed to 0 °C while the yellow precipitate which formed dissolved to give a clear solution. The solution was recooled to −60 °C and added slowly to a solution of **11** (5.3 g, 15 mmol) in THF (300 mL) kept at −30 °C under argon. Stirring was continued for 30 min at this temperature, and the mixture was then allowed to warm to 0 °C. The mixture was quenched and processed in the usual manner to give **17** (5.3 g, 93%) as a foam, which contained traces of impurities by TLC: NMR δ 6.70 (wide s, 3 H, aromatic and =CH), 4.57 (s, 1 H, H-5), 4.44 (br, 2 H, $=CH_2$), 1.30 (t, OCH_2CH_3).

17,19-Dimethyl-4,5-epoxy-3-methoxyfuro[*b*-6,7]- (18) and -18*H*-pyrrolo[*b*-6,7]morphinan (19). To a solution of **17** (3.00 g, 7.86 mmol) in EtOH (60 mL) was added 1 N HCl (18 mL) and 10% Pd/C (0.6 g), and the mixture was hydrogenated at an initial pressure of 50 psi for 2 h. The catalyst was removed by filtration, and the filtrate was made basic with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were processed in the usual fashion and evaporated to give 2.7 g of a foam, which was chromatographed. First eluted was **18** (792 mg, 30%). Crystallization from EtOH gave pure **18**: mp 140–141 °C; NMR δ 6.72 (s, aromatic), 5.72 (br s, 1 H, H-18), 5.45 (br s, 1 H, H-5), 3.86 (OCH_3), 2.47 (NCH_3), 2.25 (s, 19-CH_3). Anal. ($C_{21}H_{23}NO_3$) C, H, N. Next eluted was **19** (807 mg, 31%), which gave crystals containing 0.5 mol of solvent, mp 185–189 °C, from ethanol: NMR δ 8.30 (br s, exchangeable, NH), 6.70 (s), 5.58 (unsymmetrical s, 2 H, H-5 and H-18), 2.13 (s, 19-CH_3). Anal. ($C_{21}H_{24}N_2O_2 \cdot 0.5C_2H_6O$) C, H, N.

17-(2-Ethoxypropenylidene)dihydrocodeine (20). A solution of **17** (2.0 g, 5.2 mmol) in MeOH (50 mL) was cooled in an ice bath, and $NaBH_4$ (0.1 g, 2.6 mmol) was added in one portion. The mixture was stirred in the cold for 20 min; then the excess of borohydride was destroyed by the careful, dropwise addition of HOAc so that the mixture remained basic to moist pH paper. The solvent was evaporated and the residue processed in the usual fashion to give a light yellow foam (2.0 g), which was shown by TLC to be an ~9:1 mixture of 6α/6β **20**.

7-(2-Oxopropyl)dihydrocodeine (21). The foam obtained above was dissolved in MeOH (20 mL), and 1 N HCl (8 mL) was added. The solution was stirred for 20 min and then made basic with concentrated NH_4OH, and the mixture was evaporated. Processing in the usual fashion gave 1.84 g of a foam, which showed one major spot on TLC. The foam was dissolved in 95% EtOH (25 mL), 1 N HCl (8 mL) and 10% Pd/C (0.3 g) were added, and the mixture was hydrogenated at 50 psi for 1 h. Workup in the usual fashion gave a foam, which was chromatographed to give 838 mg (45%) of **21**. Two crystallizations from EtOH gave pure **21**: mp 71–73 °C; NMR δ 4.62 (d, 1 H, H-5, J = 6 Hz). Anal. ($C_{21}H_{27}NO_4$) C, H, N.

7-(2-Hydroxy-2-methylpropyl)dihydrocodeine (22). A solution of **21** (1.07 g, 3.0 mmol) in toluene (15 mL) was added dropwise to a 0 °C solution of MeLi (7.5 mmol) in Et_2O (30 mL) under argon. Stirring was continued for 20 min and the mixture was quenched with water and processed in the usual manner to give a foam, which was chromatographed. Pure fractions were combined to give 824 mg (74%) of **22** as a foam. The tartrate salt of **22** could not be obtained in crystalline form. Anal. ($C_{22}H_{31}NO_4 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

***N*-(Cycloalkylmethyl)-7α-methyl-14-hydroxydihydromorphinone (26).** A mixture of **23** (10 mmol) and DMF-DMA (10 mL) was refluxed in an oil bath for 3–4 h. The crystals which formed on cooling the mixture in ice were collected and washed with Et_2O to give **25H** (37% yield), mp 253–258 °C dec, or **25P** (40% yield), mp 223–226 °C. **25B** was not isolated from the mixture but directly hydrogenated. Intermediates **25** were hydrogenated in 95% EtOH as above to give **26H** directly in 95% yield as impure crystals, mp 220–226 °C. Chromatography, followed by crystallization from EtOH, gave **26H**·0.5H_2O, mp 230–233 °C dec (lit.[5] mp 226–228 °C). Anal. ($C_{19}H_{23}NO_4 \cdot 0.5H_2O$) C, H, N. **26P** was obtained in 62% yield after chromatography and obtained as crystals, mp 113–114 °C, from EtOH. Anal. ($C_{22}H_{27}NO_4$) C, H, N. **26B** was obtained in 24% overall yield from **23B** and was converted to the *d*-tartrate monohydrate, mp 200–203 °C. Anal. ($C_{23}H_{29}NO_4 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

Compounds **26** were O-demethylated to **27** by use of BBr_3 in $CHCl_3$ as reported for **8** above. Chromatography gave **27P** in 50% yield, which gave a crystalline hemisolvate from EtOH. Anal. ($C_{21}H_{25}NO_4 \cdot 0.5C_2H_6O$) C, H, N. **27B** was obtained in 47% yield as a crystalline solid, mp 194–197 °C, from EtOH. Anal. ($C_{22}H_{27}NO_4$) C, H, N.

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Methotrexate Analogues. 14. Synthesis of New γ-Substituted Derivatives as Dihydrofolate Reductase Inhibitors and Potential Anticancer Agents

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The γ-*tert*-butyl ester (**1**), γ-hydrazide (**2**), γ-*n*-butylamide (**3**), and γ-benzylamide (**4**) derivatives of methotrexate (MTX) were synthesized from 4-amino-4-deoxy-N^{10}-methylpteroic acid (APA) and the appropriate blocked L-glutamic acid precursors with the aid of the peptide bond forming reagent diethyl phosphorocyanidate. The affinity of these side chain modified products for dihydrofolate reductase (DHFR) from *Lactobacillus casei* and L1210 mouse leukemic cells was determined spectrophotometrically or by competitive radioligand binding assay, and their cytotoxicity was evaluated against L1210 leukemic cells in culture. The results provide continuing support for the view that the "γ-terminal region" of the MTX side chain is an attractive site for molecular modification of this anticancer agent.

Previous work in this laboratory[1,2] and others[3,4] has shown that the γ-terminus of the glutamate side chain in methotrexate (MTX) is a region of significant "bulk tolerance"[5]—i.e., that large changes in chemical structure

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