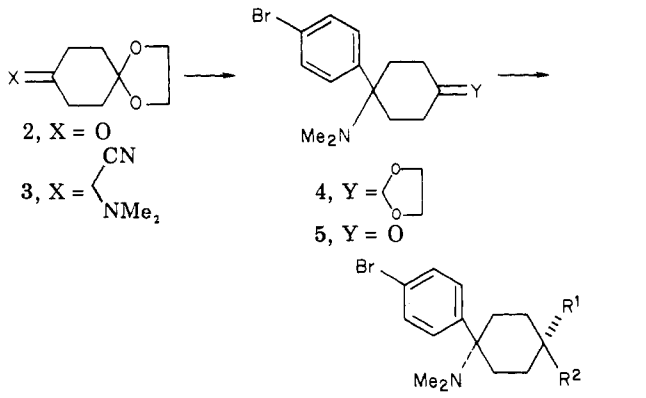
Scheme I



1, $R^1 = CH_2CH_2C_6H_5$; $R^2 = OH$
6, $R^1 = OH$; $R^2 = CH_2CH_2C_6H_5$

°C (78% yield),[6] by means of KCN and Me_2NH·HCl (Scheme I). Displacement of the cyano group[8] by means of a Grignard reagent obtained from *p*-dibromobenzene and a single equivalent of Mg gave amino ketal **4**, mp 254–255.5 °C (HCl salt, 30%); this was then hydrolyzed to the corresponding ketone **5**, mp 115–118 °C (69%). Condensation of **5** with the Grignard reagent from β-phenethyl bromide led to a 1:1 mixture of the amino alcohols **1** and **6**. These proved readily separable on silica gel: elution with 5% MeOH in CH_2Cl_2 gave the trans isomer **1** (HCl salt), mp 242–243 °C. Elution with 20% MeOH in CH_2Cl_2 gave the cis isomer (HCl salt, 1.5 H_2O), mp 208–210 °C.[9]

References and Notes

(1) O. Schaumaun, *Pharmazie*, 4, 364 (1949).
(2) A. H. Beckett and A. F. Casey, *J. Pharm. Pharmacol.*, **6**, 986 (1954).
(3) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(4) The test compound was administered subcutaneously to male CF-1 mice (18–22 g) as a suspension or solution in 0.25% aqueous methylcellulose. Fifteen minutes later they were subjected to the tail-flick, tail-pinch and HCl-writhing measurements of analgesia. Briefly, a high-intensity light was directed at the middle third of the animal's tail simultaneously with the start of a photoelectric timer. The number of seconds required for the animal to flick its tail out of the light path was recorded. Animals with response latencies greater than $\bar{X}$ + 2 SD of control were scored as analgesic. Then a bulldog arterial clamp was applied to the base of the tail. A lack of turning in response to that stimulus was scored as analgesia. Finally, the mice received 0.2 mL of 0.08 N HCl intraperitoneally and they were observed for 15 min for writhing. The absence of writhing response was scored as analgesia. Six mice were used at each dose level, and doses at 0.3 log intervals were tested. ED_{50} and 95% confidence intervals were calculated by the method of Spearman and Karber. The upper and lower confidence intervals were never more than 2 and 0.5 times the ED_{50}, respectively.
(5) C. B. Pert and S. H. Snyder, *Science*, **179**, 1011 (1973).
(6) All new compounds gave satisfactory analyses for C, H, and N.
(7) Prepared by a modification of the procedure of M. Haslanger and R. G. Lawton, *Tetrahedron Lett.*, 155 (1974).
(8) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, **24**, 46 (1954).
(9) The stereochemistry assignment was based upon X-ray crystallography, performed graciously by D. J. Duchamp.

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Articles

(2,6-Methano-3-benzazocin-11β-yl)alkanones. 1. Alkylalkanones: A New Series of *N*-Methyl Derivatives with Novel Opiate Activity Profiles

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A general stereospecific synthesis of (*N*-methyl-2,6-methano-3-benzazocin-11β-yl)alkanones is described and applied to the preparation of a series of alkyl ketones wherein the alkyl group is a straight or terminally branched chain containing from one to six carbon atoms. Several compounds with methoxy groups in the aromatic ring are in the morphine range of potency; they are uniformly inactive as phenazocine antagonists. Phenolic analogues range up to 100 times as potent as morphine. Those containing five or six carbon atoms in the alkyl group exhibit phenazocine antagonist activity, in one case equivalent to naloxone. This compound (**3e**) is selective for phenazocine in its antagonist action.

Several years ago it was demonstrated that the potent narcotic antagonist nalorphine is an analgesic in man[2,3] but that its use is attended by psychic effects which preclude its clinical acceptance. Initially the compound was found to possess no morphine-like addiction liability;[4] later it was found that physical dependence could develop after chronic administration but that the abstinence syndrome occurring after drug withdrawal is qualitatively and quantitatively different from that produced by the narcotic analgesics.[5] These observations have encouraged the search for new clinically acceptable analgesics to focus attention on compounds which show narcotic antagonism as one aspect of their pharmacological action profiles.[6] In order to evaluate the subjective effects of candidate compounds, a method was developed[7] whereby scores on a questionnaire are compared with scores obtained when using reference drugs. The LSD scale, for example, measures psychotomimetic changes. In contrast to morphine and codeine,[8] nalorphine[9,10] and other analgesics with high antagonist potency, such as levallorphan[10] and

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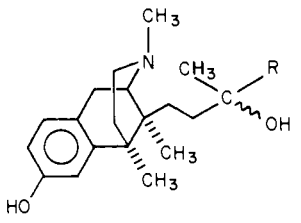
cyclazocine,[9] have been shown to elevate scores on the LSD scale, whereas analgesics with weak narcotic antagonist properties, such as pentazocine, elevate the LSD scale only at high doses.[11] Similar clinical observations earlier led Keats and Telford[12] to suggest that potent narcotic antagonism in the animal coupled with potent analgesia in man is associated with psychotomimetic effects, whereas potent analgesia without potent narcotic antagonism is free of psychotomimetic effects.

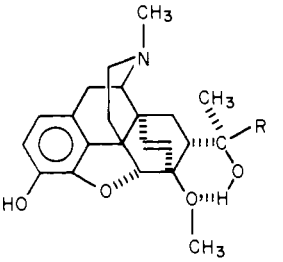
From a chemical structure point of view, the psychotomimetic narcotic antagonists are morphinan or 2,6-methano-3-benzazocine (i.e., benzomorphan) derivatives in which the nitrogen atom bears a substituent containing at least three carbon atoms, e.g., allyl or cyclopropylmethyl. Recently GPA-1657,[13] profadol,[14] and etazocine,[15] all of which contain a nitrogen bearing a methyl group, have been reported to exhibit weak narcotic antagonism in animals when compared with nalorphine. These compounds show little or no narcotic antagonism in humans; they are partially morphine-like and do not elevate LSD scale scores.[8,16] In view of these results, the Keats and Telford suggestion might be restated as follows: Among compounds which are narcotic antagonists in animals and analgesics in man, those with three or more carbon atoms on the nitrogen atom might be associated with psychotomimetic effects, while those with a methyl group on the nitrogen atom might be devoid of those effects. The validity of this statement cannot, as yet, be fully tested because of the lack of *N*-methyl compounds whose narcotic antagonist effects are demonstrable in humans as well as in animals. A solution to this problem could result from the discovery of *N*-methyl compounds with higher antagonist *potencies* than the compounds referred to above. The goal of this work was to discover such compounds with the hope that, if successful, the question of their psychotomimetic potential might eventually be addressed.

Our laboratory recently reported[17] that one of the alcohol carbon stereoisomers of **1a** (racemic form) is an antagonist



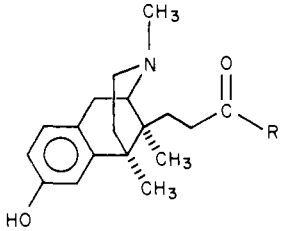
1

1a, R = $C(CH_3)_3$
b, R = $CH_2CH_2CH(CH_3)_2$

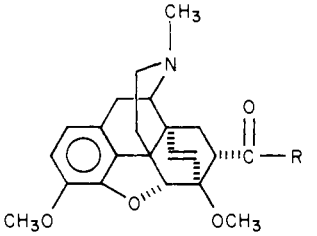


2

2a, R = $CH_2CH_2CH(CH_3)_2$



3



4

4a, R = CH_3
b, R = $CH_2CH(CH_3)_2$

of phenazocine in the rat tail-flick assay about one-third as potent as nalorphine but lacks potency as an agonist in the mouse writhing assay. In an attempt to increase agonist activity, both stereoisomers of **1b** were prepared,[18] since the corresponding ring-C-bridged oripavinemethanol **2a** is one of the most potent narcotic agonists so far reported.[19] The stereoisomers of **1b** are three and five times as potent as nalorphine as antagonists of phenazocine but still lack agonist potency. A consideration of the structures of *N*-methyl-2,6-methano-3-benzazocines which have been reported to exhibit narcotic antagonism, along with what was at that time known about the effects of some prostaglandins and opiates in vitro, led us to speculate[1] that perhaps in the series of ketones **3** appropriate modifications of R might result in mixed agonist/antagonist compounds of high potency which could serve as candidates for evaluation as clinically acceptable strong analgesics. This paper details the synthesis and preliminary pharmacology of the series **3** (and the corresponding methyl ethers), where R is a straight or terminally branched alkyl group containing from one to six carbon atoms.

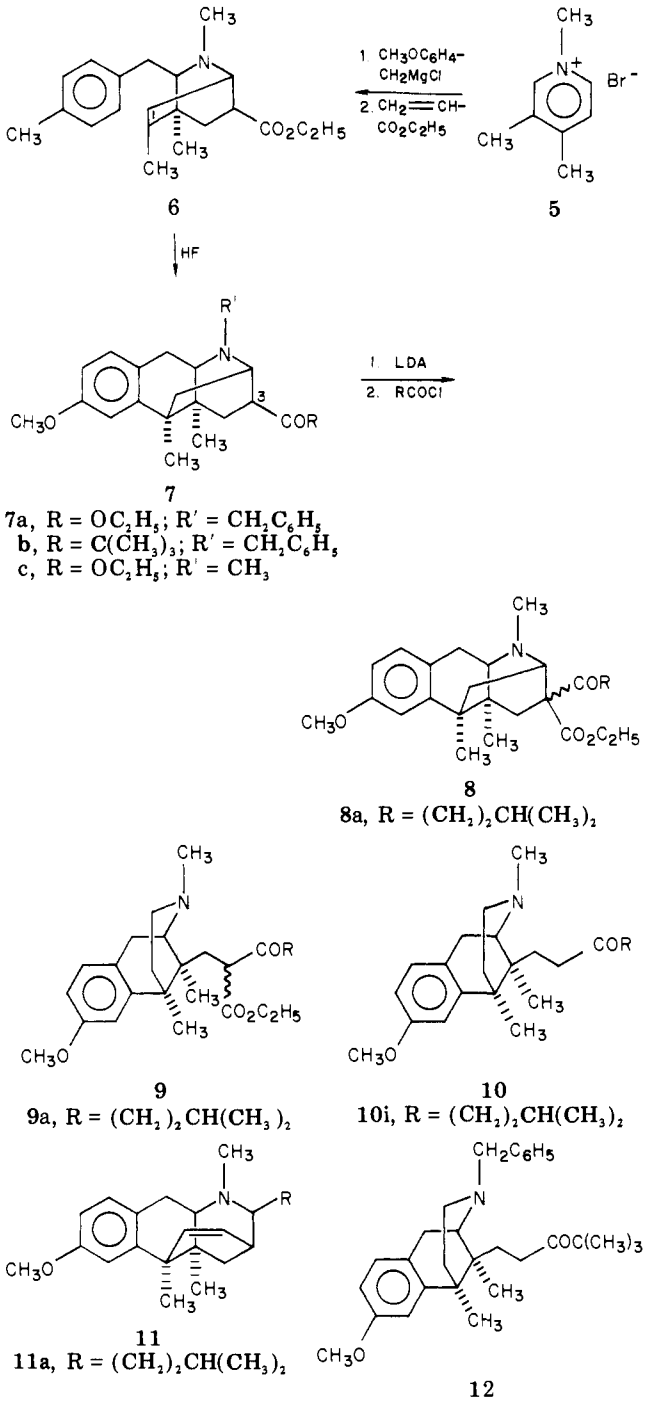
Chemistry. We have previously shown[17] that the conversion of the ester **7a** (Scheme I) to the ketone **7b**, followed by reductive ring opening with formic acid to give **12**, proceeds cleanly and in good yield. For the preparation of ketones **10**, where the α carbon of the R group is not quaternary, difficulties were encountered at two stages. First, the conversion of the ester **7c** (obtained from **5** via **6**) to the corresponding ketones required for the reductive ring-opening reaction generally proceeded in poor yield after tedious laboratory procedures. Second, reductive ring opening of these ketones was accompanied by formation of 3,5-ethenobenzo[*g*]quinolines **11**,[20] which further reduced the overall yield. We therefore devised a simplified procedure for the conversion of the ester **7c** to the ketones **10** in synthetically useful yields and without the formation of the byproduct **11**.

Consideration[20] of the proposed mechanism of formation of **10** and **11** from ketones **7** suggested that replacement of the hydrogen at C-3 of **7** with a group which could later be removed would preclude the formation of **11** during the ring-opening process. This, in turn, would allow the use of TMAF[21] which greatly reduces reaction time.[20] The carboethoxy group was chosen as a likely candidate, since the β-keto esters **8** should be readily available[22] from the ester **7c**, and the ring opened β-keto esters **9** should readily undergo hydrolysis and decarboxylation to give the desired ketones **10**.

Thus, the α anion of **7c** was generated by reaction with lithium diisopropylamide in tetrahydrofuran below −70 °C. Addition of 4-methylpentanoyl chloride, followed by warming to room temperature and workup, resulted in a mixture consisting of both C-3 epimers of **8a** and both C-3 epimers of **7c**. One epimer of **8a** was obtained pure at this point by crystallization from pentane, and its structure was confirmed by IR, NMR, and mass spectra and by elemental analysis. Treatment of this compound with either formic acid in mesitylene at 110–120 °C for 22 h or in TMAF at 150 °C for 15 min resulted, in each case, in a greater than 95% yield of **10i**. An intermediate presumed to be **9a** was observed by thin-layer chromatography during the heating periods. That ring opening occurred prior to the loss of the carboethoxy group is shown by the fact that **11a** was not formed. The overall yield of **10i** from **7c** via crystalline **8a** was 38%.

We then found that the mixture of **7c** epimers and **8a** epimers which resulted from the acylation of **7c** anion could be cleanly separated by simply partitioning the mixture between 0.1 N hydrochloric acid and ether. Basic workup of the acid layer led to recovery of **7c** epimers accounting for 32% of the starting ester and which could be recycled without further purification. The ether layer afforded the mixture of **8a** epimers which, since the

Scheme I



6 5

7

7a, R = OC_2H_5; R' = $CH_2C_6H_5$
b, R = $C(CH_3)_3$; R' = $CH_2C_6H_5$
c, R = OC_2H_5; R' = CH_3

8

8a, R = $(CH_2)_2CH(CH_3)_2$

9

9a, R = $(CH_2)_2CH(CH_3)_2$

10

10i, R = $(CH_2)_2CH(CH_3)_2$

11

11a, R = $(CH_2)_2CH(CH_3)_2$

12

stereochemistry of C-3 is destroyed as a result of ring opening, was subjected directly to formic acid/mesitylene or TMAF treatment. This procedure gave **10i** in 77% overall yield from **7c** after taking into account the recovery of the **7c** epimers. Using this procedure the compounds of Table I were prepared. The phenols **3** were obtained from the methyl ethers **10** by refluxing the latter in 48% hydrobromic acid. Compounds **3e** and **3i** were resolved by crystallization of their mandelic acid salts.

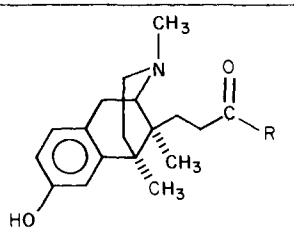
Pharmacology. The phenolic compounds **3a–j** and the corresponding methyl ethers **10a–j** were assayed by the following procedures by subcutaneous administration of aqueous solutions of the salts (bases were dissolved in aqueous lactic acid): the mouse acetylcholine writhing[23] and rat intracarotid bradykinin[24] tests for agonist activity, and the rat tail-flick test[25] for agonist activity and antagonist activity vs. the narcotic phenazocine. The results are shown in Table I, along with comparative data for morphine, naloxone, and buprenorphine. In the homologous series **10a–f**, agonist activity in both the acetylcholine writhing and tail-flick tests increases as R is extended through propyl and butyl (**10c** and **10d**, respectively, each about equal to morphine) and thereafter drops off. A similar trend is observed for the series **10g–j**; maximum activity occurs when R is isobutyl (**10h**, about equal to morphine) and thereafter drops off. None of the compounds in the **10** series shows phenazocine antagonist activity. Data for the corresponding derivatives of tetrahydro-6,14-*endo*-ethenothebaine have appeared for only the methyl and isobutyl ketones **4a** and **4b**, 1.2 and 9 times, respectively, as potent as morphine when tested in rats by a tail pressure method.[26]

In the homologous series **3a–f**, maximum potency in all three tests for agonism is again observed when R is propyl or butyl (**3c** and **3d**, respectively) and thereafter drops off. Note, however, the appearance of potent antagonism (equal to naloxone) when R is pentyl (**3e**). This compound does not have rat tail-flick agonist activity but does retain agonist activity in the writhing and bradykinin assays. Antagonist potency drops off in the hexyl compound **3f**, as does agonist activity. The structure–activity relationships for the series **3g–j** is similar to that of the series **10g–j** with regard to agonist activity; maximum potency occurs when R is isobutyl (**3h**). However, in the **3** series antagonist activity appears when R is isoamyl (**3i**). In this compound, the appearance of antagonist activity is also accompanied by retention of potent agonist activity in the writhing and bradykinin assays, while tail-flick agonist activity is reduced to minimal rather than eliminated. This profile of activity is qualitatively and quantitatively similar to that of buprenorphine. Resolution of **3e** and **3i** showed that all of the biological activity resides in the (–) isomers.

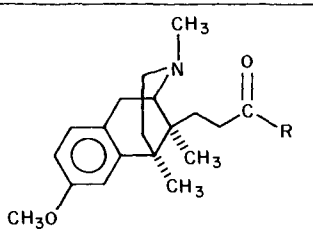
The antagonist activities of **3e** and **3i** were studied in more detail. Foldes et al.[27] have reported experiments (with five narcotics and three narcotic antagonists) designed to investigate in humans whether or not various antagonists exhibit a more pronounced effect against the pharmacological actions of narcotics in their parent series than against those of structurally less closely related narcotics. No such specificity of action was observed in their study, which suggests that antagonists reverse narcotic action without regard for the identity of the narcotic producing the action. The AD_{50} values of naloxone, cyclazocine, **3e**, and **3i** measured in our laboratory against the ED_{80-90} doses of phenazocine, morphine, and meperidine as agonists in the rat tail-flick assay are shown in Table II. In agreement with the Foldes et al. observations, naloxone, cyclazocine, and **3i** show little or no selectivity for any of the three agonists. By contrast, **3e** exhibits an order of magnitude greater selectivity for phenazocine over morphine and meperidine. Phenazocine and meperidine, however, may each bind to the opiate receptor in a similar way, since they are affected similarly by sodium ion (sodium ratios of 13 and 17, respectively) in their ability to inhibit stereospecific binding of [^{3}H]-naloxone to rat brain homogenates.[28] Morphine may bind in a somewhat different way, since its sodium ratio is 37.[28] Thus, it is not likely that the selectivity of **3e** as an antagonist is due to differences among the agonist–receptor complexes. On the other hand, it is possible that **3e** may be an example of an antagonist which exhibits selectivity for agonists of its own structural class, i.e., 2,6-methano-3-benzazocines. This question is currently being investigated.

The appearance of antagonist activity in the *N*-methyl ketone series **3** as the chain R is extended to five carbon

Table I. Physical Properties and Biological Activities of (2,6-Methano-3-benzazocin-11β-yl)alkanones



3



10

compd[a]	R	mp, °C	formula[b]	ED_{50}[c]	AD_{50}[d]	ED_{50}[e]	ED_{50}[f]
3a	CH_3	170–173	$C_{19}H_{27}NO_2$	0.25 (0.19–0.32)	*i* at 40	2.5 ± 0.78[g]	0.19 (0.10–0.40)[g]
3b	C_2H_5	265–268	$C_{20}H_{29}NO_2 \cdot HCl$	~0.18[h]	*i* at 1.0	0.99 ± 0.14	
3c	C_3H_7	264–266	$C_{21}H_{31}NO_2 \cdot HCl$	0.023 (0.018–0.031)	*i* at 80	0.099 ± 0.014	0.019 (0.008–0.031)
3d	C_4H_9	283–285	$C_{22}H_{33}NO_2 \cdot HCl$	0.017 (0.011–0.032)	*i* at 0.1	0.039 ± 0.006	0.012 (0.007–0.024)
3e	C_5H_{11}	252–255	$C_{23}H_{35}NO_2 \cdot HCl$	0.24 (0.16–0.36)	0.008 (0.004–0.015)	*i* at 120	0.043 (0.031–0.073)
(+)-**3e**	C_5H_{11}	212–214	$C_{23}H_{35}NO_2 \cdot CH_3SO_3H$	~11[h]	*i* at 80	*i* at 95	*i* at 50
(−)-**3e**	C_5H_{11}	212–214	$C_{23}H_{35}NO_2 \cdot CH_3SO_3H$	0.19 (0.11–0.43)	0.005 (0.003–0.009)	*i* at 95	0.022 (0.012–0.039)
3f	C_6H_{13}	206–209	$C_{24}H_{37}NO_2 \cdot HCl$	12 (8.3–16)	0.04 (0.02–0.06)	*i* at 120	2.2 (0.8–5.6)
3g	$CH(CH_3)_2$	263–266	$C_{21}H_{31}NO_2 \cdot HCl$	0.11 (0.07–0.16)	*i* at 80	24 ± 7.7	0.12 (0.04–0.25)
3h	$CH_2CH(CH_3)_2$	251–254	$C_{22}H_{33}NO_2 \cdot HCl$	0.019 (0.014–0.025)	*i* at 0.01	0.067 ± 0.006	0.019 (0.008–0.036)
3i	$(CH_2)_2CH(CH_3)_2$	260–263	$C_{23}H_{35}NO_2 \cdot HCl$	0.074 (0.060–0.10)	0.30 (0.18–0.51)	47% at 240	0.032 (0.016–0.059)
(+)-**3i**	$(CH_2)_2CH(CH_3)_2$	240–242	$C_{23}H_{35}NO_2 \cdot HCl$	*i* at 10	*i* at 20	*i* at 120	
(−)-**3i**	$(CH_2)_2CH(CH_3)_2$	240–242	$C_{23}H_{35}NO_2 \cdot HCl$	0.016 (0.011–0.021)	0.088[i]	46% at 120	
3j	$(CH_2)_3CH(CH_3)_2$	117–119	$C_{24}H_{37}NO_2$	5.3 (3.9–7.3)	0.029 (0.018–0.046)	*i* at 120	
10a	CH_3	183–186	$C_{20}H_{29}NO_2 \cdot HCl$	3.5 (2.9–4.1)		66% at 120	
10b	C_2H_5	217–221	$C_{21}H_{31}NO_2 \cdot CH_3SO_3H$	1.9 (1.6–2.2)	*i* at 1.0	5.9 ± 0.95	
10c	C_3H_7	176–179	$C_{22}H_{33}NO_2 \cdot CH_3SO_3H$	0.89 (0.62–1.2)	*i* at 80	2.0 ± 0.22	
10d	C_4H_9	209–212	$C_{23}H_{35}NO_2 \cdot HCl$	0.63 (0.52–0.75)	*i* at 1.0	1.35 ± 0.14	
10e	C_5H_{11}	212–214	$C_{24}H_{37}NO_2 \cdot HCl$	1.5 (1.1–2.1)	*i* at 10	30 ± 7.4	
10f	C_6H_{13}	188–190	$C_{25}H_{39}NO_2 \cdot C_7H_8O_3S$	20% at 25	*i* at 80	*i* at 120	
10g	$CH(CH_3)_2$	211–214	$C_{22}H_{33}NO_2 \cdot CH_3SO_3H$	5.0 (3.0–8.2)	*i* at 80	42% at 120	
10h	$CH_2CH(CH_3)_2$	146–148	$C_{23}H_{35}NO_2 \cdot CH_3SO_3H$	1.0 (0.74–1.4)	*i* at 80	4.3 ± 0.52	
10i	$(CH_2)_2CH(CH_3)_2$	229–231	$C_{24}H_{37}NO_2 \cdot HCl$	2.0 (1.5–2.4)	*i* at 80	16 ± 3.3	2.4 (1.3–3.8)
10j	$(CH_2)_3CH(CH_3)_2$	197–200	$C_{25}H_{39}NO_2 \cdot HCl$	7.5 (4.6–16)	*i* at 80	70% at 120	
morphine				0.60 (0.43–0.85)		3.9 ± 0.5	2.3 (1.1–4.0)
naloxone				60 (50–76)	0.008 (0.006–0.012)		
buprenorphine				0.059 (0.031–0.095)	0.11[i]	14% at 120	0.004 (0.002–0.008)

[a] All compounds are racemic unless otherwise indicated. [b] All compounds were analyzed for C, H, and N; analytical results were within ±0.4% of the theoretical values. [c] Acetylcholine writhing test (mouse), mg of base/kg sc (95% confidence limits). [d] Phenazocine antagonism (rat), mg of base/kg sc (95% confidence limits). [e] Tail-flick test (rat), mg of base/kg sc ± SE. [f] Intracarotid bradykinin test (rat), mg of base/kg sc (95% confidence limits). [g] This value determined on the methanesulfonate salt, mp 265–268 °C, $C_{19}H_{27}NO_2 \cdot CH_3SO_3H$. [h] Nonlinear assay. [i] Dose–response curve too flat for the determination of confidence limits.

Table II. Antagonist Activities of 3e, 3i, Naloxone, and Cyclazocine Measured against Phenazocine, Morphine, and Meperidine as Agonists

	AD_{50}, mg/kg sc			
agonist	naloxone	cyclazocine	3e	3i
phenazocine	0.008 (0.006–0.012)	0.028 (0.018–0.043)	0.008 (0.004–0.015)	0.30 (0.18–0.51)
morphine	0.004 (0.003–0.006)	0.029 (0.020–0.042)	0.098 (0.061–0.16)	0.58 (0.34–0.99)
meperidine	0.004 (0.002–0.006)	0.024 (0.017–0.034)	0.19 (0.12–0.29)	0.73 (0.43–1.2)

atoms contrasts dramatically with the series of ring-C-bridged oripavinemethanols 2, where antagonist activity is not found when the corresponding R group is extended to butyl, regardless of alcohol stereochemistry or of the substituent on the nitrogen atom.[29,30] The different structure–activity relationships for the two series may be due to the ability of the R group of 3 to interact with a portion of the receptor which is not accessible to the R group of 2 because the latter is restricted by the C_6–C_7 bond and by the intramolecular hydrogen bond.[31] This interpretation suggests that additional aspects of the pharmacology of 3e, 3i, and related compounds may be different from those observed for the more classical opioid agonists and antagonists. These studies are in progress. Compounds 3e and 3i, in view of the high antagonist potencies of these *N*-methyl derivatives, appear to be good candidates for testing the validity of our restatement of the Keats and Telford suggestion.[32]

Experimental Section

Melting points were determined by the capillary method and are uncorrected. IR, NMR, and mass spectra substantiated the structures of all new compounds. Where analyses are indicated by the symbols of the elements, analytical results are within ±0.4% of the theoretical values.

Ethyl 3-[(4-Methoxyphenyl)methyl]-2,4,8-trimethyl-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (6). To 2000 mL of a stirred 0.16 M ethereal solution of 4-$CH_3OC_6H_4CH_2MgCl$ was added 50.5 g (0.25 mol) of **5**. Stirring was continued at room temperature overnight. The reaction was quenched with 1000 mL of saturated aqueous NH_4Cl. Drying and evaporation of the ether layer left a residue, which was immediately taken up in 250 mL of benzene and 54 mL (0.5 mol) of ethyl acrylate and refluxed overnight. The cooled mixture was diluted with ether and extracted twice with 250 mL of 1 N HCl. The combined extracts were basified with NH_4OH and extracted with ether, and the extracts were dried, filtered, and evaporated to give 70.8 g of a syrup. This was taken up in 700 mL of acetone and a solution of 26.5 g (0.21 mol) of $(COOH)_2 \cdot 2H_2O$ in 265 mL of acetone was added. Crystallization at room temperature gave a first crop of 26.1 g, mp 185–200 °C. NMR and mass spectra showed this material to be isomeric with **6** and was not characterized further. Two additional crops (33.0 g; mp 150–154 °C and 6.1 g; mp 150–155 °C) were obtained for a total yield of 36%. This material was of adequate purity for chemical purposes. An analytical sample was obtained by conversion of a sample of the crude oxalate to the base and then back to the oxalate, mp 154–157 °C. Anal. [$C_{21}H_{29}NO_3 \cdot (COOH)_2$] C, H, N.

(2α,3β,4aβ,5α,10aβ)-(±)-Ethyl 1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-1,4a,5-trimethyl-2,5-methanobenzo[*g*]quinoline-3-carboxylate (7c). To 31.6 g (0.073 mol) of **6** as the crude oxalate was added liquid hydrogen fluoride to a final volume of 300 mL. After standing at room temperature for 24 h, excess hydrogen fluoride was allowed to evaporate. The residue in 300 mL of water was basified with ammonium hydroxide and extracted twice with ether. Drying and evaporation of the extracts left 22.5 g of a syrup, which crystallized from 90 mL of 95% ethanol: 17.8 g, mp 97–100 °C. A second crop was obtained (2.7 g; mp 95–97 °C) for a total yield of 82%. Two recrystallizations from hexane gave material with mp 98–100 °C. Anal. ($C_{21}H_{29}NO_3$) C, H, N.

General Procedure for the Acylation of the Ester 7c. A solution of 0.165 mol of butyllithium in hexane was stirred under nitrogen and cooled to −10 °C. A solution of 0.165 mol of diisopropylamine in 300 mL of tetrahydrofuran (THF) was added in a fine stream. The reaction mixture was then cooled to below −70 °C and 0.15 mol of **7c** in 300 mL of THF was added dropwise. Following this addition a solution of 0.165 mol of the acid chloride in 300 mL of THF was added. Following this addition, the reaction mixture was allowed to come to room temperature and poured into 750 mL of water. The aqueous layer was extracted twice with ether, and the combined organic layers were washed with brine, dried, and evaporated. This residue was partitioned between 800 mL each of 0.1 N hydrochloric acid and ether. The ether layer was washed with water, and the combined aqueous layers were washed once with ether, combining the ether layers. Drying and evaporation of the latter yielded a residue suitable for use in the ring-opening reaction. The aqueous layer was basified with ammonium hydroxide and extracted with ether, and the extract was dried and evaporated to yield the **7c** epimers suitable for reuse in the acylation.

(2α,3β,4aβ,5α,10aβ)-(±)-Ethyl 1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-1,4a,5-trimethyl-3-(4-methyl-1-oxopentyl)-2,5-methanobenzo[*g*]quinoline-3-carboxylate (8a). This compound was obtained by crystallization from pentane of the ether residue after acid extraction as described above, mp 97–100 °C. Anal. ($C_{27}H_{39}NO_4$) C, H, N.

General Procedures for Reductive Ring Opening of Keto Esters 8. A. Formic Acid/Mesitylene Method. The ether layers' residue from the acylation procedure was dissolved in 10 volumes of mesitylene. Then 0.13 mL of formic acid per 1 mL of mesitylene was added, and the mixture was stirred and refluxed for 22 h. The cooled mixture was treated with 1 equiv of 10% sodium hydroxide, and the mesitylene layer was dried and evaporated. The products were obtained from this residue by crystallization of the base or salt from EtOH or MeOH with or without added Et_2O.

B. TMAF Method. For each gram of **8**, 5 mL of TMAF[21] was used. The mixture was held at 150–160 °C for 15 min. After cooling, the mixture was diluted with H_2O, basified with 10% NaOH, and extracted twice with Et_2O. The combined extracts were washed twice with H_2O, dried, filtered, and evaporated. The products were obtained from this residue as described in section A.

Conversion of the Methyl Ethers 10 to the Phenols 3. For each gram of **10**, 5–10 mL of 48% HBr was used. The mixture was refluxed for 1 h, cooled, basified with NH_4OH, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated. The product may be obtained from this residue by crystallization of a salt from MeOH or EtOH, with or without added Et_2O. Isolated yields were generally 70–75%.

Resolution of 3e and 3i. A solution of 6.3 g (0.04 mol) of *d*-mandelic acid and 29.2 g (0.08 mol) of **3e** base in 525 mL of acetone was allowed to crystallize in an ice bath. The solid was filtered, washed with ice-cold acetone, and air-dried to give 12.9 g of *d*-mandelate salt. The filtrate was evaporated and the residue partitioned between dilute NH_4OH and Et_2O. Drying and evaporation of the Et_2O left 18.5 g of syrup, which was combined with 6.3 g (0.04 mol) of *l*-mandelic acid in 525 mL of acetone. After cooling the mixture in an ice bath, the solid was filtered, washed with ice-cold acetone, and air-dried to give 14.4 g of *l*-mandelate salt. The filtrate was treated as just described to give 6.6 g of syrupy base, which was then treated with 1.5 g of *d*-mandelic acid in 125 mL of acetone to give an additional 3.4 g of *d*-mandelate salt. The combined *d*-mandelate salts were recrystallized twice from acetone to give 9.3 g: mp 196–198 °C; $[\alpha]^{25}_D$ −5.2° (*c* 1.0, EtOH). A sample of this salt was converted to the base using dilute NaOH and Et_2O; the base was then converted to (−)-**3e** methanesulfonate salt, which crystallized from MeOH/Et_2O: $[\alpha]^{25}_D$ −25.7° (*c* 1.13, EtOH).

The *l*-mandelate salt was purified by recrystallization from

acetone: mp 195–197 °C, $[\alpha]^{25}_D$ + 5.3° (*c* 1.06, EtOH). Conversion to the base and treatment as described above gave (+)-**3e**·CH_3SO_3H $[\alpha]^{25}_D$ + 26.7° (*c* 1.12, EtOH).

Compound **3i** was similarly resolved. The *d*-mandelate salt had mp 190–192 °C, $[\alpha]^{25}_D$ −6.9° (*c* 1.01, EtOH), and gave (−)-**3i**·HCl from EtOH/Et_2O, $[\alpha]^{25}_D$ −32.2° (*c* 1.00, EtOH). The *l*-mandelate salt had mp 191–193 °C and gave (+)-**3i**·HCl from EtOH/Et_2O, $[\alpha]^{25}_D$ +32.1° (*c* 1.00, EtOH).

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References and Notes

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