

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 triacetox derivative, followed by subsequent hydrolysis as follows: the residue was diluted with 10 mL of $\text{CF}_3\text{CO}_2\text{H}$ 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 $\text{CHCl}_3/\text{Et}_2\text{O}$ (1:1) to give a pure product with an R_f of 0.32 (in CHCl_3) on TLC. The triacetox 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 ($\text{CH}_3\text{OH}/\text{CHCl}_3$, 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, $\text{C}=\text{CH}_2$), 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. ($\text{C}_{19}\text{H}_{18}\text{NO}_3\text{Br}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$) 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 triacetox 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 ($\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 2.8–4.4 (broad signals, H at C-4, C-5, C-6a, C-7, NCH_2 , $\text{C}=\text{CH}$), 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. ($\text{C}_{19}\text{H}_{17}\text{NO}_3\cdot\text{HCl}\cdot\text{H}_2\text{O}$) C, H, N.

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Analgesic Narcotic Antagonists. 8.¹ 7 α -Alkyl-4,5 α -epoxymorphinan-6-ones

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The preparation of a series of 7 α -alkylated dihydrocodeinones is described. *N*-(Cyclopropylmethyl) (P series) or *N*-(cyclobutylmethyl) (B series) 7 α -methyl (a series) or 7 α ,8 β -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 7 α -methyl- (12) or 7 α -(hydroxymethyl) dihydrocodeinone (**13**). Treatment of **11** with lithium reagents, followed by hydrogenation, gave a mixture of 7 α -alkyl (15c-f) compounds and the corresponding 4,5-epoxy-cleaved products **16**. Reaction of **11** with α -ethoxyvinyl lithium gave intermediate **17**, which on hydrolysis and hydrogenation yielded the 6,7-furyl (**18**) or pyrrolyl (**19**) derivative. *N*-(Cycloalkylmethyl)-14-hydroxydihydronorcodeinones **23P,B** reacted with dimethylformamide dimethyl acetal to give **25P,B**, which were hydrogenated to the 7 α -methyl compounds **26P,B** and O-demethylated to give **27P,B**. The 7 α -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 reported² that reaction of thebaine with lithium dimethylcuprate yields 7 β -methyl dihydrothebaine- ϕ (**1**). The facile preparation of this 4,5 α -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 4,5 α -epoxy counterparts of these previously reported

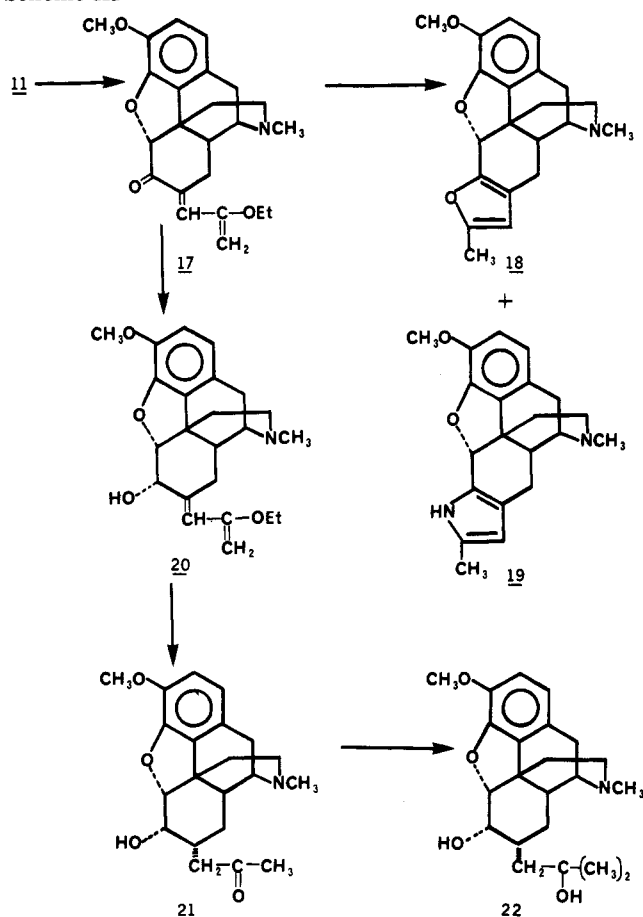
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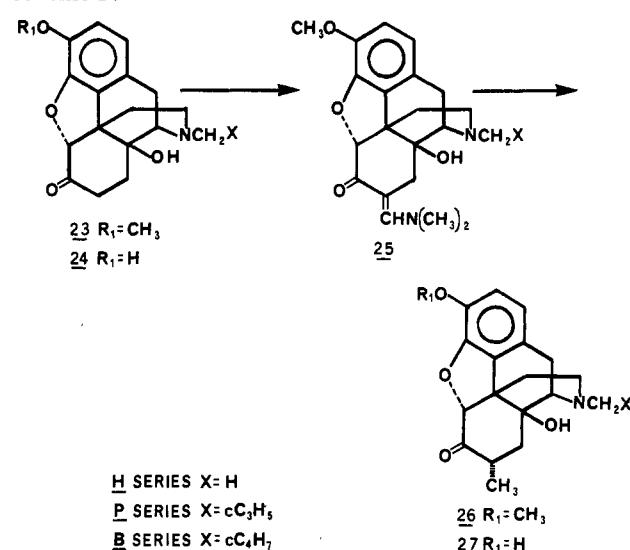
Scheme III



etition of this reaction utilizing tetramethylmethanedi-amine-acetic anhydride¹⁸ 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-7 α -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 7 α -substituted 4,5 α -epoxy-6-oxo compounds (15) and the corresponding products of epoxy ring cleavage (16). Thus, we were able to obtain various 7 α -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 -eth-

Scheme IV



oxyvinylolithium 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 NaBH₄ to give mainly the 6 α 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)dihydrocodeinone derivatives 7 and 8 by the circuitous route outlined in Scheme I, we applied our new preparation of 7 α -methyl compounds to the 14-hydroxydihydrocodeinone series. Treatment of *N*-(cyclopropylmethyl) and *N*-(cyclobutylmethyl) compounds 23²² 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 BBr₃. Direct reaction of the 3-hydroxy compounds 24 with DMF-DMA was attempted but resulted in O-alkylation as has been reported²³ with reagents of this type.

Results and Discussion

The *N*-methyl compounds were tested for antinociceptive activity in the acetic acid mouse writhing²⁴ and heat stimulus rat tail-flick²⁵ assays. The results of these assays are presented in Table I. These data indicate that the introduction of a methyl group into the 7 α position in *N*-methyl compounds does not significantly change the antinociceptive activity when comparison is made to the

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Table I. Agonist Activity

compd (salt)	ED ₅₀ , μ mol/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)
dihydro-codeinone ^d	2.4 (1.6-3.6)	5.2 (3.6-7.5)
dihydro-morphinone ^d	0.3 (0.1-0.4)	1.3 (1.2-1.5)
5-methyldihydro-morphinone ^e	0.8 (0.3-1.9)	2.5 (1.8-3.6)
14-hydroxydi-hydrocodeinone ^f	1.5 (0.9-2.4)	2.9 (0.8-5.5)

^a Corresponding 3-hydroxy compound; ED₅₀ = 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; ED₅₀ = 3.0 and >28. ^c Inactive at dose indicated.

^d Data from ref 4. ^e Metopon; new data. ^f Oxycodone; new data.

corresponding unsubstituted dihydrocodeinones. Increasing the size of the group in the 7 α 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 7 α -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 H₂O; 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 ED₅₀ or AD₅₀ values. Processing in the usual manner implies that the combined organic phases were washed with dilute NH₄OH, dried (MgSO₄), 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

Table II. Agonist and Narcotic Antagonist Activity

compd (salt)	ED ₅₀ , μ mol/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 (0.3-1.8)	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.

gel 60 G (E. Merck) using a loading factor of 1 g of material to 100 g of gel. Elution was with CHCl₃-MeOH mixtures (30:1 to 4:1, v/v) containing concentrated NH₄OH (0.2-2%). NMR were determined in CDCl₃ 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 $\pm 0.4\%$ of the theoretical values.

4-Hydroxy-3-methoxy-7 α ,8 β ,17-trimethylmorphinan-6-one (3b). Compound 2 (20.0 g, 64 mmol) in CH₂Cl₂ (400 mL) was added to a solution of (Me)₂CuLi (165 mmol) prepared in Et₂O (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 NH₄Cl solution (1.0 L). After concentrated NH₄OH was added to pH ~12 and the solution was stirred for 30 min, the organic phase was separated and washed twice with dilute NH₄OH. The aqueous phase was extracted with additional CH₂Cl₂, 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-5 α , *J* = 13 Hz), 3.80 (OCH₃), 2.43 (NCH₃), 1.08 (unsymmetrical d, 3 H, 8 β -CH₃, *J* = 6 Hz), 0.90 (symmetrical d, 3 H, 7 α -CH₃, *J* = 6 Hz). A portion of this material was crystallized from EtOAc to give pure 3b, mp 154-155.5 °C. Anal. (C₂₀H₂₇NO₃) C, H, N.

4-Hydroxy-3-methoxy-7 α -methyl- or -7 α ,8 β -dimethylmorphinan-6-ones (4). To a rapidly stirred solution of 3a (13.0 g, 41.2 mmol) in CHCl₃ (150 mL) containing powdered, anhydrous K₂CO₃ (8.5 g, 61.8 mmol) was added dropwise a solution of BrCN (5.5 g, 51.9 mmol) in CHCl₃ (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 NH₄OH and extracted with CHCl₃. The CHCl₃ 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-7 α ,8 β -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-7 α -methyl- or -7 α ,8 β -dimethylmorphinan-6-ones (5). A mixture of **4a** (5.00 g, 16.6 mmol), NaHCO₃ (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 NH₄OH 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-5 α , J = 12.5 Hz), 3.78, 0.87 (d, 7 α -CH₃). Anal. (C₂₂H₂₉NO₃) 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. (C₂₂H₃₁NO₃·HCl·0.5C₃H₇O) 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. (C₂₄H₃₃NO₃·HCl·0.5C₃H₇O) C, H, N.

1-Bromo-17-(cycloalkylmethyl)-4,5 α -epoxy-3-methoxy-7 α -methyl- or -7 α ,8 β -dimethylmorphinan-6-ones (6). A solution of Br₂ (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 CHCl₃ 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 CHCl₃ layer was separated, the aqueous phase was washed several times with CHCl₃, and the organic extracts were backwashed with dilute NH₄OH. 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 (OCH₃), 3.16 (1 H, broad), 0.96 (d, 7 α -CH₃). The following were obtained in a similar manner as homogeneous foams: **6Pb** (58% yield), **6Ba** (54% yield), and **6Bb** (33% yield).

17-(Cycloalkylmethyl)-4,5 α -epoxy-3-methoxy-7 α -methyl- and -7 α ,8 β -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 NH₄OH. This mixture was processed with CHCl₃ 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. (C₂₂H₂₇NO₃·HCl·0.5H₂O) 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. (C₂₃H₂₉NO₃·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. (C₂₃H₂₉NO₃·HCl·0.5H₂O) 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 (–C₄H₇, 100). Anal. (C₂₄H₃₁NO₃) H, N; C: calcd, 75.56; found, 74.71.

17-(Cycloalkylmethyl)-4,5 α -epoxy-3-hydroxy-7 α -methyl- and -7 α ,8 β -dimethylmorphinan-6-ones (8). A solution of **7Pa**·HCl·0.5H₂O (1.00 g, 2.5 mmol) in CHCl₃ (30 mL) was added rapidly to a solution of BBr₃ (4.26 g, 17 mmol) in CHCl₃ (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 NH₄OH (20 mL) slurry. After stirring for 10 min, the organic phase was separated and the aqueous phase was extracted with additional portions of CHCl₃. 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. (C₂₁H₂₆NO₃·0.5C₃H₇O) 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 Et₂O: mass spectrum, m/e 353 (M⁺, 100), 337 (CH₃, 8), 312 (–C₃H₅, 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. (C₂₂H₂₇NO₃·HCl·0.5H₂O) 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 (–C₄H₇, 100). Anal. (C₂₃H₂₉NO₃·H₂O) H, N; C: calcd, 71.66; found, 72.62.

17-(Cyclopropylmethyl)-3,4-dimethoxy-7 α -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. (C₂₈H₃₁NO₃·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 (OCH₃), 3.04 [s, N(CH₃)₂], 2.43 (NCH₃). Anal. (C₂₁H₂₆N₂O₃) C, H, N.

7 α -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, 7 α -CH₃, J = 6 Hz). Anal. (C₁₉H₂₃NO₃) C, H, N. Continued elution gave 0.61 g (22%) of **3a**.

7 α -(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 NH₄OH. Extraction with CHCl₃ 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. (C₁₉H₂₃NO₄) C, H, N.

7 α -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 alkylolithium 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 H₂O. The mixture was evaporated, and the residue was partitioned between H₂O and CHCl₃. 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-Et₂O. 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*₄H₉, 100). Anal. ($C_{23}H_{31}NO_3 \cdot HCl \cdot 0.7C_2H_5O$) C, H, N.

7-(2-Ethoxypropenylidene)dihydrocodeinone (17). α -Ethoxyvinylolithium 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, =CH₂), 1.30 (t, OCH₂CH₃).

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 NH₄OH and extracted with CHCl₃. The CHCl₃ 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 (OCH₃), 2.47 (NCH₃), 2.25 (s, 19-CH₃). 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-CH₃). Anal. ($C_{21}H_{24}N_2O_2 \cdot 0.5C_2H_5O$) 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 NaBH₄ (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 6 α /6 β 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 NH₄OH, 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 Et₂O (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)-7 α -methyl-14-hydroxydihydro-morphinone (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 Et₂O 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 \cdot 0.5H₂O, 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 BBr₃ in CHCl₃ as reported for 8 above. Chromatography gave 27P in 50% yield, which gave a crystalline hemisolvate from EtOH. Anal. ($C_{21}H_{25}NO_4 \cdot 0.5C_2H_5O$) 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