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B/C-*cis*- and -*trans*-1,3,4,9,10,10a-Hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (Homo- and Homoisomorphinan) Derivatives as Analgesics

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N-Alkyl derivatives of B/C-*cis*- and B/C-*trans*-6-hydroxy-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene have been prepared. The analgesic potency and physical dependence capacity of these compounds were determined. The *N*-methyl derivatives were analgesically equipotent with morphine. None of these compounds except the *N*-methyl-B/C-trans isomer **2b** suppressed or precipitated the abstinence syndrome. Compound **2b** was a narcotic agonist. The *N*-methyl-B/C-cis compound **2a** appears to warrant further examination for its potential as a potent analgesic having no physical dependence liability.

Chemical modifications of 6,7-benzomorphan and morphinan have produced many compounds possessing interesting profiles with respect to narcotic antagonist and analgesic activities.[1] The structure–activity effects of substituents at positions 2, 5, 9, and 2′ of 6,7-benzomorphan and positions 3, 4, and 17 of morphinan have been intensively studied.

In order to investigate further the structure–activity relationships of 6,7-benzomorphans and morphinans, we have designed compounds where ring C of 6,7-benzomorphan or ring D of morphinan has been modified by introducing an extra methylene group between the nitrogen and bridgehead carbon (homobenzomorphan and homomorphinan).[2] This modification creates a somewhat conformationally flexible nitrogen-containing ring and should affect the steric environment around the nitrogen and above the aromatic ring. The importance of this steric environment for binding to the receptor site has been proposed by Lewis,[3] Belleau,[4] and Cochran.[5]

On the other hand, it has been reported that replacement of the *N*-methyl group of 6,7-benzomorphan and morphinan by an allyl or a cyclopropylmethyl group furnishes good narcotic antagonist activity.[6] It was, therefore, of interest to introduce these substituents into the homobenzomorphan or homomorphinan skeleton and to evaluate the effect of these modifications on the antagonistic and other pharmacological properties.

In this paper we report the synthesis of *N*-allyl (**5a,b**) and *N*-cyclopropylmethyl (**7a,b**) derivatives of B/C-*cis*- (homo-) and -*trans*-6-hydroxy-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (homoisomorphinan) and the analgesic potency, antagonistic activity, and physical dependence capacity of these compounds as well as the *N*-methyl derivatives **2a,b**.

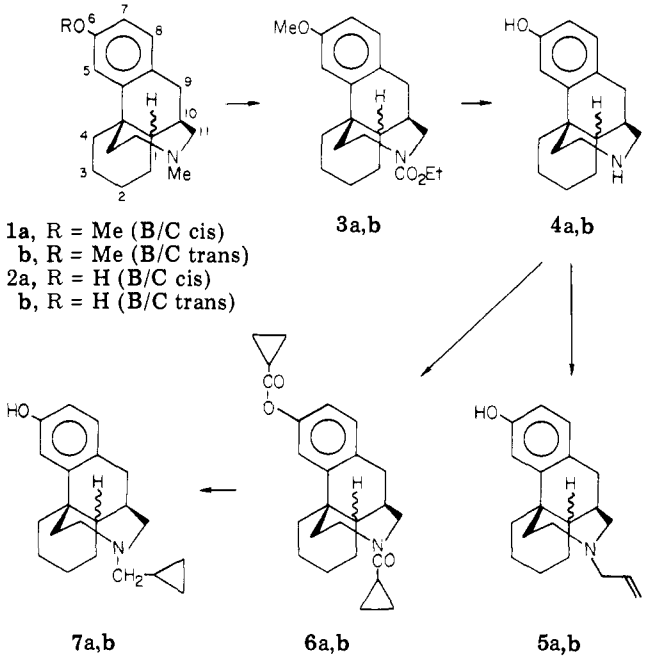
Chemistry. The synthesis of *N*-methyl derivatives of homo- and homoisomorphinan **1a**, **1b**, **2a**, and **2b** was reported in our previous paper.[2a] Treatment of the *N*-methyl derivative **1a** with $ClCO_2Et$ in refluxing benzene gave carbamate **3a**.[7] When refluxed with 12 M HCl, the 6-methoxy carbamate **3a** was converted to the 6-hydroxy-*N*-nor compound **4a**. Alkylation of **4a** with allyl bromide gave the *N*-allyl compound **5a**.[6b,8] Compound **4a** was acylated with cyclopropylcarbonyl chloride followed by lithium aluminum hydride reduction to give 6-hydroxy-*N*-cyclopropylmethyl derivative **7a**.[6b,8] Homoiso counterparts **4b**, **5b**, and **7b** were obtained from **1b** by similar procedures.

Pharmacology. In Table I are given analgesic activities (Eddy hot-plate test[9,10]) and physical dependence capacities [monkey, single-dose suppresion (SDS)[10]] of compounds **1a**, **1b**, **2a**, **2b**, **5a**, **5b**, **7a**, and **7b**. These compounds, except **5a**, exhibit good analgesic potencies ranging from the morphine to codeine level, maximum activity being shown by compound **2a**. The 6-methoxy

Table I. Analgesic Activity and Physical Dependence Capacity (PDC) of Homo- and Homoisomorphinan Derivatives

Compd	ED_{50},[a] mg/kg	PDC[b]
1a[c]	3.4 (2.3-5.2)	
2a·HBr	0.8 (0.6-1.1)	None[d]
5a[c]	Inactive	None[e]
7a[c]	6.2 (4.5-8.5)	None[f]
1b[c]	8.1 (5.8-11.2)	
2b·HBr	2.1 (1.6-2.8)	High[g]
5b[c]	19.6 (12.9-29.8)	None[h]
7b[c]	~15[i]	None[h,j]
Morphine hydrochloride	1.2 (0.9-1.3)	High

[a] Eddy hot-plate assay (95% SE limits), sc injection, mice (ref 9 and 10). [b] Physical dependence capacity, monkey, single dose suppression (ref 10). [c] Titrated with dilute HCl for solution. [d] Neither suppressed nor precipitated abstinence at 0.4-6.4 mg/kg. [e] Neither suppressed nor precipitated abstinence at 0.5-1.0 mg/kg. [f] Neither suppressed nor precipitated abstinence at 0.5-8.0 mg/kg. [g] Incomplete suppression of abstinence at 4.0 mg/kg, a narcotic agonist, less potent and shorter acting than morphine. [h] Neither suppressed nor precipitated abstinence at 0.5-4.0 mg/kg. [i] Toxic at 50 mg/kg. [j] There appears to be a delay in the development of abstinence signs, though the drug does not reverse existing signs or alter the ultimate severity of the syndrome.



derivatives **1a** and **1b** are about one-fourth as potent as the corresponding 6-hydroxy derivatives **2a** and **2b**. Replacement of the *N*-methyl group by allyl or cyclopropylmethyl significantly decreases activity. These tendencies are similar to those of the 6,7-benzomorphan and morphinan series.[6] It is noteworthy that B/C-cis isomers are more potent than trans isomers. The configuration at position 10a of the former corresponds to that of position 14 of morphinan, and the configuration of the latter corresponds to that of isomorphinan (morphinans are less potent than isomorphinans in analgesic activity[1a]).

As for physical dependence capacity in the rhesus monkey, compounds **2a**, **5a**, **5b**, **7a**, and **7b** did not suppress the morphine abstinence syndrome and could be said to have no physical dependence capacity.[10] Most remarkably, the B/C-*cis*-6-hydroxy-*N*-methyl compound **2a**, a potent analgesic, neither suppressed nor precipitated abstinence, one of the few analgesically potent morphine-like structures which appears to have no physical dependence liability.[11] The B/C-*trans*-6-hydroxy-*N*-methyl compound **2b**, comparable with morphine in analgesic activity, suppressed abstinence.

Interestingly, none of the *N*-allyl and *N*-cyclopropylmethyl derivatives (**5a**, **5b**, **7a**, and **7b**) appeared to have any narcotic antagonist activity, judged by the lack of precipitation of abstinence syndrome in the morphine-dependent monkey. These results were somewhat unexpected as several reports have indicated that there exists a definite association between the analgesic potency of the *N*-methyl compound and the antagonist potency of its *N*-allyl or *N*-cyclopropylmethyl counterparts for rigid, morphine-like structures.[12]

We have found a new series of compounds having unique correlation between analgesic activity, antagonist potency, and physical dependence capacitiy. The B/C-*cis*-6-hydroxy-*N*-methyl compound **2a** appears to warrant further examination for its potential as a potent analgesic having no dependence liability.

Experimental Section

All melting points were determined with a micromelting point apparatus (Yanagimoto) and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyama. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical values. IR spectra were recorded on a Japan Spectroscopic IR-E spectrophotometer. NMR spectra were recorded, at 100 MHz, on a JEOL MH-100 spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a JEOL JMS-01SG mass spectrometer. All structures are consistent with IR, NMR, and mass spectral data.

B/C-*cis*- (4a) and -*trans*-6-Hydroxy-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (4b). $ClCO_2Et$ (1.2 g, 11.1 mmol) was rapidly added to a refluxing solution of **1a** (1.97 g, 6.9 mmol) in C_6H_6 (70 mL). The mixture was refluxed for 3 h. The cooled mixture was washed with 10% HCl and H_2O and dried. Evaporation of the C_6H_6 gave 2.3 g (97.5%) of carbamate **3a**.

A mixture of carbamate **3a** (2.31 g, 6.7 mmol), 12 M HCl (40 mL), and and AcOH (25 mL) was refluxed for 40 h. The reaction mixture was evaporated, and the residue was dissolved in H_2O, basified with 20% NaOH solution, and extracted with Et_2O. The aqueous layer was neutralized with 12 M HCl, basified with 12 M NH_4OH, and extracted with $CHCl_3$. After drying, the solvent was removed in vacuo to give 1.3 g (75%) of crude **4a** as a colorless solid mass. Recrystallization from MeOH–Me_2CO gave pure **4a**, mp 203–207 °C. Anal. ($C_{17}H_{23}NO$) C, H, N.

Compound **4b** was obtained from **1b** by a similar procedure in 65% yield: mp 216–220 °C (from MeOH–Me_2CO). Anal. ($C_{17}H_{23}NO$) C, H, N.

B/C-*cis*- (5a) and -*trans*-6-Hydroxy-12-allyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (5b). A mixture of **4a** (100 mg, 0.36 mmol), allyl bromide (100 mg, 0.83 mmol), and K_2CO_3 (250 mg) in DMF (2.5 mL) was heated at 95–100 °C for 3 h. After cooling, the mixture was diluted with H_2O, basified with 12 M NH_4OH, extracted with $CHCl_3$, and dried. The residue from the $CHCl_3$ solution was chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (9:1) gave 90 mg (78%) of **5a** as a colorless syrup: mass spectrum *m/e* 297.212 (M^+, calcd for $C_{20}H_{27}NO$, 297.209).

Similarly, compound **5b** was obtained by allylation of **4b** in 80% yield. **5b·HBr** gave mp 220-225 °C (from MeOH–Me_2CO). Anal. ($C_{20}H_{27}NO$·HBr) C, H, N.

B/C-*cis*- (7a) and -*trans*-6-Hydroxy-12-cyclopropylmethyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (7b). To a solution of **4a** (100 mg, 0.39 mmol) in pyridine (2.5 mL) was added cyclopropylcarbonyl chloride (350 mg, 3.35 mmol) with stirring and ice cooling. After an additional hour with stirring at room temperature, the mixture was poured into ice-cooled 10% HCl (50 ml) and then extracted with Et_2O. The Et_2O layer was washed with 20% NaOH and H_2O and dried. Evaporation of the solvent gave 150 mg (100%) of

the 6,7-bis(cyclopropylcarbonyl) derivative **6a** as a light-yellow syrup. This was refluxed with $LiAlH_4$ (0.3 g, 7.9 mmol) in THF (50 mL) for 3.5 h. The cooled mixture was treated with saturated Rochelle salt solution, extracted with $CHCl_3$, and dried. Evaporation of the solvent gave 110 mg (92.6%) of **7a** as colorless crystals. Recrystallization from Me_2CO-Et_2O gave pure **7a**, mp 170–172 °C. Anal. ($C_{21}H_{29}NO$) C, H, N.

Compound **7b** was obtained from **4b** by similar acylation and the subsequent reduction in 90% yield: mp 140–141.5 °C (from Me_2CO-Et_2O). Anal. ($C_{21}H_{29}NO$) C, H, N.

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Agonist Effects of β-Phenethylamines on the Noradrenergic Cyclic Adenosine 3′,5′-Monophosphate Generating System in Rat Limbic Forebrain. Stereoisomers of *p*-Hydroxynorephedrine

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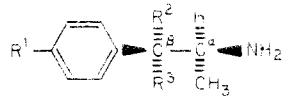
Significant agonist activity for the specific noradrenergic cyclic adenosine 3′,5′-monophosphate (cAMP) generating system in rat limbic forebrain requires a β-3,4-dihydroxyphenethylamine with a β-hydroxyl group in the *R* configuration. Thus, neither of the enantiomers of *p*-hydroxynorephedrine nor of *p*-hydroxynorpseudoephedrine mimics the agonist activity of (*R*)-norepinephrine. It has yet to be established whether or not one of the *p*-hydroxynorephedrines exhibits antagonist activity in this same system.

In rats, (*S*)-amphetamine (*d*-amphetamine) [(*S*)-**1**] is converted predominantly in the liver to (*S*)-*p*-hydroxyamphetamine [(*S*)-**2**]. The latter is then transported to



(*S*)-**1**, $R^1 = R^2 = R^3 = H$
(*S*)-**2**, $R^1 = OH$; $R^2 = R^3 = H$
(α*S*,β*R*)-**3**, $R^1 = R^2 = OH$; $R^3 = H$
(α*S*,β*S*)-**4**, $R^1 = OH$; $R^2 = H$; $R^3 = OH$

the brain and converted in noradrenergic neurons by dopamine β-hydroxylase to a metabolite identified as *p*-hydroxynorephedrine.[1-3] The absolute configuration of (*S*)-**2** follows from the known absolute configuration of (*S*)-**1**,[4] and the major metabolite of (*S*)-**2** is most likely (α*S*)-*p*-hydroxynorephedrine [(α*S*,β*R*)-**3**].[5] It has not been established conclusively, however, whether the major metabolite of (*S*)-**2** is (α*S*,β*R*)-**3** or (α*S*)-*p*-hydroxynorpseudoephedrine [(α*S*,β*S*)-**4**] or whether both stereoisomers are produced together. The metabolite of (*S*)-**2**, however, can displace endogenous norepinephrine in nerve terminals and can be released upon nerve stimulation,[6] and it thus can serve as a false neurotransmitter.[7] The metabolite of (*S*)-**2** has also been implicated in the persistent reduction of brain norepinephrine after administration of (*S*)-**1** and in the development of tolerance to certain pharmacologic actions of (*S*)-**1**.[7-9]

In related studies in our laboratories, we have demonstrated that slices of the rat limbic forebrain contain a cyclic adenosine 3′,5′-monophosphate (cAMP) generating system which displays properties of a norepinephrine receptor with α and β characteristics.[10,11] Since stereoselectivity is observed for pharmacologic α- and β-receptors,[12] and since the norepinephrine receptor coupled adenylate cyclase system in the limbic forebrain shows stereoselective blockade by (+)-butaclamol,[13] it was of interest to prepare the enantiomers of *p*-hydroxynorephedrine (**3**) and *p*-hydroxynorpseudoephedrine (**4**) and to examine their effect on this receptor system in comparison with that elicited by the enantiomers of norepinephrine[14] (**5**). For a more extensive assessment of the