TABLE II

ANTIINFLAMMATORY ACTIVITY[a]

No.	Dose,[b] mg/kg	Inhib of edema[c]	Toxicity[d]
1	2.5	27.8	−
	10	46.0	−
	50	54.4	−
	200	67.1	−
2	200	8.0	−
3	200	19.7	−
4	200	0	−
5	200	5.5	−
6	50	41.2	−
	100	52.9	−
	200	68.8	+
7	50	30.2	−
	100	44.6	−
	200	70.9	−
8	200	8.7	−
9	200	0	−
10	200	33.0	+++
11	200	19.7	−
Indomethacin	2.5	31.3	−
	10	56.6	++
	20	57.5	+++
Phenylbutazone	50	30.4	−
	100	40.6	−

[a] Antiinflammatory activity was evaluated by the inhibitory effect on rat paw edema induced by injection of 0.05 ml of 1% carrageenin in sterile 0.9% NaCl.[2] [b] Test compounds were administered orally 1 hr before the injection of carrageenin. At each dose level, three to six rats were used. [c] Foot volume was measured at 3, 4, and 5 hr after the carrageenin injection and the mean of three measurements was calculated in each rat. Inhibition of edema is expressed as $(1 - T/C) \times 100$, where T is mean edema volume of treated group and C is the mean volume of control group. [d] −, no blood in feces, body weight gain normal; +, no blood in feces, body weight decreased; ++, blood in feces, body weight decreased; +++, symptoms of ++ but some animals died during the 4 days after administration.

6 ml of AcOH was heated at 90–100° for 1 hr. After cooling, the reaction mixture was poured into 600 ml of cold H_2O. A resultant oily substance was extracted (Et_2O), and the etheral layer was washed (H_2O) and dried (Na_2SO_4). The solvent was removed by distillation to give 3.2 g of an oily residue, which was chromatographed on silica gel and eluted with $CHCl_3$. Recrystallization (MeOH) gave 1.1 g (31%) of yellow needles of ester, mp 86–86.5°.

Ethyl 1-cinnamoyl-5-methoxy-2-methyl-3-indolylacetate (6) was prepared analogously, mp 68–69° (from EtOH–H_2O).

Pharmacological Tests.—Antiinflammatory activity of these compounds was tested in carrageenin-induced foot edema of rats.[2] Test materials were suspended in 0.5% solution of sodium carboxymethylcellulose and given by stomach tube 1 hr before the injection of carrageenin. For toxicity tests of these compounds, blood in feces was determined the day after the carrageenin test and the body weight of each rat was recorded daily for the following 4 days. These results are expressed as percentage of the inhibition in Table II.

Acknowledgments.—The authors are indebted to Messrs. Yasushi Nakamura, Seitetsu Arasaki, and Tsuyoshi Kobayashi for technical assistance, Messrs. C. Saito and H. Awata for the pharmacological screening data, and Mr. Iwai and coworkers for the elementary analytical data.

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Absolute Configuration of Some Benzomorphan Analgetics and Related Compounds

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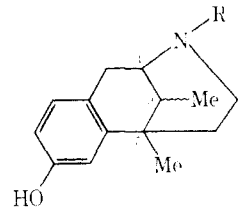
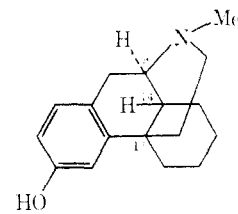
The analgetic potency of several 6,7-benzomorphan derivatives **1** is influenced both by the relative con-



1a. R = Me
b. R = $(CH_2)_2Ph$
c. R = $CH_2CH{=}CMe_2$
d. R = CH_2-c-C_3H_5
e. R = H
f. R = $CH_2CH{=}CH_2$



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figurations of the 5,9-dimethyl substituents (β diastereoisomers are more potent than α forms) and by absolute configuration within a particular enantiomorphic pair (in all cases examined, the activity of both α and β racemates largely resides in the *levo* antipode).[1,2] In related derivatives that are analgetic antagonists (*e.g.*, **1c** and **d**), activity differences between (±) diastereoisomers are insignificant, but pronounced potency variations among enantiomers are still found.[3] The relative 5,9-dialkyl configurations of several benzomorphan diastereoisomers are known (α-*cis* and β-*trans* with respect to the hydroaromatic ring) from rates of quaternization and pmr data,[4] and a recent X-ray analysis of the α-N-allyl derivative (**1f**)[5] supports these assignments. Knowledge of absolute configuration is confined to the α-(−)-5,9-diethyl analog of **1a** which has been shown to share common geometry with (−)-morphine through its synthesis from an intermediate derived from natural thebaine,[6] although there is evidence by the method of stereoselective adsorbents[7] that α-(−)-metazocine (**1a**) and phenazocine (**1b**) are both related to morphine. Ord data are now presented which (along with some chemical transformations) firmly establish the absolute configurations of benzomorphan enantiomers of both the α and β type.

Numerical characteristics of ord curves recorded for α-(−)- and β-(+)-**1a** (metazocine), levorphanol, and related compounds in EtOH or H_2O are shown in Table I. All samples exhibit Cotton effects attributed to the phenolic chromophore because the midpoints between

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TABLE I

NUMERICAL CHARACTERISTICS OF ORD CURVES OF α-(−)- AND β-(+)-2′-HYDROXY-2,5,9-TRIMETHYL-6,7-BENZOMORPHAN AND OF LEVORPHANOL

No.	Isomer	Form	λ_{max}, mμ	Mol rotation, [φ], deg
1	α-(−)-**1a**	Base	293 trough	−40,425
			275 peak	+8,800
			244[a]	−6,125
2		HBr	289 trough	−31,225
			276 peak	+31,820
			273[b]	+20,605
			260[b]	+6,240
			247 trough	−7,175
3		MeI	288 trough	−39,910
			272 peak	+32,095
			269[b]	+16,875
			263[b]	+10,440
4	β-(+)-**1a**	Base	294 peak	+37,975
			272 trough	−3,675
			240 peak	+7,360
5		HBr	290 peak	+34,500
			270 trough	−6,240
			245 peak	+6,240
6		MeI	290 peak	+33,570
			268 trough	−8,390
			253 peak	Near zero
7	Levorphanol[c] (**2**)	Base	290 trough	−40,460
			288[b]	−33,050
			268 peak	+16,190
8		HCl	291 trough	−45,320
			268 trough	+18,880

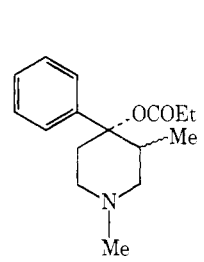
[a] Limit of measurement. [b] Fine structure. [c] A. F. Casy and M. M. A. Hassan, *J. Pharm. Pharmacol.*, **19**, 132 (1967).

trough and peak wavelengths are close to the uv maximum range of simple phenols. The sign of Cotton effects is governed chiefly by the immediate stereochemical environment of the chromophore[8] and will therefore reflect C-5 rather than C-9 geometry in the benzomorphans since the latter asymmetric feature is further removed from the phenolic function. The identity of Cotton effect sign and the similarity of peak and trough characteristics of the ord curves of (−)-metazocine and levorphanol (**2**) (Table I, **1**, **7**) establish the configurational identity of their corresponding C-5 and C-13 centers, while the identity of 1–9 and 9–14 centers follows from established relative configurations. Since the absolute configuration of levorphanol is known,[9] that of α-(−)-metazocine is *1R*:*5R*:*9R*. The virtual mirror-image relationship of the α-(−)- and β-(+)-metazocine ord curves (Table I, **1**, **4**) establishes the C-5 configurational identity of α-(−) and β-(−) isomers and demonstrates the negligible influence of C-9 geometry upon ord characteristics of the benzomorphans in the 240–350-mμ region. Hence the absolute configuration of β-(−)-metazocine is *1R*:*5R*:*9S*.

Since variations in ord properties have proved a sensitive probe for the detection of conformation changes in appropriate cases,[8] hydrohalides and methiodide salts were included in this study (pmr evidence of conformational differences between α- and β-benzomorphan bases and salts will be given elsewhere). Ord curves of the β-base–HBr–MeI **1a** trio showed only minor differences, the most notable being a progressive depression and shift to longer wavelengths in the salt curves of the 240-mμ peak of the base (Table I, **4**–**6**). The conformational significance of this change is doubtful, however, because curves of the α-trio (compounds in which marked conformational differences are unlikely) also showed small differences (the broad 275-mμ peak of the α-base became sharper and developed fine structure on its lower wavelength shoulder in the salts) (Table I, **1**–**3**). The absence of conclusive ord data of conformational change in the β-benzomorphans further reflects the lack of influence of asymmetric portions of the molecule more than one carbon atom removed from the phenolic chromophore upon ord characteristics.

It follows that C-5, rather than C-9 geometry has the predominant influence upon activity in diastereoisomeric benzomorphans since both analgetic or analgetic-antagonist properties of the (±) derivatives **1a**–**d** reside largely in the α-(−) or β-(−) enantiomers, all of which have a *5R* configuration.[1-3] Stereochemical correlations follow from the facts that α-(−)-**1b** derives from α-(−)-**1a**[10] which is formed by reductive methylation of α-(−)-**1e** (this work); the same secondary base yields α-(−)-**1c** and -**1d**[11] while β-(+)-**1e** yields β-(+)-**1c** and -**1d**[11] and **1a** (this work).

Configurational influences upon activity in benzomorphan and prodine diastereoisomers provide evidence of comparative drug–receptor uptake modes in the two classes, the C-3 and -4 asymmetric centers of the prodines being analogous to those at C-9 and -5, respectively, of the benzomorphans (see **3** and **4**). The



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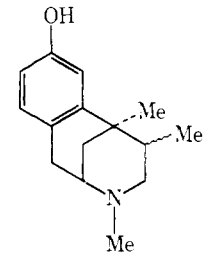

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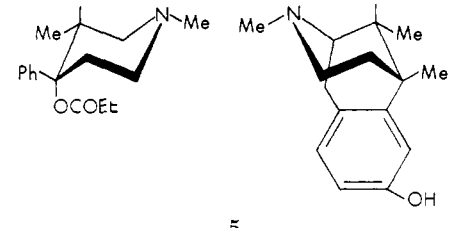
configurations of α-(+)- and β-(+)-prodine have recently been assigned as *3R*:*4S*(α) and *3S*:*4S*(β).[12] These results establish the governing influence of C-4 stereochemistry (as found for C-5 in the benzomorphans) but also show that the more active enantiomers of the prodines and metazocines bear a mirror-image relationship with reference to the piperidine ring as shown in **5** for the α isomers drawn in their most favored conformations. This finding lends further support to



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(11) N. F. Albertson, private communication.

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the view of differing uptake modes for 4-phenylpiperidine analgetics and fused-ring derivatives containing the same structural feature, already advanced on the basis of comparative structure–activity relationships.[13]

Experimental Section

Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points, determined with a Fisher-Johns apparatus, are uncorrected. Ord curves were recorded with a Cary Model 60 photoelectric spectropolarimeter using 0.1–0.2% solutions in EtOH or H_2O (we thank Mr. K. O. Oikawa, University of Alberta, for this data). Supply of α-(−)- and β-(+)-**1e** by Dr. N. F. Albertson of the Sterling Winthrop Research Institute, Rensselaer, is gratefully acknowledged.

Isomeric 1,5,9-Trimethylbenzomorphans (1a) and Derivatives.—A mixture of α-(−)-**1e** (0.7 g), 40% CH_2O solution (0.45 ml), 5% Pd–C (0.16 g), and EtOH (25 ml) was shaken with H_2 (atmospheric pressure, room temperature) until gas absorption ceased. The product was filtered and the filtrate was concentrated to give α-(−)-**1a**, mp 184–186° (lit.[14] 183–184.5°). It gave a **hydrobromide,** mp 248–250° (lit.[14] 238–241°). Reductive methylation of β-(+)-**1e** gave β-(+)-**1a**, mp 181–183° (lit.[14] 183–184.5°), hydrobromide mp 274–276° dec (lit.[14] 238–242°). *Anal.* ($C_{13}H_{22}BrNO$) C, H. A mixture of α-(−)-**1a** (0.2 g), MeI (1 ml), and $CHCl_3$ (300 ml) was stirred at 38° under reflux for 5 days, concentrated to 25 ml, and diluted with Et_2O. The solid which separated was recrystallized from EtOH–Et_2O to give α-(−)-**1a methiodide,** mp 240–245°. *Anal.* ($C_{16}H_{24}INO$) C, H, N. β-(+)-**1a methiodide** was prepared similarly, mp 312–316°. *Anal.* C, H.

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A Racemic Form of 5-Ethyl-5-(3-hydroxy-1-methylbutyl)barbituric Acid as a Metabolite of Pentobarbital[1]

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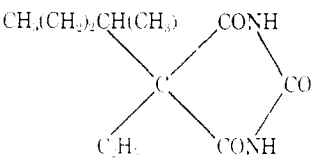
The availability of the racemic form of 5-ethyl-5-(3-hydroxy-1-methylbutyl)barbituric acid (II), recently synthesized by Dickert, Shea, and McCarty,[2] prompts us to report the isolation of this compound from the urine of dogs given anesthetic doses of pentobarbital (I). Following the removal of the (+) and (−) diastereoisomers in the reported manner,[3] the new metabolite separated from the filtrate as long, blunt needles. Elementary analysis, the uv spectrum, and a positive iodoform test suggested its probable structure. The melting points of the pure compound and its acetate derivative differed from those of the optically active isomers. However, the chromatographic behavior and ir spectrum of the racemic product were identical with those of the (+) enantiomorph. The new metabolite did not depress the melting point of the synthetic compound.



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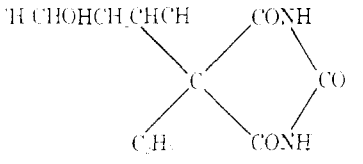

II

The discovery of the racemic alcohol in urine increases the probability that all four enantiomorphs of 5-ethyl-5-(3-hydroxy-1-methylbutyl)barbituric acid are involved in the metabolism of pentobarbital. Isotope dilution experiments with the optically active diastereoisomers[3,4] have undoubtedly given an erroneously low estimate of the quantitative importance of the urinary excretory products derived from penultimate oxidation of the drug. In dogs the two unconjugated alcohols accounted for about 50% of the excreted isotope.[3] Inasmuch as the usual chromatographic methods do not distinguish between the corresponding optically active and racemic forms, the estimates of Titus and Weiss[5] probably include the unknown enantiomorphs. Their data indicated that the unconjugated penultimate alcohols accounted for 62% of the recovered isotope.

Inasmuch as the sum of the conjugated and unconjugated optically active forms of 5-ethyl-5-(3-hydroxy-1-methylbutyl)barbituric acid exceeds 50% of the dose of pentobarbital,[5,6] these metabolites must be formed from different optical isomers of the drug. The strongly dextrorotatory ($[\alpha]^{28}D$ +26.6°) alcohol may be presumed to be derived from the *d* enantiomorph of pentobarbital by the addition of another *d* center. The weakly levorotatory ($[\alpha]^{28}D$ −5.6°) metabolite would then involve the *l* form of the drug and the same *d* center introduced by hydroxylation. On this basis the new metabolite may be designated as *dd* + *ll*. Since this substance depressed the melting point of the *dd* form, it is probably a racemic compound rather than a racemic mixture. An attempt to racemize the *dd* alcohol did not succeed.

Experimental Section[7]

Optically Active Isomers of 5-Ethyl-5-(3-hydroxy-1-methylbutyl)barbituric Acid (II).—The 24-hr urine from 15 dogs given 12.5 g (50 mg/kg) of sodium pentobarbital by mouth was brought to pH 6.5 and extracted continuously with ether for 48 hr. The combined extracts (1750 ml) were shaken ten times with 150-ml portions of H_2O. After evaporation *in vacuo* to 15 ml and brief storage at 4°, the aqueous extract deposited 612 mg of the crude dextrorotatory alcohol. Reduction of the volume of the filtrate to 3 ml yielded 1490 mg of the crude levorotatory alcohol. Both alcohols were purified as described previously.[3]

No evidence of racemization was detected when a saturated aqueous solution of the pure dextrorotatory alcohol was heated in a sealed tube at 100° for 24 hr.

(1) This work was supported by U. S. Public Health Service Research Grant NB-06288. Technical assistance by Mrs. Dorothy Lang is gratefully acknowledged.
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