Analgesic Narcotic Antagonists. 15.[1] Potent Narcotic Agonist 7β-(Arylalkyl)-4,5α-epoxymorphinans

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Structure–activity correlations in 7β-(arylalkyl)-3-methoxy- or -hydroxy-4,5α-epoxymorphinans have been investigated. 6β-Hydroxy-7α-hydroxymethyl compounds **7** with 7β-substituents CH_2CH_2R [**a**, R = H; **b**, R = CH_2CH_3; **c**, R = C_6H_5; **d**, R = $CH_2C_6H_5$; **f**, R = $CH_2CH_2C_6H_5$; **g**, R = $(CH_2)_3C_6H_5$; **h**, R = $(CH_2)_4C_6H_5$] were prepared. Wittig condensations with previously reported 4,5α-epoxy-7β-formyl-7α-(hydroxymethyl)-6β,7α-*O*-isopropylidene-3-methoxy-17-methylmorphinan-6β-ol (**3**), followed by dilute acid removal of the blocking group and then hydrogenation, gave saturated compounds **7**. Compounds with a 6α,7α-oxymethylene ring, **18c,d,f,g**, were prepared from 7β-formyl derivative **16** and the appropriate Wittig reagent, followed by hydrogenation. Both the 6β-hydroxy-7α-hydroxymethyl and 6α,7α-oxymethylene series containing 7β-arylalkyl groups with an alkyl chain length of 2 to 4 are potent narcotic agonists. The most potent 17-methyl compound, 4,5α-epoxy-7α-(hydroxymethyl)-17-methyl-17β-(4-phenylbutyl)morphinan-3,6β-diol (**8f**) was 700 times more potent than morphine in the acetic acid induced mouse writhing assay. 17-Methyl compounds in the **c**, **d**, **f**, **g** series were converted to 17-cyclopropylmethyl (**P** series) or 17-cyclobutylmethyl (**B** series) derivatives. Narcotic antagonistic activity could not be demonstrated for these potent agonist 17-cycloalkylmethyl derivatives. These pharmacological results parallel those previously reported for tertiary alcohol derivatives of the *endo*-ethenotetrahydrooripavines. Structural considerations confirm the existence of a lipophilic site extending upward and outward from where the C ring of morphine and congeners bind to opiate receptors.

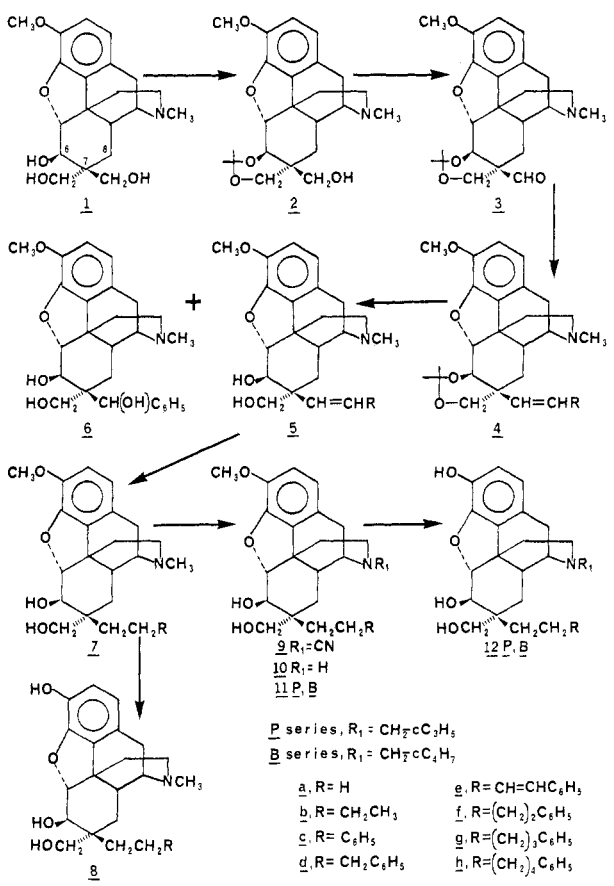
In Part 1 of this series,[2] we described our rational for the incorporation of lipophilic groups into the C ring of the morphine nucleus. These appendages were intended to interact with a lipophilic site hypothesized to exist near the region where the C ring of morphine is bound onto the opiate receptor. The existence of this specific receptor site[3] was advanced as one factor to explain the potent agonist activity observed with tertiary alcohols derived from Diels–Alder adducts[4] of thebaine with methyl vinyl ketone.

In an attempt to utilize this specific receptor site for the preparation of clinically useful opiate analgesic agents, we prepared a series of C8-alkyl derivatives of the morphinan skeleton.[2,5,6] Pharmacological results obtained with these compounds indicated that the lipophilic site was not in the proximity to where C8 is bound to the receptor. Likewise, our studies with C7-alkyl[7,8] and -arylalkyl[8] addends, in which the newly introduced group was in the 7α-position (i.e., equatorial) of the morphinan nucleus, did not lead to potent narcotic agonists. A similar observation was made by Quick et al.[9] for a series of related 7-alkanoyl-substituted hydromorphones. We recently devised methods that allowed the preparation of nonepimerizable 7β-substituted-dihydromorphine derivatives.[10] To our surprise, the first members of this series in which the substituting 7β-group was phenylbutyl showed potent narcotic agonist activity. The present report describes our efforts directed toward further clarifying structure–activity relationships within this latter series of compounds.

Chemistry. Methods detailing the preparation of the 7β-phenylbutyl compounds series **f**, via intermediate **e**, including studies confirming the structural assignments, have been described by us.[10] We have used this same methodology for the preparation of new compounds, series **a–d**, **g**, **h**, from **1** with the exception that saturated Wittig reagents were used in condensations with aldehydes **3** and **16**. Intermediate **3**[10] for the 6β-hydroxy-7α-hydroxymethyl series (see Scheme I) was prepared from 7,7-bis(hydroxymethyl)dihydroisocodeine (**1**)[11] by reaction with acetone, yielding 6β,7α-dioxolane **2** as the major product. Oxidation of the primary alcohol function in **2** with Me_2SO–TFAA[12] at −60 °C gave the 7β-formyl compound **3**.

Wittig anions for condensations with **3** were generated from the appropriate triphenylphosphonium salts[13] with either NaH–Me_2SO[14] (method A) or phenyllithium[13b] (method B). The initial condensation product **4** was not

Scheme I



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(1) For paper 14, see Kotick, M. P. *J. Org. Chem.*, in press.
(2) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166.
(3) Lewis, J. W.; Bentley, K. W.; Cowen, A. *Annu. Rev. Pharmacol.* **1971**, *11*, 241.
(4) For a review of the chemistry of these compounds, see Bentley, K. W. *Alkaloids (N.Y.)* **1971**, *13*, 1.
(5) Polazzi, J. O.; Schut, R. N.; Kotick, M. P.; Howes, J. F.; Osgood, P. F.; Razdan, R. K.; Villarreal, J. E. *J. Med. Chem.* **1980**, *23*, 174.
(6) Kotick, M. P.; Polazzi, J. O. *J. Heterocycl. Chem.* **1981**, *18*, 1029.

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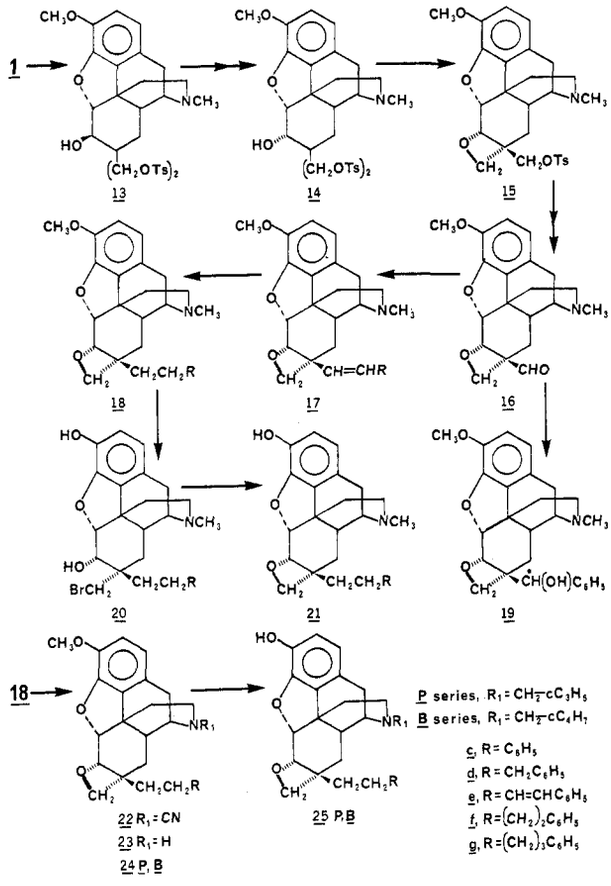
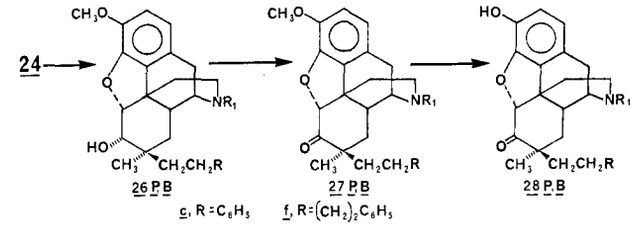
Scheme II



Scheme III



isolated but converted to **5** by removal of the isopropylidene blocking group with dilute acid. Triphenylphosphine oxide was separated from the resultant mixture by selective extraction from the acidic solution. In the preparation of **5d**, where a low yield of **4d** was obtained by method B, we also isolated α-hydroxybenzyl derivative **6**, as a single isomer. Hydrogenation of **5** to **7**, over 10% Pd/C in aqueous EtOH, proceeded slowly. Occasionally, we experienced difficulty in this reduction. The utilization of fresh charges of catalyst and/or chromatography to remove traces of $(C_6H_5)_3PO$ overcame this problem.

The 3-methoxy group was cleaved from **7** to give morphine derivatives **8** by using refluxing 48% HBr. *N*-Cycloalkylmethyl compounds **11** were prepared from *N*-methyl derivatives **7** by use of the cyanogen bromide–acid hydrolysis–alkylation sequence previously described.[2]

Cleavage of the 3-methoxy (**11**) to the *N*-cycloalkylmethyl-3-hydroxy compounds (**12**) was effected with refluxing HBr.

Our general approach to the 6α,7α-oxetane series (see Scheme II) has been described.[10] Briefly, aldehyde **16** was prepared from **1** by the following sequence: tosylation of the primary hydroxy groups to give **13**, oxidation of the C6β-hydroxy to a ketone, and, then, borohydride reduction to the 6α-ol **14**, which was oxymethylene ring closed in aqueous NaOH–dioxane to **15**. Displacement of the remaining tosyloxy group with NaOAc in DMF and then saponification to the alcohol and oxidation gave aldehyde **16**. Wittig condensation with **16** gave crude **17c,d,e,g**, from which $(C_6H_5)_3PO$ was removed by extraction. Hydrogenation of **17**, often with difficulty, yielded 7β-arylalkyl-6α,7α-oxymethylenes **18**. Reaction of **16** directly with phenyllithium yielded a mixture of the diastereoisomers **19**, which could be resolved by chromatography.

Treatment of **18** with refluxing HBr cleaved both the 3-methoxy function and the oxymethylene ring to give 7α-bromomethyl 3,6α-diols **20**. These intermediates were not further characterized but directly ring closed to the 6α,7α-oxymethylene compounds **21** by base treatment.

N-Cyano compounds **22** were prepared in the usual manner.[2] Due to the acid lability of the oxymethylene ring, hydrolysis of **22** to nor compounds **23** was accomplished under basic conditions. Refluxing **22** with 12 equiv of KOH in aqueous dioxane for 5–7 days gave moderate yields of **23**. Further transformations to *N*-cycloalkylmethyl compounds **24** and **25** were carried out in a manner analogous to that described previously.

Our previous work has shown that morphine compounds having a sp^2 hybridized functionality at C6 often exhibit interesting pharmacological properties.[15] The oxymethylene compounds **24** were, therefore, converted to the 6-oxo analogues by a previously utilized route[10,11] (see Scheme III). Reductive cleavage of the oxymethylene ring in **24** with a 3:1 mixture of $LiAlH_4$–$AlCl_3$ gave 6α-hydroxy-7α-methyl-7β-arylalkyl compounds **26**. Oxidation with Me_2SO–TFAA gave the C6-oxo compounds **27**, which were converted to 3-hydroxy analogues **28** with refluxing HBr.

Results

The target *N*-methyl and *N*-cycloalkylmethyl compounds prepared in the course of this work were assayed for narcotic agonist activity by using acetic acid induced writhing in the mouse.[16] The results of these assays for *N*-methyl compounds are recorded in Table I, while those for *N*-cycloalkylmethyl derivatives are presented in Table II. Selected *N*-cycloalkylmethyl compounds listed in Table II were also tested for morphine antagonist activity in both the mouse[17] and rat tail-flick[18] systems. None of

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(8) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Howes, J. F.; Bousquet, A. R. *J. Med. Chem.* **1981**, *24*, 1445.
(9) Quick, J.; Herlihy, P. Razdan, R. K.; Howes, J. F. *J. Med. Chem.* **1982**, *25*, 983. See also Herlihy, P.; Dalzell, H. C.; Howes, J. F.; Razdan, R. F. *Ibid.* **1982**, *25*, 986, for some related work.
(10) Leland, D. L.; Kotick, M. P. *J. Org. Chem.*, in press.
(11) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1981**, *24*, 717.
(12) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. Huang, S. L.; Uman, J. G.; Swern, D. *Ibid.* **1976**, *41*, 3329.
(13) (a) $(C_6H_5)_3PCH_3Br$, $(C_6H_5)_3P(CH_2)_2CH_3Br$, and $(C_6H_5)_3PCH_2C_6H_5Br$ were from Aldrich Chemical Co. (b) $(C_6H_5)_3P(CH_2)_2C_6H_5Br$: Lambert, J. B.; Mark, H. W.; Magyar, E. S. *J. Am. Chem. Soc.* **1977**, *99*, 3059. (c) $(C_6H_5)_3P(CH_2)_4C_6H_5Br$: mp 135–139 °C, was prepared as described in ref 12b. (d) $(C_6H_5)_3P(CH_2)_5C_6H_5Br$: Bennet, D. J.; Kirby, E. W. *J. Chem. Soc. C* **1968**, 442.
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(17) Cowan, A.; Lewis, J. W.; MacFarlane, I. R. *Br. J. Pharmacol.* **1977**, *60*, 537.

Table I. Narcotic Agonist Activity (Mouse Writhing Assay) of *N*-Methyl Compounds

compd	R	ED_{50}, μmol/kg, sc (95% CL)[a]
5a	H	>28
5d[b]	$CH_2C_6H_5$	1.1 (0.4-2.9)
5g	$(CH_2)_3C_6H_5$	4.0 (2.5-6.4)
5h[b]	$(CH_2)_4C_6H_5$	13.9 (11.7-16.4)
6	*c*	2.3 (0.3-17.2)
7a[b]	H	2.7 (1.5-4.7)
7b[b]	CH_2CH_3	13.7 (7.6-24.8)
7c	C_6H_5	0.028 (0.009-0.085)[d]
7d[b]	$CH_2C_6H_5$	0.39 (0.01-1.4)
7f	$(CH_2)_2C_6H_5$	0.014 (0.009-0.017)
7g[b]	$(CH_2)_3C_6H_5$	2.3 (1.6-3.4)
7h	$(CH_2)_4C_6H_5$	4.5 (1.3-15.9)
8b	CH_2CH_3	0.56 (0.13-2.1)
8c	C_6H_5	0.004 (0.0005-0.21)
8d	$CH_2C_6H_5$	0.85 (0.37-1.9)
8f	$(CH_2)_2C_6H_5$	0.003 (0.0024-0.0046)
8g[b]	$(CH_2)_3C_6H_5$	12.0 (9.6-15.0)
8h[b]	$(CH_2)_4C_6H_5$	>19
18c[e]	C_6H_5	0.9 (0.06-12.1)
18d[e]	$CH_2C_6H_5$	0.046 (0.03-0.07)
18f[e]	$(CH_2)_2C_6H_5$	0.005 (0.001-0.019)
18g[e]	$(CH_2)_3C_6H_5$	1.3 (1.1-1.6)
19[f]	*c*	6.8 (2.2-21.1)
19[f]	*c*	11.9 (5.3-26.9)
21c[e]	C_6H_5	0.048 (0.01-0.17)
21d[e]	$CH_2C_6H_5$	0.019 (0.008-0.047)
21f[e]	$(CH_2)_2C_6H_5$	0.024 (0.015-0.38)
21g[e]	$(CH_2)_3C_6H_5$	0.028 (0.008-0.083)
codeine		10.3 (2.7-40)
morphine		2.1 (1.1-4.0)
dihydrocodeinone		2.4 (1.6-3.6)
dihydromorphinone		0.25 (0.12-0.44)

[a] Compounds that were prepared as salts (see below) were administered in distilled water; free bases were dissolved by the addition of 1 N HCl and then further diluted. All compounds were administered by the subcutaneous route. [b] HCl salt. [c] 7β-(α-Hydroxybenzyl). [d] Repeat 0.014 (0.0023-0.053). [e] *d*-Tartrate salt. [f] Diastereoisomeric at the substituting α carbon.

these compounds were, however, active at a dose of 10 mg (ca. 20 μmol)/kg in antagonizing the effects of an ED_{80} of morphine.

The introduction of unsaturated substituents into the 7β-position of 6β-hydroxy-7α-(hydroxymethyl)-4,5α-epoxymorphinans, to give compounds **5**, does not enhance narcotic agonist activity. An alkyl group in the same 7β-position, i.e., **7a** and **7b**, likewise does not give particularly potent compounds. The arylalkyl compounds **7c–h**, in contrast, exhibit agonist activity that is dependent on the length of the methylene bridge between the tertiary C7 carbon and the aryl group. The most potent compounds, **7c** and **7f**, both contain an even number of carbons in this bridge. Increasing the length of the bridge to ≥5 in **7g,h** results in a decrease in potency. The same general structure–activity trends observed with the 3-methoxy compounds **7** are reflected in the 3-hydroxy series **8**. The phenols **8c** and **8f** are more potent agonists, by about seven- and five-fold, respectively, then their 3-methoxy counterparts. Compound **8f**, the most potent *N*-methyl compound prepared in this study, is approximately 700 times as potent an agonist as morphine in our assay system.

The oxymethylene ring at the 6α,7α-positions enhances agonist potency in **18d,f** when compared to **7d,f**. The most potent member of this series, **18f**, has four methylene units connecting the tertiary carbon and the aryl ring. The

(18) Harris, L. S.; Pierson, A. K. *J. Pharmacol. Exp. Ther.* **1964**, *143*, 141.

Table II. Narcotic Agonist Activity (Mouse Writhing Assay) of *N*-(Cycloalkylmethyl) Compounds

compd	R	R_1	ED_{50}, μmol/kg, sc (95% CL)[a]
11Pc[b]	C_6H_5	CH_2-c-C_3H_5	0.61 (0.47-0.76)
11Pd	$CH_2C_6H_5$	CH_2-c-C_3H_5	0.13 (0.05-0.33)
11Pf[b]	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	0.22 (0.11-0.43)
11Pg[b]	$(CH_2)_3C_6H_5$	CH_2-c-C_3H_5	0.40 (0.25-0.61)
11Bc[b]	C_6H_5	CH_2-c-C_4H_7	0.70 (0.06-7.3)
11Bd	$CH_2C_6H_5$	CH_2-c-C_4H_7	0.04 (0.007-0.15)
11Bf[b]	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	0.52 (0.19-1.4)
11Bg[b]	$(CH_2)_3C_6H_5$	CH_2-c-C_4H_7	0.30 (0.09-1.0)
12Pc	C_6H_5	CH_2-c-C_3H_5	0.95 (0.26-3.5)
12Pd[b]	$CH_2C_6H_5$	CH_2-c-C_3H_5	0.47 (0.18-1.3)
12Pf	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	11.0 (6.9-17.6)
12Pg[b]	$(CH_2)_3C_6H_5$	CH_2-c-C_3H_5	>19
12Bc	C_6H_5	CH_2-c-C_4H_7	2.5 (1.8-3.6)
12Bd[b]	$CH_2C_6H_5$	CH_2-c-C_4H_7	0.57 (0.25-1.3)
12Bf[b]	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	21.3 (12.4-36.3)
12Bg[b]	$(CH_2)_3C_6H_5$	CH_2-c-C_4H_7	>18
24Pc	C_6H_5	CH_2-c-C_3H_5	0.57 (0.22-1.5)
24Pd[c]	$CH_2C_6H_5$	CH_2-c-C_3H_5	1.07 (0.77-1.5)
24Pf[c]	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	0.61 (0.41-0.93)
24Bc[c]	C_6H_5	CH_2-c-C_4H_7	>16
24Bd[c]	$CH_2C_6H_5$	CH_2-c-C_4H_7	4.4 (0.69-27.8)
24Bf[c]	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	2.8 (1.1-7.3)
25Pc	C_6H_5	CH_2-c-C_3H_5	0.04 (0.02-0.07)
25Pd	$CH_2C_6H_5$	CH_2-c-C_3H_5	0.003 (0.001-0.1)
25Pf[c]	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	0.015 (0.006-0.3)
25Bc	C_6H_5	CH_2-c-C_4H_7	0.39 (0.25-0.55)
25Bd[c]	$CH_2C_6H_5$	CH_2-c-C_4H_7	0.06 (0.048-0.08)
25Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	0.05 (0.018-0.10)
26Pf[b]	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	0.50 (0.15-1.5)
26Bc[b]	C_6H_5	CH_2-c-C_4H_7	1.0 (0.78-1.3)
26Bf[b]	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	11.3 (8.2-15.6)
27Pf[b]	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	2.0 (1.1-3.5)
27Bc	C_6H_5	CH_2-c-C_4H_7	0.19 (0.008-0.05)
27Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	5.6 (1.8-16.9)
28Pf	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	0.11 (0.10-0.19)
28Bc[b]	C_6H_5	CH_2-c-C_4H_7	0.04 (0.02-0.11)
28Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	0.17 (0.06-0.39)

[a] Compounds that were prepared as salts (see below) were administered in distilled water; free bases were dissolved by the addition of 1 N HCl and then further diluted. All compounds were administered by the subcutaneous route. [b] HCl salt. [c] *d*-Tartrate salt.

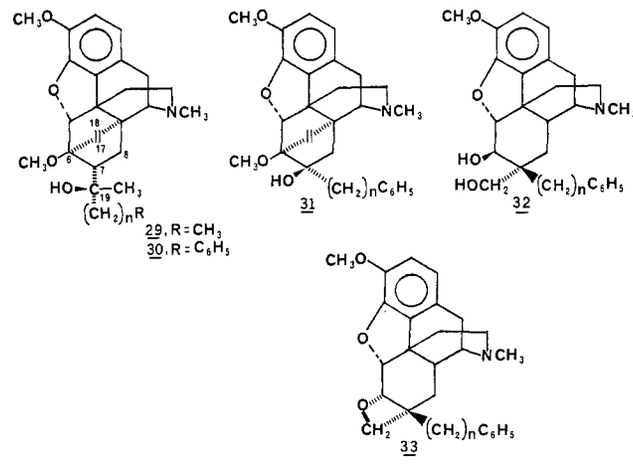
corresponding 3-phenols **21** are all potent agonists with insufficient differences in ED_{50}'s to allow conclusions to be drawn. The presence of an additional alcohol function at the α carbon on the C7β side chain in **6** or **19** does not make a contribution to agonist potency.

The more potent *N*-methyl-7β-arylalkyl compounds that were obtained in the initial phases of this work were converted to the corresponding *N*-cyclopropylmethyl (**P** series) or *N*-cyclobutylmethyl (**B** series) analogues. In both series **11** and **12**, the homologue with a three methylene–C7-aryl bridge are the most potent members of these cycloalkylmethyl series. For oxymethylene compounds **24P**, the most potent members are **24Pc** and **24Pf**; in the **24B** series, none of the compounds are particularly potent. Potency in the 3-hydroxy series, **25P** and **25B**, likewise peaks when the C7 and aryl groups are separated by three methylenes. The most potent member of this series, **25Pd**, is ca. 700 times as potent an agonist as is morphine.

Compounds with sp^2 hybridization at C6, **27** and **28**, were potent agonists. A comparison of these *N*-cycloalkylmethyl series with the corresponding *N*-cycloalkylmethyl-6β-hydroxy-7α-hydroxymethyl series **11** and **12**, or oxymethylene compounds **24** and **25**, reveals that intricate structure–potency relationships exist within these compounds.

To summarize, both the 6β-hydroxy-7α-hydroxymethyl and 6α,7α-oxymethylene series containing 7β-arylalkyl

Chart I



groups with an alkyl chain length of two to four methylene units are potent agonists. Narcotic antagonist activity was not demonstrated for any compounds prepared in the course of the present work.

Discussion

The previous discovery of potent narcotic agonist activity in the homologous series of C19 tertiary alcohols **29** (Chart I) resulted in the hypothesis[3] that a specific site exists on the opiate receptor for the lipophilic groups that had been incorporated into this region of the morphine molecule. Structure–activity studies revealed that agonist potency for **29** is maximal when $n = 2$ or 3. Further increases in n result in a dimunition of potency. This potency profile is even more pronounced in the analogous series **30** in which a phenyl group has been placed at the end of the alkyl chain. In series **30**, there is over a 1000-fold increase in potency when the methylene bridge is extended from $n = 0$ to $n = 1$, a further 10-fold increase between $n = 1$ and $n = 2$, and, then, a 10-fold decrease in potency between $n = 2$ and $n = 3$. In the related series **31**,[19] which most closely resembles our presently reported compounds in structure, potency is likewise maximized when $n = 2$ or 3.

Prior consideration of the potencies of compounds **30**, which contain terminal aryl groups, allowed the lipophilic site to be mapped onto the putative opiate receptor surface. The maximal agonist potency observed in **30** when $n = 2$ places this binding site at a distance centered about 6 Å from C7 of the receptor-bound morphine molecule.[20] The pharmacological results obtained during the present work are in agreement with these previous findings. A comparison of the molecular models of **32** and **33**, in which $n = 3$ or 4 and for which the methylene units are in a fully extended configuration, with **29–31** places the aryl group within the same locale on a receptor surface.

The presence of an alcohol function at C19 is not a prerequisite for potent agonist activity in the *endo*-ethenotetrahydrooripavines.[20] Hydrogen bonding between the 6-methoxy group and the tertiary C19 alcohol has likewise been eliminated as contributing to the potencies of **29** and **30**.[21] This finding is further confirmed by this work. The oxetane ring in **33** does not appreciably alter potency; likewise, our potent 7α-methyl compounds **27** and **28** cannot form hydrogen bonds due to the absence of an exocyclic hydroxy function.

The most significant structural difference between **29–31** and **32–33** is the absence of the 6,14-etheno bridge. The C ring in **29–31** is fixed by C_{17}–C_{18} into a boat conformation. This etheno bridge results in a rigid, cage-like structure in this region of the morphine molecule. The presently reported compounds are not so constrained. The oxetane ring in **33** does limit the flexibility of the C ring. Series **32** are, however, not so constrained but may have a conformational preference in solution imposed by the presence of the various C7-substituents.

These observations, together with our previous work[1,22] and those with 2,6-methano-3-benzazocine-11-propanols[23] which lack a rigid C-ring structure, diminishes the contribution of ring C rigidity to the agonist potencies observed with **29–31**. This allows the conclusion that the main contributory factor to the potencies of **29–33** and related compounds is the presence of an exocyclic lipophilic aromatic group in the morphine C-ring region extending up and outward from C7. This aromatic binding site has also been implicated in the explanation of the pharmacological activities observed with enkephalins[24] and other structural classes of narcotic analgesic agents.[25]

The lack of narcotic antagonist activity in *N*-cycloalkylmethyl derivatives of **32** and **33**, in retrospect, is not surprising. Morphine antagonist activity in **29** is restricted to *N*-cycloalkylmethyl derivatives in which the groups on C19 are small.[3,20] Attempts are being made to explain this phenomenon.[26]

This paper completes our work in the area of analgesic narcotic antagonists. The at first elusive lipophilic site on the opiate receptor, which we initially postulated as existing near C8, has been found extending outward from the 7β-position (7-up) of the morphine nucleus. This is exactly where model-building studies with **29–31** indicated it could be found.

Experimental Section

Methods have been previously described.[2] Processing in the usual manner implies that the combined organic phases were washed with dilute NH_4OH, dried ($MgSO_4$), and filtered, and the filtrate was evaporated at a 40–45 °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) with $CHCl_3$–MeOH mixtures containing 0.25 to 1%, v/v, concentrated NH_4OH. All compounds gave NMR and mass spectra consistent with the indicated structures and in accord with those which we previously reported.[10]

7β-(Arylalkylidene)-4,5α-epoxy-7α-(hydroxymethyl)-3-methoxy-17-methylmorphinan-6β-ols (5). Method A. A suspension of 50% NaH (0.66 g, 13.8 mmol) in mineral oil was washed three times with hexane while under an argon atmosphere. Me_2SO (10 mL) was added, and the mixture heated at 60–70 °C until the evolution of H_2 ceased (ca. 30 min). The mixture was cooled to 25 °C, and the appropriate phosphonium salt (13.8 mmol) in Me_2SO (50 mL) was added dropwise. After 10 min, **3** (5.0 g, 12.5 mmol) in Me_2SO (50 mL) was added rapidly dropwise. Stirring was continued for 30 min at room temperature, followed by heating of the mixture at 65–70 °C for 30 min. The cooled mixture was diluted with water and extracted with toluene. The

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Table III. 6β-Hydroxy-7α-(hydroxymethyl)-7β-substituted-4,5α-epoxymorphinans

compd	R	R_1	yield, %	mp, °C	recrystn solvent[a]	formula[b]
7a	H		58[c]	200-204	E	$C_{21}H_{29}NO_4 \cdot HCl$
7b	CH_2CH_3		53[c]	>270	E	$C_{23}H_{33}NO_4 \cdot HCl$
7c	C_6H_5		72[d]	240-242	E	$C_{27}H_{33}NO_4$
7d	$CH_2C_6H_5$		81[c]	267-270	M-EA	$C_{28}H_{35}NO_4 \cdot HCl$
7f	$(CH_2)_2C_6H_5$		89[e]	196-198	EA-C	$C_{29}H_{37}NO_4$
7g	$(CH_2)_3C_6H_5$		83[c]	200-202	M-EA	$C_{30}H_{39}NO_4 \cdot HCl$
7h	$(CH_2)_4C_6H_5$		67[d]	160-161	E	$C_{31}H_{41}NO_4$
8b	CH_2CH_3		81[d]	224-226	M-EA	$C_{22}H_{31}NO_4$
8c	C_6H_5		54[d]	259-262	M-EA	$C_{26}H_{31}NO_4$
8d	$CH_2C_6H_5$		62[d]	240-245	E	$C_{27}H_{33}NO_4$
8f	$(CH_2)_2C_6H_5$		82[d]	192-193	EA	$C_{28}H_{35}NO_4$
8g	$(CH_2)_3C_6H_5$		88[d]	212-216	M-EA	$C_{29}H_{37}NO_4 \cdot HCl$
8h	$(CH_2)_4C_6H_5$		67[d]	249-251	E	$C_{30}H_{39}NO_4 \cdot HCl \cdot H_2O$
11Pc	C_6H_5	CH_2-c-C_3H_5	85[d]	261-264	E	$C_{30}H_{37}NO_4 \cdot HCl$
11Pd	$CH_2C_6H_5$	CH_2-c-C_3H_5	44[f]	198-199.5	E	$C_{31}H_{39}NO_4$
11Pf	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	63[d]	256-258	M-EA	$C_{32}H_{41}NO_4 \cdot HCl$
11Pg	$(CH_2)_3C_6H_5$	CH_2-c-C_3H_5	75[d]	240-243	E	$C_{33}H_{43}NO_4 \cdot HCl$
11Bc	C_6H_5	CH_2-c-C_4H_7	74[d]	~200[g]	E	$C_{31}H_{39}NO_4 \cdot HCl$
11Bd	$CH_2C_6H_5$	CH_2-c-C_4H_7	62[d]	152-154	EA	$C_{32}H_{41}NO_4$
11Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	62[d]	256-258	M-EA	$C_{33}H_{43}NO_4 \cdot HCl$
11Bg	$(CH_2)_3C_6H_5$	CH_2-c-C_4H_7	77[d]	247-250	E	$C_{34}H_{45}NO_4 \cdot HCl$
12Pc	C_6H_5	CH_2-c-C_3H_5	34[d]	252-254	E	$C_{29}H_{35}NO_4$
12Pd	$CH_2C_6H_5$	CH_2-c-C_3H_5	36[d]	>200 dec	M-EA	$C_{30}H_{37}NO_4 \cdot HCl$
12Pf	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	86[d]	214-216	E-A	$C_{31}H_{39}NO_4$
12Pg	$(CH_2)_3C_6H_5$	CH_2-c-C_3H_5	57[d]	168-174	M-EA	$C_{32}H_{41}NO_4 \cdot HCl$[h]
12Bc	C_6H_5	CH_2-c-C_4H_7	77	255-257	E	$C_{30}H_{37}NO_4$
12Bd	$CH_2C_6H_5$	CH_2-c-C_4H_7	49	>280	M-EA	$C_{31}H_{39}NO_4 \cdot HCl$
12Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	95	222-225	M-EA	$C_{32}H_{41}NO_4 \cdot HCl$
12Bg	$(CH_2)_3C_6H_5$	CH_2-c-C_4H_7	93	182-186	M-EA	$C_{33}H_{13}NO_4 \cdot HCl$

[a] C = chloroform; E = ethanol; EA = ethyl acetate; M = methanol; W = water. [b] Compounds had C, H, and N analyses within ±0.4% of the calculated values. [c] HCl salt crystallized directly. [d] Yield of free base after chromatography. [e] Free base crystallized directly. [f] Directly crystallized from toluene. [g] Softens. [h] C: calcd, 71.16; found, 70.69.

organic phase was evaporated, and the residue, consisting of 4 and $(C_6H_5)_3PO$, dissolved in EtOH (200 mL) and 1 N HCl (50 mL) was added. The mixture was gently boiled on the steam bath for 30 min and then evaporated to a small volume. The acidic concentrate was diluted with H_2O and washed several times with toluene. The aqueous solution was then made basic with concentrated NH_4OH, and further processing was carried out as described below.

Method B. To a suspension of the phosphonium salt (23 mmol) in Et_2O (200 mL), under argon at room temperature, was added phenyllithium (23 mmol, 1.9 M solution in 7:3 C_6H_6–Et_2O), and the mixture was stirred for 1–2 h. A solution of **3** (4.0 g, 10 mmol) in 1:1 toluene–Et_2O (100 mL) was added to the dark solution, and stirring was continued for 2 h. The reaction was quenched by the addition of H_2O, concentrated NH_4OH was added, and the intermediate **4** was extracted with $CHCl_3$. Evaporation of the organic phase was followed by the addition of EtOH and 1 N HCl, and the mixture was boiled for 30 min and then further processed as described below.

Compound **5a** was prepared by method A. Crystals of **5a** precipitated from the basic aqueous solution and were obtained in 78% yield. Recrystallization from H_2O gave pure **5a**, mp 181–182 °C. Anal. ($C_{21}H_{27}NO_4$) C, H, N. Intermediate **5b** was prepared by method B and not further purified but directly hydrogenated to **7b**. In a similar manner, **5c** was prepared by method A and purified by chromatography to give an 89% yield of the desired product as a foam. Compound **5d** was prepared by method B and purified by chromatography to give a 38% yield of **5d** as a foam. The HCl salt, mp >280 °C, was obtained in crystalline form from EtOH. Anal. ($C_{28}H_{33}NO_4 \cdot HCl$) C, H, N. The preparation of **5e** and **5f** has been reported.[10] Compound **5g** was prepared by method B and obtained as a foam, after chromatography, in 68% yield. Crystallization from EtOH gave pure **5g**, mp 168–170 °C. Anal. ($C_{30}H_{37}NO_4$) C, H, N. Compound **5h** was prepared by method A and purified by chromatography to give a 70% yield of **5h** as a foam. The HCl salt, mp >260 °C, was obtained in crystalline form from EtOH. Anal. ($C_{31}H_{39}NO_4 \cdot HCl$) C, H, N.

4,5α-Epoxy-7β-(α-hydroxybenzyl)-7α-(hydroxymethyl)-3-methoxy-17-methylmorphinan-6β-ol (6). This compound was obtained as a side product in the preparation of **5** by method B. Material obtained by chromatography from several reactions, which migrated as a single spot on TLC, was combined and crystallized from MeOH–EtOAc to give a sample of pure **6**, mp 265–267 °C. Anal. ($C_{26}H_{31}NO_5$) C, H, N.

7β-(Arylalkyl)-4,5α-epoxy-7α-(hydroxymethyl)-3-methoxy-17-methylmorphinan-6β-ols (7). Hydrogenation of **5**, as the free base or HCl salt, was carried out over 10% Pd/C (10–25%, w/w) at 50 psi in aqueous EtOH acidified with HCl (ca. pH 2) until the uptake of H_2 ceased (2–24 h). After the catalyst was removed by filtration, the filtrate was evaporated to a crystalline residue. In cases where crystallization did not occur, the HCl salt was converted to the free base, and further purification was carried out by chromatography or crystallization as indicated in Table III.

7β-(Arylalkyl)-4,5α-epoxy-3-hydroxy-7α-(hydroxymethyl)-17-methylmorphinan-3,6β-diols (8). A mixture of **7** (free base or HCl salt) and concentrated HBr (1.0 g in 10–15 mL) was immersed in a preheated oil bath (ca. 140 °C) and refluxed for 10 to 20 min. The reaction mixture was cooled, diluted with H_2O, and adjusted to pH 10–11 by the addition of concentrated NH_4OH. The basic solution was extracted with three portions of $CHCl_3$, the organic extracts were processed in the usual manner, and the residue was chromatographed. Crystals of the free base or HCl salt were obtained from the solvents indicated in Table III.

7β-(Arylalkyl)-17-cyano-4,5α-epoxy-7α-(hydroxymethyl)-3-methoxymorphinan-6β-ols (9). To a rapidly stirred mixture of **7** (1.0 equiv) in $CHCl_3$ (1 g in 15 mL) containing K_2CO_3 (1.5 equiv) was added dropwise a solution of BrCN (1.2 equiv) in $CHCl_3$ (1 g in 15 mL). The mixture was stirred at room temperature for 30 min and then refluxed for 2 h. The insoluble material was removed by filtration, and the filtrate was evaporated. The residue was evaporated with EtOH until a foam formed. This foam, obtained in nearly quantitative yield and homogeneous by TLC, was hydrolyzed to **10** as described below.

7β-(Arylalkyl)-4,5α-epoxy-7α-(hydroxymethyl)-3-methoxymorphinan-6β-ols (10). A mixture of **9** and 2 N HCl (1 g in 15–25 mL) was refluxed for 8 to 18 h. The solution was cooled, made basic by the addition of concentrated NH_4OH, and extracted with $CHCl_3$. Processing of the $CHCl_3$ extracts in the usual fashion was followed by chromatography to give **10**, as a foam, the yield

Table IV. *N*-(Cycloalkylmethyl)-6α,7α-(oxymethylene)-7β-substituted-4,5α-epoxymorphinans

compd	R	R_1	yield, %	mp, °C	recrystn solvent[a]	formula[a]
24Pc	C_6H_5	CH_2-c-C_3H_5	60[b]	144-146.5	EA	$C_{30}H_{35}NO_3$
24Pd	$CH_2C_6H_5$	CH_2-c-C_3H_5	93[d]	152-157	E-W	$C_{31}H_{37}NO_3 \cdot C_4H_6O_6$
24Pf	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	99[c]	110-115	E	$C_{32}H_{39}NO_3 \cdot C_4H_6O_6$
24Bc	C_6H_5	CH_2-c-C_4H_7	99[c]	137-146	E	$C_{31}H_{37}NO_3 \cdot C_4H_6O_6$
24Bd	$CH_2C_6H_5$	CH_2-c-C_4H_7	89[d]	130-144	E	$C_{32}H_{39}NO_3 \cdot C_4H_6O_6$
24Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	99[c]	128-134	E	$C_{33}H_{41}NO_3 \cdot C_4H_6O_6$
25Pc	C_6H_5	CH_2-c-C_3H_5	53[d]	188-190	EA	$C_{29}H_{33}NO_3$
25Pd	$CH_2C_6H_5$	CH_2-c-C_3H_5	43[d]	foam		$C_{30}H_{35}NO_3$
25Pf	$(CH_2)_2C_6H_5$	CH_2-c-C_3H_5	81[c]	147-170[e]	EA	$C_{31}H_{37}NO_3 \cdot C_4H_6O_6 \cdot 0.5EA$
25Bc	C_6H_5	CH_2-c-C_4H_7	42[d]	200-202	EA	$C_{30}H_{35}NO_3$
25Bd	$CH_2C_6H_5$	CH_2-c-C_4H_7	62[c]	160-176	EA	$C_{31}H_{37}NO_3 \cdot C_4H_6O_6$
25Bf	$(CH_2)_2C_6H_5$	CH_2-c-C_4H_7	82[d]	158-159	E	$C_{32}H_{39}NO_3$

[a] See Table III for explanation. [b] Crystallized directly as the free base. [c] Crystallized directly as the salt. Yield of free base prior to salt formation. [d] Yield of free base after chromatography. [e] Foams.

being based on the NCH_3 compounds 7: **10c**, 88%; **10d**, 81%; **10f**, 75%; **10g**, 67%. These foams were used in the alkylation reactions described below.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-7α-(hydroxymethyl)-3-methoxymorphinan-6β-ols (11P,B). A solution of **10** in DMF (1 g in 20 mL) containing $NaHCO_3$ (2.5 equiv) and cycloalkylmethyl bromide (1.2 equiv) was heated in an oil bath at 100 °C while under argon until the reaction was complete as indicated by TLC (3–20 h). The mixture was cooled and filtered to remove insolubles. The filtrate was evaporated with an oil pump, and the residue was dissolved in H_2O. This mixture was adjusted to pH 10–11 with NH_4OH and extracted with three portions of toluene. The organic phase was processed in the usual manner, the residue was chromatographed, and the product was crystallized as the free base or HCl salt as indicated in Table III.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-3-hydroxy-7α-(hydroxymethyl)morphinan-6β-ols (12P,B). A suspension of the 3-methoxy compound **11** in 48% HBr (1 g in 10 mL) was placed in a preheated, 140 °C oil bath, and the mixture was refluxed for 10–20 min. The cooled solution was diluted with H_2O and made basic with NH_4OH. This was extracted with EtOAc or $CHCl_3$, the organic extracts were processed in the usual fashion, and the residue was chromatographed. Pure **12** was crystallized as the free base or HCl salt. Further details are given in Table III.

7β-(Arylalkyl)-4,5α-epoxy-3-methoxy-17-methyl-6α,7α-(oxymethylene)morphinans (18). The intermediates **17** were prepared from **16** by method A or method B described above for **5**, followed by processing of the reaction mixture as detailed. Compound **17c** was prepared by method A. Upon completion of the reaction with the phosphonium ylide, the mixture was poured into H_2O. The pH of this solution was adjusted to ca. 2, and the aqueous solution was extracted several times with toluene to remove $(C_6H_5)_3PO$. The aqueous phase was made basic with 50% NaOH, and **17c** was extracted into $CHCl_3$. A mixture of the two isomers of **17c** was obtained in nearly quantitative yield. Hydrogenation of **17c** was carried out in aqueous EtOH at 50 psi, with several changes of catalyst (10% Pd/C) until the reduction was complete as indicated by TLC. Workup gave **18c**, as a foam, in 74% yield based on **16**. This was converted to the *d*-tartrate salt, which was crystallized and recrystallized from EtOH to give pure **18c**·*d*-tartrate, mp 192–197 °C. Anal. ($C_{27}H_{31}NO_3 \cdot C_4H_6O_6$) C, H, N. Intermediate **17d** was prepared by method B, except that THF was used as the solvent for the addition of **16**. Workup by selective extraction, followed by chromatography, gave a 44% yield of **17d**. Hydrogenation for several days gave **18d** as a glass in 68% yield from **17d**. The *d*-tartrate salt, mp 191–192 °C, was obtained as crystals from MeOH–EtOAc. Anal. ($C_{28}H_{33}NO_3 \cdot C_4H_6O_6$) C, H, N. The preparation of **18f**, via **17f**, has been reported.[10] Compound **17g** was prepared by method A and obtained as a glass in 36% yield after chromatography. Hydrogenation gave **18g** as a glass in 66% yield. Conversion to the *d*-tartrate salt, followed by crystallization from EtOH, gave an analytical sample of **18g**·*d*-tartrate, mp 130–136 °C. Anal. ($C_{30}H_{37}NO_3 \cdot C_4H_6O_6$) C, H, N.

4,5α-Epoxy-7β-(α-hydroxybenzyl)-3-methoxy-17-methyl-6α,7α-(oxymethylene)morphinan (19). A solution of **16** (1.72 g, 5.0 mmol) in toluene (100 mL) under argon was treated dropwise with phenyllithium (10 mmol). After the solution was stirred for 30 min, ice and H_2O were added, and the organic phase was processed in the usual fashion to give 2.08 g (99%) of **19** as a foam. Chromatography allowed resolution of two isomers. The faster migrating isomer crystallized from EtOAc–Et_2O to give **19**, mp 222–223 °C. Anal. ($C_{26}H_{29}NO_4$) C, H, N. The slower migrating isomer, **19**, was crystallized from EtOAc to give needles, mp 237–240 °C. Anal. C, H, N.

7β-(Arylalkyl)-4,5α-epoxy-3-hydroxy-17-methyl-6α,7α-(oxymethylene)morphinans (21). A mixture of **18** and 48% HBr (1 g in 10–20 mL) was refluxed in a preheated oil bath for 15 min. The cooled solution was diluted with H_2O and made basic with NH_4OH, and the 6α-hydroxy-7β-bromomethyl intermediate **20** was extracted with $CHCl_3$ or EtOAc. After processing of the organic phase and evaporation, the residue was dissolved in dioxane (30 mL), and 1 N NaOH (10 mL) was added. The mixture was heated at 60–70 °C for 90 min and then evaporated to dryness. The residue was dissolved in H_2O, and the pH was adjusted to ca. 8 with HOAc. Extraction with $CHCl_3$ was followed by chromatography. Compound **21c** was obtained as a foam in 40% yield. The *d*-hemitartrate, mp 200–208 °C, crystallized as the hemisolvate from EtOH. Anal. ($C_{26}H_{29}NO_3 \cdot 0.5C_4H_6O_6 \cdot 0.5C_2H_6O$) C, H, N. In the same manner, **21d** was obtained in 64% yield, and the *d*-tartrate salt, mp 234–236 °C, crystallized from aqueous EtOH to give hydrated material. Anal. ($C_{27}H_{31}NO_3 \cdot C_4H_6O_6 \cdot 0.25H_2O$) C, H, N. Compound **21f** was previously described. The free base **21g** was obtained in 70% yield and converted to the *d*-tartrate salt. Several recrystallizations from EtOH gave the hydroscopic salt, mp 144–153 °C. Anal. ($C_{29}H_{35}NO_3 \cdot C_4H_6O_6 \cdot 0.25H_2O$) C, H, N.

7β-(Arylalkyl)-4,5α-epoxy-3-methoxy-6α,7α-(oxymethylene)morphinans (23). The *N*-cyano compounds were prepared as described above for **9**. Compound **18c** (16.6 g, 39.7 mmol) gave 16.3 g of **22c** as a foam. This foam was dissolved in dioxane (500 mL), and KOH (465 mmol) in H_2O (100 mL) was added. The mixture was refluxed for 1 week, cooled, and evaporated to a small volume. The residue was partitioned between H_2O and $CHCl_3$. Processing of the organic phase gave 16.0 g of a foam, which was chromatographed to give 12.2 g (76%) of **23c** as a foam. Crystalline **23c**, mp 101–102 °C, was obtained upon trituration with EtOH. Hydrolysis of **22d** for 5 days, followed by workup, gave **23d** in nearly quantitative yield as a glass, which was not further purified but used directly in alkylation reactions. Chromatography gave a 91% yield of **22f**, which was hydrolyzed to **23f** and purified by chromatography to give material suitable for further reactions.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-3-methoxy-6α,7α-(oxymethylene)morphinans (24P,B). These compounds were prepared as described above for **11**. Details are given in Table IV.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-3-hydroxy-6α,7α-(oxymethylene)morphinans (25P,B). These compounds were prepared as described above for **21**. Details are given in Table IV.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-3-methoxy-7α-methylmorphinan-6α-ols (26P,B). A suspension of $AlCl_3$

(1.95 g, 14.6 mmol) in Et_2O (100 mL) was cooled in an ice bath, and $LiAlH_4$ (1.66 g, 43.9 mmol) was added. After the mixture was stirred for 30 min, a solution of **24f** (7.1 g, 14.6 mmol) in Et_2O (250 mL) was added, and the mixture was refluxed for 18 h. The cooled mixture was treated sequentially dropwise with H_2O (1.7 mL), 15% NaOH (1.7 mL), and H_2O (5.1 mL) and then filtered through Celite. The filtrate was diluted with EtOAc and washed with H_2O. Evaporation gave 5.8 g of a glass, which was chromatographed to give 4.43 g (62%) of **26Pf** as a glass. A portion of this material was converted to the HCl salt, which was obtained as white crystals, mp 118–122 °C, from EtOAc. Several recrystallizations from EtOAc gave analytically pure material with an indefinite melting point. Anal. ($C_{32}H_{41}NO_3$·HCl) C, H, N. In a similar manner, **26Bc** was obtained as a foam in 84% yield. Crystals of the HCl salt, mp 169–171 °C, were obtained from EtOAc. Anal. ($C_{31}H_{39}NO_3$·HCl) C, H, N. Compound **26Bf** was obtained in 65% yield and crystallized as the HCl salt: mp sinters at 116 °C, melts at 123–130 °C. Anal. ($C_{33}H_{43}NO_3$·HCl) C, H, N.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-3-methoxy-7α-methylmorphinan-6-ones (27P,B). To a solution of Me_2SO (1.0 mL, 14.3 mmol) in CH_2Cl_2 under argon at −60 °C was added slowly, dropwise, trifluoroacetic anhydride (1.5 mL, 10.7 mmol) in CH_2Cl_2 (7 mL). After 10 min, a solution of **26Pf** (3.48 g, 7.1 mmol) in CH_2Cl_2 (50 mL) was added slowly. The mixture was kept at −60 °C for 90 min, then TEA (3 mL) was added, and the mixture was warmed to room temperature. After the mixture was washed with H_2O, evaporation of the organic phase gave 3.47 g of **27Pf** as a foam. The HCl salt, mp 105–110 °C, was recrystallized several times from EtOAc and best analyzed as containing 0.33 mol of EtOAc. Anal. ($C_{32}H_{39}NO_3$·HCl·0.33EtOAc) C, H, N. The free base of **27Bc** was obtained as crystals, mp 150–151 °C, in 77% yield after chromatography and crystallization from EtOAc–Et_2O. Anal. ($C_{31}H_{37}NO_3$) C, H, N. Compound **27Bf** was obtained in quantitative yield as crystals, mp 149–152 °C. Recrystallization from EtOAc gave a 96% yield of pure **27Bf**, mp 150–151.5 °C. Anal. ($C_{33}H_{41}NO_3$) C, H, N.

7β-(Arylalkyl)-17-(cycloalkylmethyl)-4,5α-epoxy-3-hydroxy-7α-methylmorphinan-6-ones (28P,B). A mixture of **27** and 48% HBr was refluxed for 15 min and processed as described previously. Chromatography gave **28Pf** in 63% yield as a foam. Crystals of **28Pf**, mp 183.5–185 °C, were deposited from EtOAc. Anal. ($C_{31}H_{37}NO_3$) C, H, N. Compound **28Bc** was obtained in 42% yield after chromatography. The HCl salt, mp sinters above 200 °C, crystallized from EtOAc. Anal. ($C_{30}H_{35}NO_3$·HCl) C, H, N. The foam obtained upon workup of **28Bf** crystallized upon titration with EtOAc. These crystals, obtained in 53% yield, were recrystallized from EtOAc to give pure **28Bf**, mp 186–188.5 °C. Anal. ($C_{32}H_{39}NO_3$) C, H, N.

Registry No. **3**, 85455-22-7; **5a**, 85534-09-4; **5b**, 85552-56-3; **5c**, 85534-10-7; **5d**, 85534-11-8; **5d**·HCl, 85534-12-9; **5g**, 85534-13-0; **5h**, 85534-14-1; **5h**·HCl, 85534-15-2; **6**, 85534-16-3; **7a**, 85534-17-4; **7a**·HCl, 85534-18-5; **7b**, 85534-19-6; **7b**·HCl, 85534-20-9; **7c**, 85534-21-0; **7d**, 85534-23-2; **7d**·HCl, 85534-22-1; **7f**, 85455-23-8; **7g**, 85534-25-4; **7g**·HCl, 85534-24-3; **7h**, 85534-26-5; **8b**, 85534-27-6; **8c**, 85534-28-7; **8d**, 85534-29-8; **8f**, 85455-24-9; **8g**, 85434-31-7; **8g**·HCl, 85534-30-1; **8h**, 85534-33-4; **8h**·HCl, 85534-32-3; **10c**, 85534-34-5; **10d**, 85534-35-6; **10f**, 85534-36-7; **10g**, 85534-37-8; **11Bc**, 85552-58-5; **11Bc**·HCl, 85552-57-4; **11Bd**, 85534-45-8; **11Bf**, 85534-47-0; **11Bf**·HCl, 85534-46-9; **11Bg**, 85534-49-2; **11Bg**·HCl, 85534-48-1; **11Pc**, 85534-39-0; **11Pc**·HCl, 85534-38-9; **11Pd**, 85534-40-3; **11Pf**, 85534-42-5; **11Pf**·HCl, 85534-41-4; **11Pg**, 85534-44-7; **11Pg**·HCl, 85534-43-6; **12Bc**, 85534-56-1; **12Bd**, 85534-58-3; **12Bd**·HCl, 85534-57-2; **12Bf**, 85534-60-7; **12Bf**·HCl, 85534-59-4; **12Bg**, 85534-62-9; **12Bg**·HCl, 85534-61-8; **12Pc**, 85534-50-5; **12Pd**, 85534-52-7; **12Pd**·HCl, 85534-51-6; **12Pf**, 85534-53-8; **12Pg**, 85534-55-0; **12Pg**·HCl, 85534-54-9; **16**, 85455-05-6; (*E*)-**17c**, 85534-63-0; (*Z*)-**17c**, 85534-64-1; **17d**, 85534-65-2; **17f**, 85534-66-3; **17g**, 85534-67-4; **18c**, 85534-68-5; **18c** *d*-tartrate, 85534-69-6; **18d**, 85534-70-9; **18d** *d*-tartrate, 85534-71-0; **18f**, 85455-07-8; **18g**, 85534-72-1; **18g** *d*-tartrate, 85534-73-2; **19** (isomer 1), 85534-74-3; **19** (isomer 2), 85534-75-4; **20c**, 85534-76-5; **20d**, 85534-77-6; **20g**, 85552-59-6; **21c**, 85534-78-7; **21c** *d*-hemitartrate, 85534-79-8; **21d**, 85534-80-1; **21d** *d*-tartrate, 85534-81-2; **21f**, 85455-08-9; **21g**, 85534-82-3; **21g** *d*-tartrate, 85534-83-4; **22c**, 85534-84-5; **22d**, 85534-85-6; **22f**, 85534-86-7; **23c**, 85534-87-8; **23d**, 85534-88-9; **23f**, 85534-89-0; **24Bc**, 85534-90-3; **24Bd**, 85534-91-4; **24Bf**, 85534-92-5; **24Pc**, 85534-93-6; **24Pd**, 85534-94-7; **24Pf**, 85534-95-8; **25Bc**, 85534-96-9; **25Bd**, 85534-97-0; **25Bf**, 85534-98-1; **25Pc**, 85534-99-2; **25Pd**, 85535-00-8; **25Pf**, 85535-01-9; **26Bc**, 85535-02-0; **26Bc**·HCl, 85535-03-1; **26Bf**, 85535-04-2; **26Bf**·HCl, 85535-05-3; **26Pf**, 85535-06-4; **26Pf**·HCl, 85535-07-5; **27Bc**, 85535-08-6; **27Bf**, 85535-09-7; **27Pf**, 85535-10-0; **27Pf**·HCl, 85535-11-1; **28Bc**, 85535-12-2; **28Bc**·HCl, 85535-13-3; **28Bf**, 85535-14-4; **28Pf**, 85535-15-5; $(C_6H_5)_3PCH_3Br$, 1779-49-3; $(C_6H_5)_3P(CH_2)_2CH_3Br$, 6228-47-3; $(C_6H_5)_3PCH_2C_6H_5Br$, 1449-46-3; $(C_6H_5)_3P(CH_2)_2C_6H_5Br$, 53213-26-6; $(C_6H_5)_3P(CH_2)_4C_6H_5Br$, 37748-19-9; $(C_6H_5)_3P(CH_2)_5C_6H_5Br$, 17483-25-9; phenyllithium, 591-51-5.

2-(6-Carboxyhexyl)cyclopentanone Hexylhydrazone. A Potent and Time-Dependent Inhibitor of Platelet Aggregation

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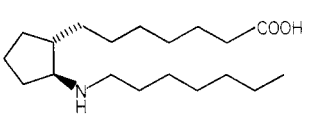
Two new azaprostanoids, a hydrazone (**3**) and hydrazide (**4**), have been prepared by the condensation of 2-(6-carboxyhexyl)cyclopentanone with *n*-hexylhydrazine and caproic acid hydrazide. Preliminary results with the stable hydrazide **4** indicate that it inhibits arachidonic acid (AA) induced human platelet aggregation and that, unlike 13-azaprostanoic acid (**1**), its site of action is at the cyclooxygenase level. Results with the unstable hydrazone derivative **3** indicate it to be a potent and time-dependent inhibitor of AA-induced human platelet aggregation, with its site of action also at the cyclooxygenase level.

In a continued search for modulators of platelet prostaglandin action, we prepared the azaprostanoid derivatives **3** and **4**. The rational for the synthesis of these compounds was based on our previous observations of antiplatelet activity for the simple *trans*-13-azaprostanoic acid (**1**).[1] This derivative appears to act as a direct thromboxane antagonist at the receptor level.[2] We



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speculated that the nonbonding electrons of nitrogen in the 13-azaprostanoic acid might be mimicking the π system

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(1) Venton, D. L.; Enke, S. E.; Le Breton, G. C. *J. Med. Chem.* **1972**, *22*(7), 824.

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