to 8 ml of rat plasma and the mixture was incubated at 37° on a Dubnoff metabolic shaker. Samples (1.0 ml) were removed at 0, 5, 10, 30, and 60 min and assayed for the presence of ester 1 or lactone 3.

The 1.0-ml sample was placed in a 10-ml glass-stoppered centrifuge tube. HCl (0.5 ml, 3 *N*) and 5.0 ml of an isooctane–absolute EtOH mixture (95:5, v/v) were added to the tube. The tube was stoppered, shaken by hand, and allowed to stand. After the layers separated the uv absorption of the extract was determined against a blank treated similarly to that of the sample but not containing the compounds (1 or 3). An aliquot of this isooctane–EtOH extract was then treated with an equal volume of 2% $NaHCO_3$ solution to remove the free acid. The amount of free acid was determined by observing the reduction in the uv absorption of the organic phase at 226 mμ (ε 11,600) for 1 and 229 mμ (ε 54,154) for 3. Similar experiments with 3, carried out in the absence of enzyme, showed no chemical hydrolysis took place at the times indicated. Further, hydrolysis product 4 under similar conditions was shown not to undergo lactonization under identical incubation conditions and during the same intervals of time.

Note **Added in Proof.** After submission of this manuscript we learned that the title compound had also been prepared in 81% yield from a 4-substituted 3,6-dichlorocoumarin.[25]

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Stereoisomeric 5,9-Dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans, Strong Analgesics with Non-Morphine-Like Action Profiles

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The eight optically active stereoisomers and the corresponding four racemic forms of 5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1) have been prepared. Depending on their configurations these compounds are potent analgesics or inactive substances in mice. The analgesics attain potencies up to about a hundred times that of morphine but they do not show morphine-like side effects in mice nor do they suppress abstinence in withdrawn morphine-dependent monkeys. Their therapeutic ratios are favorable and, in the case of **1a**-1 and **1a**-2, exceptionally good. Configuration–activity relationships are discussed. *R* configuration of the *N*-tetrahydrofurfuryl group is a major prerequisite for high analgesic potency.

Recently, *N*-furylmethyl substituents have been shown to confer opioid agonist and/or antagonist properties to the molecules of strong analgesics, the action profiles of the novel compounds being closely related to the nature of the *N*-furylmethyl group.[1] In the course of our continuing efforts to develop strong, nonaddicting analgesics further modifications of the *N*-furylmethyl residue of appropriate 2′-hydroxy-6,7-benzomorphans have been accomplished. We now wish to report on the chemistry and pharmacology of the stereoisomeric 5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans and to discuss configuration–activity relationships.

Chemistry. According to the well-established stereochemistry of 5,9-dimethyl-2′-hydroxy-6,7-benzomorphan[2] the cis, diaxial fusion of the iminethano system allows only two (racemic) diastereoisomers (the α form with cis and the β form with trans orientation of the methyl groups with respect to the hydroaromatic ring). Consequently, due to the additional chiral carbon atom 2″ introduced into the molecule with the *N*-tetrahydrofurfuryl substituent, the 5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan 1 comprises four racemic diastereoisomers and the corresponding eight optically active forms. All these 12 substances which may be subdivided into compounds **1a** of the α series and compounds **1b** of the β series have been prepared.

Syntheses were achieved by alkylation of 5,9-dimethyl-2′-hydroxy-6,7-benzomorphans (**2**) with tetrahydrofurfuryl bromides (**3**). As shown in Table I the type of reaction product(s) obtained depends on the stereoisomeric forms of **2** and **3** used in the synthesis. Satisfactory separations of diastereoisomeric mixtures resulting from application of methods B, C, and D could be achieved by fractional crystallization guided by thin-layer chromatography. Racemic compounds 1 were also prepared by mixing equal parts of the corresponding antipodes and crystallization of the mixtures (method E). Further synthetic routes are described in the patent literature.[3]

The absolute stereochemistry of the compounds 1 obtained by method A follows unequivocally from the well-

Table I. Reaction Product(s) 1 Obtained with Different Stereoisomeric Forms of 2 and 3

Method	Form of 2	Form of 3	Reaction product(s) 1
A	Optically active	Optically active	One single optically active compound
B	Optically active	Racemic	Two optically active diastereoisomers
C	Racemic	Optically active	Two optically active diastereoisomers
D	Racemic	Racemic	Two racemic diastereoisomers

documented[4] absolute configurations of their benzomorphan precursors 2 and the absolute configurations of the tetrahydrofurfuryl bromides 3 which, in their turn, can be derived from those of the corresponding tetrahydrofurfuryl alcohols.[5] The chemical data for the stereoisomers 1 are summarized in Table II.

Pharmacology. The new compounds were tested for analgesia, morphine antagonism, and toxicity in mice (NMRI mice, both sexes, 19–24 g, ten animals per dose, subcutaneous application of the hydrochlorides). Analgesia was studied using the tail-clip method,[6] the hot-plate test,[7] and the writhing test.[8] ED_{50} and ED_{100} values were estimated by graphic evaluation of dose–response curves. Acute toxicity (observation period of 14 days) was determined using LD_{50} calculations according to Litchfield and Wilcoxon.[9] In the course of the evaluation of analgesia the mice were also observed with regard to the occurrence of side effects, especially the Straub tail phenomenon.[10] Morphine antagonist activity (suppression of morphine analgesia in mice) was tested using a procedure[1] based on Haffner's tail-clip

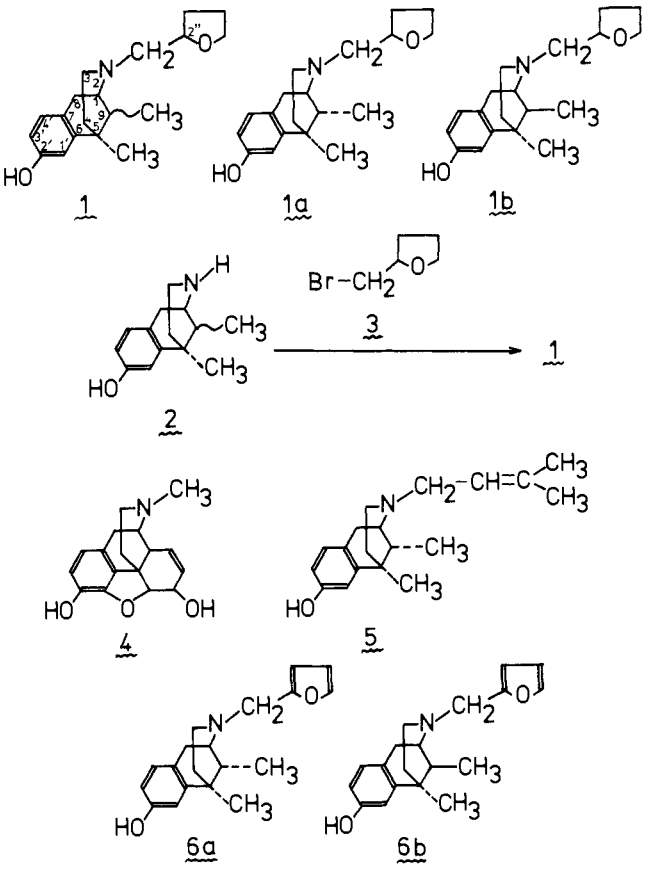

Table II. Chemical Data of the Stereoisomeric 5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans 1

Compd[a]	Configuration	$[\alpha]^{25}D$[b]	Mp, °C[c]	R_f, TLC[d]	Method[e]	% yield
1a-1	1*R/S*, 5*R/S*, 9*R/S*, 2''*R/S*		169	0.30	E[f]	80.0
1a-1·HCl	1*R/S*, 5*R/S*, 9*R/S*, 2''*R/S*		225–226		F	86.4
1a-2	1*R*, 5*R*, 9*R*, 2''*R*	−98.6	145–146	0.30	A[g]	66.5
1a-3	1*S*, 5*S*, 9*S*, 2''*S*	+98.1	145–146	0.30	A	63.7
1a-4	1*R/S*, 5*R/S*, 9*R/S*, 2''*S/R*		175–176	0.35	E	90.1
1a-4·HCl	1*R/S*, 5*R/S*, 9*R/S*, 2''*S/R*		295–296		F[h]	60.0
1a-5	1*R*, 5*R*, 9*R*, 2''*S*	−106.3	204–205	0.35	A[i]	72.9
1a-6	1*S*, 5*S*, 9*S*, 2''*R*	+106.7	204–205	0.35	A[j]	66.3
1b-1	1*R/S*, 5*R/S*, 9*S/R*, 2''*R/S*		150	0.45	E	87.5
1b-1·HCl	1*R/S*, 5*R/S*, 9*S/R*, 2''*R/S*		276–277		F	88.0
1b-2	1*R*, 5*R*, 9*S*, 2''*R*	−108.5	171	0.45	A	71.3
1b-2·HCl	1*R*, 5*R*, 9*S*, 2''*R*	−73.6	257		F	91.5
1b-3	1*S*, 5*S*, 9*R*, 2''*S*	+109.7	171	0.45	A	77.4
1b-3·HCl	1*S*, 5*S*, 9*R*, 2''*S*	+73.1	257		F	87.0
1b-4	1*R/S*, 5*R/S*, 9*S/R*, 2''*S/R*		119–120	0.40	E	96.3
1b-4·HCl	1*R/S*, 5*R/S*, 9*S/R*, 2''*S/R*		259–260		F	96.6
1b-5	1*R*, 5*R*, 9*S*, 2''*S*	−97.5	144	0.40	A	68.6
1b-5·HCl	1*R*, 5*R*, 9*S*, 2''*S*	−98.2	290–291		F	94.7
1b-6	1*S*, 5*S*, 9*R*, 2''*R*	+97.7	144	0.40	A	67.5
1b-6·HCl	1*S*, 5*S*, 9*R*, 2''*R*	+98.1	290–291		F	96.5

[a] Empirical formulas (molecular weights) of the stereoisomers 1a and 1b and their hydrochlorides: $C_{19}H_{27}NO_2$ (301.43) and $C_{19}H_{27}NO_2$·HCl (337.90), respectively. Analyses of the bases (C, H, and N) and the hydrochlorides (C, H, Cl, and N) agree with calculated values within ±0.4%. Ir and NMR spectra are consistent with assigned structures and configurations. [b] Perkin-Elmer polarimeter 241, MeOH, *c* 1.000 g/100.0 ml. [c] Uncorrected melting or decomposition points were taken in a Tottoli apparatus (bases crystallized from MeOH-H_2O and hydrochlorides from EtOH-Et_2O). [d] Silica gel plates were DC Fertigplatten Kieselgel 60 from Merck, Darmstadt. EtOAc-MeOH-concentrated NH_4OH [90:10:0.5 (freshly prepared)] was used for the compounds 1a and toluene-MeOH (70:30) for the compounds 1b. Detection with iodine vapor. [e] For methods A–E see Table I, with subsequent comments, and the Experimental Section. All HCl salts were prepared from the corresponding bases as described for **1a**-1·HCl (method F). [f] Also prepared along with 1a-4·HCl by method D. [g] Also prepared along with 1a-5 by method B. [h] Also prepared along with 1a-1 by method D. [i] Also prepared along with 1a-2 by method B. [j] Also prepared along with 1a-2 by method C.

Table III. Pharmacological Data of the Stereoisomeric 5,9-Dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans 1

Compd[a]	Analgesia: Tail clip,[b] ED_{50}, mg/kg sc, mice	Analgesia: Hot plate,[c] ED_{100}, mg/kg sc, mice	Analgesia: Writhing,[d] ED_{50}, mg/kg sc, mice	Toxicity,[e] LD_{50}, mg/kg sc, mice	Therapeutic ratio, LD_{50}/ED_{100}, mice	Straub tail,[f] mice	Suppression of abstinence,[g] monkeys
1a-1·HCl	0.3	0.01	0.02	268 (201–356)	26,800	–	No[h]
1a-2·HCl	0.2	0.01	0.01	94 (80–111)	9,400	–	No[h]
1a-3·HCl	Inactive[i]	Inactive	Inactive	326 (281–378)		–	
1a-4·HCl	20	5.0	10.0	345 (308–386)	69	–	No[j]
1a-5·HCl	1.0	3.0	3.0	150 (121–186)	50	–	No[k]
1a-6·HCl	Inactive	Inactive	Inactive	650 (590–715		–	
1b-1·HCl	0.2	0.03	0.03	128 (116–148)	4,266	–	No[h]
1b-2·HCl	0.1	0.01	0.02	76 (45–128)	7,600	–	No[h]
1b-3·HCl	Inactive	Inactive	Inactive	140 (111–176)		–	
1b-4·HCl	3.0	0.10	1.5	420 (368–479)	4,200	–	No[h]
1b-5·HCl	1[l]	0.08	0.1	225 (199–254)	2,812	–	No[h]
1b-6·HCl	Inactive	Inactive	Inactive	310 (265–363)		–	
4·HCl	11.0	1.2	0.5	500 (407–615)	417	+	Yes[g]
5·HCl	Inactive	7.0	1.4	220 (190–255)	31	–	No[m]
6a·HCl	Inactive	Inactive	18	292 (261–339)		–	No[n]
6b·HCl	Inactive	Inactive	Inactive	380 (336–430)		–	

[a] Since crystalline hydrochlorides 1a-2·HCl, 1a-3·HCl, 1a-5·HCl, and 1a-6·HCl could not be obtained, solutions thereof (c 10.0 mg/ml) were prepared dissolving equimolecular amounts of the corresponding bases (89.2 mg) and 1 *N* HCl (2.97 ml) in water to a total volume of 10.0 ml. [b] Tail-clip test according to Haffner; see ref 6. [c] Hot-plate test according to Woolfe and MacDonald; see ref 7. [d] Writhing test according to Blumberg, Wolf, and Dayton; see ref 8. [e] Calculations according to Litchfield and Wilcoxon; see ref 9. [f] Straub tail phenomenon; see ref 10, present (+) or absent (−) in dose ranges tested for analgesia. [g] Suppression of abstinence signs in withdrawn morphine-dependent rhesus monkeys; see ref 11. [h] See ref 13b. [i] In Table III "inactive" means that no analgesic effect was observed up to doses causing side effects. [j] See ref 12. [k] See ref 13a. [l] Analgesic effects in doses close to those causing side effects. [m] See ref 24. [n] See ref 25.

method. Morphine-like physical dependence capacity (suppression of abstinence signs in withdrawn morphine-dependent rhesus monkeys[11]) was estimated by Swain and Seevers.[12,13] The pharmacological results obtained with the new compounds **1a** and **1b**, their *N*-furfuryl analogs **6a** and **6b**, and morphine (**4**) and pentazocine (**5**) as standards are summarized in Table III.

Discussion

Depending on their stereochemistry the new compounds **1** are either analgesicly active or inactive substances. The most active representatives attain potencies up to more than 100 times that of morphine or about 700 times that of pentazocine, respectively. Such high superiority to the standards is most pronounced in the hot-plate test. Strong agonist activity has also been demonstrated in the guinea-pig ileum.[14] Subtoxic doses cause CNS depression, ataxia, and convulsions. In the relatively high dose ranges applied for the tail-clip test, those side effects are not always clearly separated from analgesic responses. Surprisingly, however, high analgesic potency is not correlated with typical opiate side effects like the Straub tail phenomenon[10] and increased locomotor activity.[15] Since Straub tail activity in relation to toxicity (Straub index) has been reported[16] to be predictive for the addiction liability of substances structurally related to morphine, compounds **1** not showing this effect might be nonaddicting analgesics in men. This assumption is strongly supported by the results of the monkey studies. All the analgesic compounds **1** fail to suppress abstinence signs in withdrawn morphine-dependent animals.[12,13] Most of the new analgesics, especially those with high potency, are superior to morphine and far superior to pentazocine with regard to their therapeutic ratios. In contrast to their *N*-furfuryl analogs **6** and pentazocine compounds **1** did not show antagonist properties in our test procedure. The pharmacological properties of the 5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans **1** are closely related to their stereochemistry. The following configuration–activity relationships are observed.

Configuration at C-1 and C-5. All substances with 1*R*,5*R* configuration (**1a**-2, 1a-5, **1b**-2, and **1b**-5) proved to be levorotatory like their precursors **2**. They exert analgesic activity whereas their dextro counterparts with 1*S*,5*S* configuration (**1a**-3, 1a-6, **1b**-3, and **1b**-6) are essentially inactive. These findings were anticipated since stereospecificity of analgesics with morphine-like structures has been well documented. Analgesic activity has been shown to reside largely in one of the antipodes of enantiomorphic pairs[17] and in the 6,7-benzomorphan series to be correlated with 1*R*,5*R* configuration which is known to be identical with that of natural (−)-morphine with regard to these common centers of asymmetry.[18] Supposing complete inertness of the (+) forms, the racemic substances **1** should be half as potent as the corresponding (−) forms. This roughly proves true as to the racemic compounds **1a**-1 and **1b**-1 with *N*-[(2″*R*)-tetrahydrofurfuryl] substituents whereas, in the case of *N*-[(2″*S*)-tetrahydrofurfuryl] substitution, the racemic compounds (**1a**-4 and **1b**-4) are less active than expected. Since dose-related suppression of the analgesic action of the (−) form by its (+) antipode could not be demonstrated with **1a**-5 and **1a**-6 in the writhing test, potential antagonism of the antipodes as a reason for the unexpectedly low analgesic potencies of the racemic *N*-[(2″*S*)-tetrahydrofurfuryl] compounds (**1a**-4 and **1b**-4) was excluded.

Configuration at C-9. As a rule, in the 5,9-dialkyl-6,7-benzomorphan series β compounds with 9*S* configuration are found to be more potent analgesics than their α diastereoisomers with 9*R* configuration.[2,18] This difference in analgesic potency is also observed in the case of the com-

pounds 1 with N-[(2''S)-tetrahydrofurfuryl] substituents (compare **1a**-5 to **1b**-5). The N-[(2''R)-tetrahydrofurfuryl] compounds, however, being roughly equipotent, do not show this difference (compare **1a**-2 to **1b**-2).

Configuration at C-2''. Among the α as well as the β compounds the diastereoisomers with 2''R configuration in the tetrahydrofurfuryl group (**1a**-2 and **1b**-2, respectively) are considerably superior to the corresponding diastereoisomers with 2''S configuration (**1a**-5 and **1b**-5, respectively) as to their analgesic activities. This difference in potency is more pronounced in the α series than in the β series. Since high analgesic potency of the N-[(2''R)-tetrahydrofurfuryl] compounds **1a**-1 and **1a**-2 is not accompanied by markedly enhanced toxicity, the therapeutic ratios of these compounds are exceptionally good. We have shown that the configuration of the N-tetrahydrofurfuryl group is of major importance for the analgesic potencies of the stereoisomers **1**. To our knowledge, benzomorphans with an N-substituent bearing a center of asymmetry have not been reported until recently when 5,9-dialkyl-2'-hydroxy-6,7-benzomorphans with N-(2,2-dialkyl-2-hydroxyethyl) substitution have been published in the patent literature.[19] The stereochemistry of these compounds, however, has not been commented on.

Experimental Section

General techniques and procedures used are stated as footnotes to Tables II and III.

5,9-Dimethyl-2'-hydroxy-6,7-benzomorphans (2). Preparation of the racemic α compound (±)-**2a** has been reported by Fry and May.[20] The optical antipodes (−)-**2a** and (+)-**2a** and the β isomers (±)-**2b**, (−)-**2b**, and (+)-**2b** have been described by Tullar and coworkers.[21]

(+)-(*R*)-Tetrahydrofurfuryl Alcohol. (+)-L-Tetrahydrofurfuryl alcohol (shown to have the *R* configuration[5]) was prepared according to Hartman and Barker.[22] Starting from 147 g (1 mol) of L-glutamic acid an overall yield of 11.9 g (11.7%) was obtained: bp 76° (16 mm); $[\alpha]^{25}D$ +15.3° (*c* 5.000, CH_3NO_2).

(−)-(*S*)-Tetrahydrofurfuryl Alcohol. (−)-(*S*)-Tetrahydrofurfuryl alcohol was prepared using the procedure given above for its (+)-*R* antipode. Starting from 147 g (1 mol) of D-glutamic acid an overall yield of 15.5 g (15.2%) was obtained: bp 76° (16 mm); $[\alpha]^{25}D$ −15.7° (*c* 5.000, CH_3NO_2).

(+)-(*R*)-Tetrahydrofurfuryl Bromide [(+)-3]. (+)-(*R*)-Tetrahydrofurfuryl alcohol (22.6 g, 0.22 mol) was allowed to react with PBr_3 according to a procedure described for racemic tetrahydrofurfuryl bromide:[23] yield after redistillation, 14.0 g (38.6%); bp 66–67° (16 mm); $[\alpha]^{25}D$ +3.9° (c 5.000, CH_3NO_2).

(−)-(*S*)-Tetrahydrofurfuryl Bromide [(−)-3]. (−)-(*S*)-Tetrahydrofurfuryl alcohol (20.0 g, 0.20 mol) was allowed to react with PBr_3 as described for the isomer above: yield after redistillation, 18.3 g (56.6%); bp 67–68° (16 mm); $[\alpha]^{25}D$ −3.8° (c 5.000, CH_3NO_2).

(−)-(1*R*,5*R*,9*S*,2''*S*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1b-5). Method A. (−)-β-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan[21] [(−)-**2b**] (13.0 g, 0.06 mol), 10.9 g (0.066 mol) of (−)-**3**, 7.55 g (0.09 mol) of $NaHCO_3$, and 120 ml of DMF were heated with stirring to 100° for 20 hr. After evaporation to dryness in vacuo the residue was treated with $CHCl_3$ (150 ml) and H_2O (50 ml). The $CHCl_3$ layer was separated, washed with H_2O, dried with Na_2SO_4, and evaporated to dryness in vacuo. For purification the residue of crude **1b**-5 was redissolved with $CHCl_3$ (90 ml) and the solution filtered through a column of 80 g of aluminum oxide (neutral, activity grade III). The column was eluted with 600 ml of $CHCl_3$ and the eluate evaporated to dryness in vacuo. The residue thus obtained was crystallized from MeOH–H_2O [2:1 (135 ml)] giving 12.4 g (68.6%) of **1b**-5, mp 144°. Recrystallization from MeOH–H_2O yielded 11.8 g of **1b**-5, melting point unchanged. Anal. ($C_{19}H_{27}NO_2$) C, H, N.

(−)-(1*R*,5*R*,9*R*,2''*S*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1a-5) and (−)-(1*R*,5*R*,9*R*,2''*R*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1a-2). Method B. (−)-α-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan[21] [(−)-**2a**] (21.7 g, 0.1 mol), 18.2 g (0.11 mol) of (±)-**3**,[23] 12.6 g (0.15 mol) of $NaHCO_3$, and 200 ml of DMF were heated with stirring to 100° for 20 hr. The reaction mixture was worked up as described above. Evaporation of the $CHCl_3$ extract yielded a residue consisting of a mixture of the diastereoisomers **1a**-5 and **1a**-2. From a solution of the residue in boiling MeCOEt (175 ml) crude crystalline **1a**-5 separated on cooling (13.6 g, mp 193–196°). Purification was effected by a second crystallization from MeCOEt (225 ml) adding 2 ml of Ac_2O to the boiling solution. Almost pure **1a**-5, mp 203–204° (TLC showed only traces of **1a**-2), was obtained in 62.7% yield (9.45 g). An additional recrystallization from MeCOEt (180 ml) furnished pure **1a**-5 (8.35 g), mp 204–205°. Anal. ($C_{19}H_{27}NO_2$) C, H, N. The first of the MeCOEt mother liquors was evaporated to dryness in vacuo to leave a residue of crude **1a**-2 which was purified by crystallization of its (−)-D-tartrate. This salt was obtained by mixing solutions of the crude base **1a**-2 in 50 ml of EtOH and 7.5 g (0.05 mol) of (−)-D-tartaric acid in 50 ml of H_2O (yield 17.1 g, mp 203–204°). Two recrystallizations from EtOH–H_2O (1:1) furnished 13.9 g of **1a**-2 (−)-D-tartrate, mp 207°. Anal. ($C_{19}H_{27}NO_2 \cdot C_4H_6O_6$) C, H, N. The tartrate was converted into the base **1a**-2 which crystallized from EtOAc–*n*-hexane [1:2 (60 ml)] in 53.2% yield: 8.05 g; mp 145–146°. Anal. ($C_{19}H_{27}NO_2$) C, H, N.

(+)-(1*S*,5*S*,9*S*,2''*R*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1a-6) and (−)-(1*R*,5*R*,9*R*,2''*R*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1a-2). Method C. These compounds were prepared following the procedure given above for **1a**-5 and **1a**-2. Starting from 1.09 g (0.005 mol) of (±)-α-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan[20] [(±)-**2a**], 0.63 g (0.0075 mol) of $NaHCO_3$, and 0.91 g (0.0055 mol) of (+)-**3**, the reaction products **1a**-6 and **1a**-2 were obtained in yields of 53.4 (0.4 g, mp 204–205°) and 60.0% (0.45 g, mp 145–146°), respectively.

(±)-(1*R*/*S*,5*R*/*S*,9*R*/*S*,2''*S*/*R*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan Hydrochloride (1a-4·HCl) and (±)-(1*R*/*S*,5*R*/*S*,9*R*/*S*,2''*R*/*S*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1a-1). Method D. (±)-α-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan[20] [(±)-**2a**] (21.7 g, 0.1 mol), 18.2 g (0.11 mol) of (±)-**3**,[23] 12.6 g (0.15 mol) of $NaHCO_3$, and 200 ml of DMF were heated with stirring to 100° for 20 hr. The reaction mixture was worked up as described above. Evaporation of the $CHCl_3$ extract yielded a residue consisting of the diastereoisomers **1a**-4 and **1a**-1. A solution of the residue in 100 ml of EtOH was acidified with 8.5 ml of concentrated HCl. Crude **1a**-4·HCl (13.9 g, mp 285°) separated. Recrystallization from EtOH (350 ml) gave 5.3 g of **1a**-4·HCl (mp 292–294°) and concentration of the mother liquor to 100 ml gave an additional crop of 6.2 g (mp 290–292°). The combined crystal fractions (11.5 g) were dissolved in boiling EtOH (320 ml). Concentration of the hot solution to 100 ml yielded 10.3 g (60.0%) of pure **1a**-4·HCl, mp 295–296°. Anal. ($C_{19}H_{27}NO_2 \cdot HCl$) C, H, Cl, N. The first of the EtOH mother liquors was evaporated in vacuo to give a residue of crude **1a**-1·HCl which was converted into the base **1a**-1. Crystallization from toluene–*n*-hexane [7:3 (100 ml)] furnished 11.2 g of almost pure **1a**-1, mp 165–167°. Recrystallization from MeOH–H_2O [2:1 (85 ml)] yielded 10.05 g (66.7%) of **1a**-1, mp 169°. Anal. ($C_{19}H_{27}NO_2$), C, H, N.

(±)-(1*R*/*S*,5*R*/*S*,9*S*/*R*,2''*R*/*S*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan (1b-1). Method E. **1b**-2 (4.0 g) and 4.0 g of **1b**-3 (each prepared by method A) were crystallized jointly from a mixture of MeOH (100 ml) and H_2O (75 ml) to give 7.6 g of **1b**-1, mp 149–150°. Recrystallization from MeOH (100 ml) and H_2O (100 ml) yielded 7.0 g (87.5%) of **1b**-1, mp 150°. Anal. ($C_{19}H_{27}NO_2$) C, H, N.

(±(−(1*R*/*S*,5*R*/*S*,9*R*/*S*,2''*R*/*S*)-5,9-Dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan Hydrochloride (1a-1·HCl). Method F. **1a**-1 (22.3 g, 0.074 mol) (prepared by method D) was dissolved in a mixture of EtOH (50 ml) and ethanolic 2 *N* HCl (40 ml). Et_2O was added to the solution until it became turbid (800 ml). **1a**-1·HCl separated from the solution yielding 21.6 g (86.4%), mp 225–226°. Recrystallization from EtOH–Et_2O gave 20.4 g of the substance, melting point unchanged. Anal. ($C_{19}H_{27}NO_2 \cdot HCl$) C, H, N.

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Emetic Activity of N-Substituted Norapomorphines

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Norapomorphine and ten of its N-substituted derivatives were prepared by modifications of procedures described earlier. In a dog emesis test the *N*-ethyl and *N*-*n*-propyl compounds had minimum effective doses of 0.00025 and 0.0005 mg/kg, respectively, when administered iv, sc, or im. In a modified Irwin mouse profile screen the minimum effective iv dose was 0.013 mg/kg for the *N*-ethyl and 0.0024 mg/kg for the *N*-*n*-propyl compound; percutaneous absorption was also observed in mice. All compounds examined caused the stereotyped apomorphine behavior syndrome but hypotensive effects were not serious.

During a study of compounds having both a high central nervous system (CNS) activity and a high therapeutic index, we decided to undertake a program to increase both the emetic potency and the therapeutic index of the well-known emetic apomorphine. Our decision was supported by Cannon's subsequent description[1] of the chemistry and pharmacology of *N*-allylnorapomorphine, whose decreased toxicity in mice and superior emetic potency in dogs was also observed in our laboratories using a sample kindly provided by Professor Cannon. As a result of the high activity shown by some of the apomorphine homologs prepared by us and by Cannon, a total synthesis of these compounds was developed by Neumeyer.[2] More recently the pharmacokinetics of compounds **1**, **2**, and **4** (see Table I) in mice[4] and dopaminergic activity of certain aporphine ethers[5] have been described. The superior potency of **4** over **2** in producing stereotyped behavior has been confirmed in studies using rats.[6]

The purpose of the present communication is to record pharmacological activity in mice and dogs for the compounds in Table I, which were acquired as gifts[1] or by synthesis, and to describe improved synthesis procedures developed, subsequent to an earlier account of the work,[7] in connection with the preparation of large samples needed for preclinical pharmacology and toxicology studies. All of the compounds in Table I were derived from morphine and thus belong to the (6a*R*)-(−) series.[8] It is now known that (6a*S*)-(+)-apomorphine is a much less potent isomer and is not an antagonist for the (−) isomer,[9] an observation that has been confirmed by others.[6]

Chemistry. At the time of our work we prepared normorphine from heroin[10] by a von Braun demethylation procedure[11] in yields of 35%; more recently developed procedures[12-15] were then not available. *N*-Alkylnormorphine precursors for compounds **3**, **4**, **7**, and **11** were prepared by reductive alkylation of normorphine by the appropriate aldehyde and $NaBH_4$ in yields of 50–80%; all were identical with materials prepared by alternative procedures.[3,16-18] The precursor of **5** was Merck's nalorphine; that of **8** was *N*-cyclopropylmethylnormorphine prepared by a literature procedure.[19]

Originally[7] the rearrangement of normorphine and its