Benzomorphans. Optically Active and *trans* Isomers

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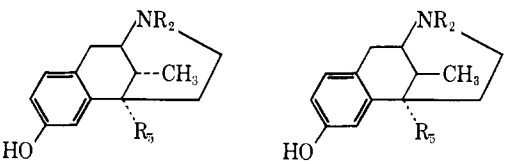
All possible stereoisomers (optical and *cis–trans*) of pentazocine and cyclazocine, as well as some related compounds, have been prepared and tested as narcotic antagonists and as strong analgetics.

In a previous communication from this laboratory,[1] the analgetic-antagonist activity of a number of N-substituted 5-methyl or -ethyl-2′-hydroxy-9-methyl-6,7-benzomorphans[2] was reported. The compounds tested were all racemic, and all had the 5,9-dialkyl groups *cis*.[3] However, it has been observed in the benzomorphan series that for 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan the analgetic activity in mice was seven times as great with the *trans* isomer as with the *cis*[4] even though the latter is more closely related sterically to morphine with its *cis*-fused B/C ring system.[5] In the case of 5-ethyl-2,9-dimethyl-6,7-benzomorphan, the *trans* isomer is again more active than the *cis* isomer.[6] This pronounced activity of the *trans* isomer extends to the morphinan series also. Gates and Webb[7] note that 3-hydroxy-N-methylisomorphinan (rings B/C *trans*) is a very potent analgetic in rats. In both series of compounds, the activity resides in the (−) isomer with little activity in the (+) isomer.

In view of the foregoing, it was desirable to extend our study to N-substituted benzomorphans of the *trans* series as well as to optically active benzomorphans in both the *cis* and *trans* series. Of special interest were the isomers of the weak antagonist pentazocine (I, R_2 = 3-methyl-2-butenyl; R_5 = methyl) and the strong antagonist cyclazocine (I, R_2 = cyclopropylmethyl; R_5 = methyl) since these compounds had been shown to be nonaddicting[8] analgetics[9] in man.

Chemistry.—May and co-workers have prepared the *cis* and *trans* isomers of 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan[10] (Ia and IIa, respectively) and of 5-ethyl-2′-hydroxy-2,6-dimethyl-6,7-benzomorphan[6] (Ic and IIc).

Both Ia and IIa were resolved at the N-methyl stage.[5,10a,11] However, our synthetic procedure[12] does not give the N-methylbenzomorphans. Accordingly,



I, *cis* II, *trans*

a, R_5 = CH_3; R_2 = CH_3
b, R_5 = CH_3; R_2 = H
c, R_5 = C_2H_5; R_2 = CH_3
d, R_5 = C_2H_5; R_2 = H

resolution was effected using the nor bases Ib and IIb and Id and IId.

cis-2′-Hydroxy-5,9-dimethyl-6,7-benzomorphan (Ib) and *trans*-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan (IId) were resolved by crystallizing the (+)-tartrates from aqueous solutions. In each case the (−)-base (+)-tartrate was the less soluble salt and was obtained in pure from by a single recrystallization from water. The salts were converted to the bases with ammonia and the bases brought to maximum rotation after a single crystallization from 95% ethanol. The crude (+)-bases, recovered from the resolution liquors, were purified through the (−)-tartrates in the same manner as for the enantiomers.

Crystallization (from 95% ethanol) of the (−)-quinic acid salts of *trans*-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIb) and of *cis*-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan (Id) gave, in each case, good separation of the *levo* base quinates. Recrystallization gave the pure *levo* salts from which the pure *levo* bases were obtained by treatment with ammonia and recrystallization from 95% ethanol.

The crude *dextro* bases were recovered by making basic the concentrated resolution liquors. They were purified by crystallization of their hydrobromides which are considerably less soluble than the racemic hydrobromides.

The N-substituted benzomorphans were prepared from the nor bases in the usual fasion. Table I summarizes the properties of the new racemic, *trans* compounds and Table II gives data for the optically active compounds.

Our assignment of the *cis* configuration to the 1,3-dichloropropene isomer boiling at 102.5° was originally made on the basis of the work of Hatch and Perry.[13] However, when we purchased a supply of supposedly *cis*-1,3-dichloropropene, vpc data showed that it contained 8.8 parts of *trans* isomer to 1 part of *cis* for a total dichloropropene content of 99%. A different supplier provided a sample, also labeled *cis*, which contained 27% *cis* and 70% *trans*; the remainder was a mixture of six compounds. Because of the discrep-

(1) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

(2) The Chemical Abstracts name is 3-substituted 1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol. For comparison with the previously prepared compounds, the benzomorphan nomenclature is being retained.

(3) The *cis* or α isomers have the 9-alkyl group in an axial position with respect to the alicyclic ring, whereas the *trans* or β isomers have an equatorial 9-alkyl group.

(4) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(5) For a discussion of the stereochemical relationships in the morphine, morphinan, and benzomorphan series, and further references see S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(6) S. E. Fullerton, J. H. Ager, and E. L. May, *ibid.*, **27**, 2554 (1962).

(7) M. Gates and W. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).

(8) H. F. Fraser and D. S. Rosenberg, *J. Pharmacol. Exptl. Therap.*, **143**, 149 (1964).

(9) A. S. Keats and J. Telford, *ibid.*, **143**, 157 (1964).

(10) (a) E. L. May, U. S. Patent 3,138,603 (1964); (b) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

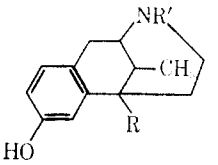
(11) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

(12) This will be reported at a later date.

(13) L. Hatch and R. Perry, *J. Am. Chem. Soc.*, **71**, 3262 (1949).

TABLE I

(±)-*trans*-BENZOMORPHAN ANALGETIC ANTAGONISTS



No.	Salt	R	R′	Mp, °C	%C Calcd	%C Found	%H Calcd	%H Found	%N Calcd	%N Found	Antagonist act., mg of base/kg *trans*	Antagonist act., mg of base/kg *cis*
1	Base	CH_3	H	209–211	77.32	77.46	8.82	8.77	6.44	6.45	...	...
2	Base	C_2H_5	H	215–217	88.52	88.68	9.14	9.10	6.07	5.95	...	...
3	HCl	CH_3[a]	CH_2-*c*-C_3H_5	242–243	70.90	71.09	8.77	8.95	11.01[b]	11.31	0.42	0.18
4	$C_2H_5SO_3H$	CH_3	CH_2-*c*-C_3H_5	233–235	62.96	62.67	8.19	8.37	8.41[c]	8.53	0.014	0.019
5	HCl	C_2H_5	CH_2-*c*-C_3H_5	271–273	70.90	70.75	8.77	8.93	11.01[b]	11.01	0.014	0.024
6	HCl	CH_3	CH_2-*c*-C_4H_7	273–275	70.90	70.04	8.77	9.05	4.35	4.51	0.06	0.37[d]
7	HBr	CH_3	$CH_3CH{=}C(CH_3)_2$	240–241	62.30	62.47	7.70	7.88	3.82	3.99	3.3	3.9
8	Base	C_2H_5	$CH_2CH{=}C(CH_3)_2$	131–132	80.23	80.35	9.76	9.86	4.68	4.60	3[e]	10.9
9	HCl	CH_3	*cis*-$CH_2CH{=}CHCl$	236–238	62.19	61.86	7.06	7.30	4.27	4.03	0.017	0.018
10	Base	CH_3	$CH_2CH{=}C{=}CH_2$	110–113	80.25	80.08	8.60	8.81	5.20	5.20	0.14	...
11	Base	CH_3[f]	$CH_2CH{=}C{=}CH_2$	152–156	80.25	80.18	8.60	8.64	5.20	5.30	...	0.11

[a] This is the 2′-methoxy compound. [b] Cl analysis. [c] S analysis. [d] This compound is also active in blocking the tail-flick reflex having an ED_{50} of 64 mg/kg or $^1/_{11}$ that of morphine. [e] This compound has an ED_{50} of 1.4 mg/kg in the tail-flick test. [f] This is the *cis* isomer.

TABLE II

No.	Salt	R_5	Optical isomer	R_5/R_9	Mp, °C	$[\alpha]^{25}D$, deg	%C Calcd	%C Found	%H Calcd	%H Found	%N Calcd	%N Found	Antagonist act., mg of base/kg
5-Alkyl-2′-hydroxy-9-methyl-2-(3,3-dimethylallyl)-6,7-benzomorphans													
12	Base	CH_3	+	*cis*	180.4–182.0	+135.5[a]					4.91	5.15	14.0
13	Base	CH_3	−	*cis*	180.6–182.2	−138.0[a]					4.91	4.83	0.9
14	HCl	CH_3	+	*trans*	254.5–255.0	+115.4[b]	70.89	70.62	8.77	8.16	4.35	4.25	13.0
15	HCl	CH_3	−	*trans*	254.0–246.0	−116.3[b]	70.89	70.82	8.77	8.62	11.01[c]	11.25	0.55
16	HCl	C_2H_5	+	*cis*	218.8–221.0	+90.7[b]	71.51	71.54	9.00	9.19	4.16	4.14	19.5
17	HCl	C_2H_5	−	*cis*	219.0–220.0	−91.7[b]	71.51	71.52	9.00	8.95	4.16	4.03	3.1
18	HCl	C_2H_5	+	*trans*	237.0–238.0	+90.7[b]	71.51	71.31	9.00	8.91	4.16	3.81	Equivocal[d] ED_{50} = inactive[e]
19	HCl	C_2H_5	−	*trans*	237.2–240.0	−90.6[b]	71.51	71.62	9.00	9.21	10.53[c]	10.25	Equivocal[d] ED_{50} = 0.34[f]
2-(Cyclopropylmethyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphans													
20	Base	CH_3	+	*cis*	195.0–196.4	+118.2[g]					5.16	5.17	2.5
21	Base	CH_3	−	*cis*	195.0–196.8	−117.2[g]					5.16	5.31	0.006
22	HCl	CH_3	+	*trans*	>300 dec	+110.0[g]					11.52[c]	11.59	10.0
23	HCl	CH_3	−	*trans*	>300 dec	−109.6[h]					11.52[c]	11.61	0.005

[a] (*c* 1, $CHCl_3$). [b] (*c* 1, 2% acetic acid). [c] Cl analysis. [d] Partial antagonism only, no dose-response relationship. [e] Inactive as an analgetic in rat tail flick test. [f] Activity in rat tail flick test; eight times morphine. [g] (*c* 1, ethanol). [h] (*c* 0.5, ethanol).

ancy between the literature assignments and the commercial assignments, samples of dichloropropene were purified by preparative, vapor phase chromatography and examined by nmr spectra. The literature assignments of Hatch and Perry were confirmed.

Biological Activity.—The compounds were tested for their ability to antagonize the effects of meperidine on the rat tail flick reflex.[14] The results obtained with the racemic, *trans* isomers are contrasted with their corresponding *cis* isomers in Table I. In the case of the N-cyclopropylmethyl (**3**–**5**), the N-*cis*-chlorallyl (**9**), and the 5,9-dimethyl-N-dimethylallyl (**7**) derivatives, there is little difference between the antagonistic potencies of the *cis* and *trans* isomers. This differs greatly from the analgetic results obtained with the N-methyl derivatives in this and the morphinan series.[3–7] On the other hand, the *trans*-N-cyclobutylmethyl compound (**6**) is six times more potent than the corresponding *cis* isomer, while the *trans*-N-dimethylallyl derivative in the 5-ethyl-9-methyl series (**8**) has only equivocal activity as an antagonist. As a matter of fact, this compound behaves like a potent analgetic in blocking the tail flick reflex. Its ED_{50} (1.4 mg/kg) indicates that it is about four times more potent than morphine in this regard. It should be mentioned that while the *cis*-N-cyclobutylmethyl compound is a relatively potent antagonist, it also has analgetic properties, being about $^1/_{11}$ as active as morphine.[15] The *trans* isomer of this compound (**6**) is a more potent antagonist with no analgetic activity. From these results it would seem that, except in the cases where there is a qualitative difference between the *cis* and *trans* isomers, configuration around the 5,9 axis does not affect the analgetic-antagonist potency of the molecule.

The results obtained with the optical isomers of the N-dimethylallyl compounds are shown in Table II. In the 5,9-dimethyl series (**12**–**15**), where there is little difference between the racemic *cis* and *trans* forms, the activity resides mainly in the (−) isomers (**13**, **15**). The (+) isomers (**12**, **14**) have only $^1/_{50}$ the potency of the (−) isomers. In the 5-ethyl-9-methyl series

(14) L. S. Harris and A. K. Pierson, *J. Pharmacol. Exptl. Therap.*, **143**, 141 (1964).

(15) S. Archer, L. S. Harris, N. F. Albertson, R. F. Tullar, and A. K. Pierson, Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 162.

(**16**–**19**), the (−) isomer of the *cis* compound (**17**) is again the most active. The separation here, however, is not as great; the (+) isomer (**16**) is nearly one-sixth as active as the (−) isomer. With the *trans* compound the antagonistic activity remains equivocal in the optical isomers. The analgetic activity, however, appears to be confined to the (−) isomer (**19**) which is 1.5 times as active as the racemic mixture (**8**).

The antagonistic activity of the optical isomers in the N-cyclopropylmethyl series is found in Table II. Again, the activity lies in the (−) isomers (**21**, **23**), but in this case the separation is very large. In the *cis* series, the (−) isomer (**21**) is over 400 times as potent as the (+) isomers. Indeed, contamination of the (+) isomers by less than 1% of (−) isomer could account for the activity seen.

Another curious fact which arises from the studies of these optical isomers is that the activity of the active or (−) isomer is consistently greater than twice that of the racemic mixture (*cf. cis*-**7** *vs.* **13**, **7** *vs.* **15**, *cis*-**8** *vs.* **21**, and **4** *vs.* **23**). It may be that the (+) isomer antagonizes the (−) isomer in a manner similar to that found by Luduena in the isoproterenol series.[16] However, experiments carried out to test this hypothesis have given no conclusive support in this regard.

Experimental Section[17]

Resolution of *cis*-2′-Hydroxy-5,9-dimethyl-6,7-benzomorphan.—The nor base (±-Ib)[18] (21.7 g, 0.1 mole) was dissolved in 250 ml of distilled water containing 7.5 g (0.05 mole) of (+)-tartaric acid. Crystallization was induced by scratching. After 1 hr at 30°, a heavy precipitate had formed. It was collected on a filter, washed with a little cold water, and dried at 60° to give 13.3 g of (−)-base (+)-tartrate, mp 305–308°.

When a solution of this salt in 400 ml of 50% aqueous ethanol was basified with excess NH_4OH and cooled to 5°, a heavy crop of *levo* base precipitated. This was collected, washed with water, and dried at 70° to give 7.6 g, mp 258–262°. After one recrystallization from 70 ml of 95% ethanol, 6.3 g of pure *levo* base was recovered. This melted at 260–262°, $[\alpha]^{25}D$ −69.3° (*c* 1, ethanol).

Anal. Calcd for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.37.

Treatment of the resolution liquor with excess NH_3 precipitated 14.0 g of crude (+)-base. A solution of this base in 270 ml of water containing 3.89 g of (−)-tartaric acid gave 8.4 g of (+)-base (−)-tartrate, mp 305–308°, after 1 hr at 25°. When this was converted to the base as above and recrystallized from alcohol, a 4.5-g crop of pure (+)-base was obtained. This melted at 260–262°, $[\alpha]^{25}D$ +70.1 (*c* 1, ethanol).

Anal. Calcd for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.43.

Resolution of *trans*-2′-Hydroxy-5,9-dimethyl-6,7-benzomorphan.—A solution of 21.7 g (0.1 mole) of (±)-IIb with 19.2 g (0.1 mole) of quinic acid in 150 ml of 95% ethanol was induced to crystallize by scratching and kept at 25° overnight. The precipitate was collected, washed with cold 95% ethanol, and dried at 60° to give 18.1 g of crude *levo* base which, after recrystallization from absolute ethanol, amounted to 7.5 g, mp 202–204°, $[\alpha]^{25}D$ −54.2° (*c* 1, ethanol).

Anal. Calcd for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.48.

After the resolution liquor was concentrated *in vacuo*, the residue dissolved readily in 100 ml of water and was made basic with NH_3. The precipitate which separated at 5° (after several hours) was collected, washed with cold water, and dried at 60° to give 11.0 g of crude (+)-base. This was dissolved in 150 ml of absolute ethanol with a slight excess of concentrated HBr and cooled to 5° for 1 hr to give 7.2 g of (+)-hydrobromide, mp 295–308°. On further standing, 4.5 g of somewhat less pure (+)-hydrobromide, mp 285–290°, separated and was purified by recrystallization from 50 ml of water to give 2.8 g, mp 305–315°. Recrystallization of these two combined crops from 200 ml of absolute ethanol gave 7.0 g of pure (+)-hydrobromide, mp >325°. Reconversion to base in the usual way gave 4.5 g of pure (+)-base, mp 202–204°, $[\alpha]^{25}D$ +54.7° (*c* 1, ethanol).

Anal. Calcd for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.32.

Resolution of *cis*-5-Ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan.—Crystallization was induced by scratching in a hot solution of 164 g of the (±)-Id and 138 g of quinic acid in 1 l. of 95% ethanol. The mixture was left at room temperature and filtered. The precipitate was washed with a little cold 95% ethanol and dried at 60° to give 115 g of (−)-*cis*-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan quinate, mp 247–248°.

This salt was converted to base by treatment with NH_3 in the usual way giving 62 g of (−)-base, mp 245–248°. Recrystallization from 400 ml of absolute ethanol gave 50 g of (−)-*cis*-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan, mp 250–252°, $[\alpha]^{25}D$ −44.1 (*c* 1, 2% acetic acid).

Anal. Calcd for $C_{15}H_{21}NO$: N, 6.05. Found: N, 6.13.

A sample of this base, converted to the hydrobromide in 2-propanol, melted at 287–289°.

When the resolution liquor was concentrated to one-third volume, diluted to 900 ml with water, and made basic with NH_3, a crystalline precipitate separated and was collected, washed with water, and dried at 60° to give 83 g of crude *dextro* base. This was purified by crystallizing its hydrobromide.

Thus, 25 g of the crude (+)-base was dissolved in 100 ml of 2-propanol with 10 ml of 62% HBr and the solution was evaporated to dryness *in vacuo*. When the residue was dissolved in 100 ml of boiling 2-propanol and cooled, the crystalline hydrobromide precipitated and was collected, washed with 2-propanol, and dried at 70° to give 23 g, mp 282–285°. One recrystallization from 100 ml of 2-propanol gave 19.3 g of the pure (+)-hydrobromide, mp 287–289°.

This salt was converted to the base by dissolving in 200 ml of warm water and treating with excess NH_3. The base amounted to 14 g, mp 247–249°, $[\alpha]^{25}D$ +44.1 (*c* 1, 2% acetic acid).

Anal. Calcd for $C_{15}H_{21}NO$: N, 6.05. Found: N, 6.03.

Resolution of *trans*-5-Ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan.—Compound (±)-IId (23.1 g, 0.1 mole) was dissolved in 400 ml water with 7.5 g (0.05 mole) of (+)-tartratic acid by warming to 70°. Crystallization was initiated at 50° by scratching, and the mixture was allowed to cool to 25° with stirring during 3 hr. The precipitate was collected, washed with water, and dried to give 10.4 g of (−)-base (+)-tartrate, mp 293–295°. A sample, recrystallized from water, had the same melting point.

When 10 g of this salt was dissolved in 100 ml of 50% ethanol and made basic with NH_3, 7.63 g of the *levo* base separated. Recrystallization from 200 ml of 95% ethanol gave 6.6 g of pure *levo* base, mp 231–232°, $[\alpha]^{25}D$ −30.1° (*c* 1, 2% acetic acid).

Anal. Calcd for $C_{15}H_{21}NO$: N, 6.05. Found: N, 5.98.

Treating the resolution liquors with NH_3 gave 13.5 g of crude (+)-base. This base, with 4.4 g of (−)-tartaric acid in 150 ml of water, after 1 hr at 25° gave 12.5 g of (+)-base (−)-tartrate, mp 292–294°. This salt was then treated with NH_3 in the usual way in 50% ethanol to precipitate the (+)-base. Recrystallization of this base from 200 ml of 95% ethanol gave 6.6 g of pure (+)-base, mp 231–232°, $[\alpha]^{25}D$ (*c* 1, 2% acetic acid).

Anal. Calcd for $C_{15}H_{21}N$: N, 6.05. Found: N, 6.04.

(±)-*trans*-O,N-Bis(cyclopropylcarbonyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan.—A solution of 4.4 g of (±)-IIb in 30 ml of pyridine was treated with 6.6 g of cyclopropylcarbonyl chloride. The solvent was removed *in vacuo* and the residue was taken up in ether and water. The ether layer was separated, dried, and treated with charcoal to remove most of the color. Evaporation of the solvent left 8.3 g of syrup, which was dissolved in a small amount of ether and cooled to give 6.5 g of crystals. Recrystallization from hexane gave 6.0 g (85%) of the title compound melting at 105–110°.

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.42; H, 7.89; N, 3.86.

(±)-*trans*-2-Cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan Ethanesulfonate.—Reduction of 5.8 g of the preceding compound with 2.7 g of $LiAlH_4$ in tetrahydrofuran gave 4.0 g of syrup. A few milligrams was converted to the hydrochloride, mp 262–264°, which was not very water soluble. The remainder of the syrup was treated in ether with 1.4 ml of ethanesulfonic acid. The salt was recrystallized from 40 ml of ethanol to give 3.4 g of **4** (Table I).

***trans*-2-Cyclopropylcarbonyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan.**—(±)-IIb (8.7 g) was converted to (±)-*trans*-

(16) F. P. Luduena, *Arch. Intern. Pharmacodyn.*, **137**, 155 (1962).

(17) Melting points are not corrected for emergent stem errors.

(18) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).

O,N-bis(cyclopropylcarbonyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan by the method previously described. All of the resulting product was refluxed with 35 ml of butyl alcohol and 5.8 g of N,N-diethylaminoethylamine for 5 hr. The solvent was removed *in vacuo*, and the residue was partitioned between dilute HCl and ether. The ether layer was separated, and the product crystallized. Recrystallization from aqueous 2-propanol afforded 9.2 g melting at 161–167°. A small portion was recrystallized from ether; mp 163–165.5°.

Anal. Calcd for $C_{18}H_{29}NO_2$: C, 75.75; H, 8.12. Found: C, 76.46; H, 8.36.

(±)-*trans*-2-Cyclopropylmethyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan Hydrochloride.—To a solution of 8.0 g of (±)-*trans*-2-cyclopropylcarbonyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan in 75 ml of acetone was added 2.3 g of KOH in 4 ml of water followed by 4 ml of methyl iodide. After 24 hr at room temperature, the solvents were removed, and the residue was taken up in water and ether. The ether layer was separated and washed with water, dilute HCl, and water. After drying and removing the solvent *in vacuo*, there remained 7.6 g of yellow liquid which was reduced with $LiAlH_4$ in tetrahydrofuran to give 6.2 g of base. The base was converted to the hydrochloride and recrystallized from 2-propanol to give 60% of **3**.

(±)-*trans*-O,N-Bis(cyclopropylcarbonyl)-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan.—To a solution of 11.6 g of (±)-IId in 100 ml of pyridine was added 13 g of cyclopropylcarbonyl chloride. One hour after the addition, the solvent was removed *in vacuo*, and the residue partitioned between water and ether. After the ether layer was washed with dilute HCl and with water, it was dried and filtered. The crude product separated as colorless cubes in quantitative yield (mp 135–137°) and gave the following analysis.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.16; H, 7.95; N, 3.81. Found: C, 75.22; H, 8.20; N, 3.79.

(±)-*trans*-2-Cyclopropylmethyl-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan.—A solution of 17.5 g of the preceding amide in THF was reduced with 6.0 g of $LiAlH_4$. The resulting syrup was converted to the hydrochloride (**5**) which was recrystallized from 2-propanol.

(±)-*trans*-O,N-Bis(cyclobutylcarbonyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan.—A solution of 10.9 g of IIb in 140 ml of warm pyridine was cooled and treated with 16.4 g of cyclobutylcarbonyl chloride to give a quantitative yield of product melting at 158–163°. This was suspended in 100 ml of hexane and brought into solution by the addition of 250 ml of ethyl acetate. The cloudy solution was treated with charcoal to give a clear yellow filtrate. This was partially evaporated and chilled to give 17.5 g (91.5%) of very pale yellow crystals melting at 166–169°.

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.53; H, 8.19. Found: C, 75.68; H, 8.51.

(±)-*trans*-2-Cyclobutylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan Hydrochloride.—A solution of the above cyclobutylcarbonyl derivative in THF was reduced with $LiAlH_4$. The product (**6**), isolated as the hydrochloride, melted at 272.6–274.8° dec after recrystallization from 2-propanol.

(±)-*trans*-2′-Hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan Hydrobromide.—The nor base IIb (3.7 g) was allowed to react with 6.0 g of dimethylallyl bromide according to the procedure used for the *cis* isomer[1] to give 11.8 g of product melting at 96–130°. Recrystallization from various solvents failed to give sharp-melting crystals (hydrate?), although the crude product ran as a single spot in several solvent systems on silica plates. The product (**7**) was converted to the hydrobromide and recrystallized from ethanol; mp 240.4–241.0° dec. This ran as a single spot on a silica plate ($CHCl_3$–MeOH–isopropylamine, 94:3:3), and was readily distinguishable from the *cis* isomer in several solvent systems on silica plates.

(±)-*trans*-5-Ethyl-2′-hydroxy-9-methyl-2-(3,3-dimethylallyl)-6,7-benzomorphan.—A mixture of 9.2 g of IId was allowed to react with 6.0 g of dimethylallyl bromide and 5.0 g of $NaHCO_3$ in 125 ml of DMF as above. The product crystallized from the HCl extracts to give 11.0 g (82%) melting at 230–232° dec. The melting point was unchanged on recrystallization from water.

Anal. Calcd for $C_{20}H_{29}NO \cdot HCl$: Cl, 10.56. Found: Cl, 10.38.

The hydrochloride was dissolved in hot water and treated with NH_4OH to liberate the base (**8**). This was recrystallized from ether–hexane.

(±)-*trans*-2-(*cis*-Chloroallyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan.—A mixture of 8.6 g of IIb, 5.0 g of $NaHCO_3$, and 4.8 g of *cis*-1,3-dichloropropene in 130 ml of DMF was refluxed for 5 hr and worked up in the usual fashion to give 12 g of dark brown oil. This was converted to 9.1 g of crude hydrochloride by dissolving in 50 ml of acetone and adding ethereal HCl. Three recrystallizations from 2-propanol gave 4.5 g of pure product (**9**).

(±)-*cis*-2-(2,3-Butadienyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan.—A solution of 5.4 g of Ib in 50 ml of DMF was refluxed with 3.3 g of 4-bromo-1,2-butadiene and 5 g of $NaHCO_3$ for 4 hr. Work-up gave 6.7 g of dark brown syrup. Tlc on a silica plate using $CHCl_3$–MeOH–isopropylamine (94:3:3) showed seven spots, the major one having an R_f of 0.78. Accordingly the product was chromatographed on 330 g of silica using the above solvent mixture for eluting. After some impurities (R_f 0.92 and 0.85) were removed, the product (**11**) was obtained. It readily crystallized (3.4 g). It was recrystallized from ethyl acetate–hexane.

(±)-*trans*-2-(3,4-Butadienyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (10) was prepared in the same manner as the *cis* isomer above. See Table I.

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