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Centrally Acting Muscle Relaxants. Isomeric 9,10-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes and Their Carbamate Esters†

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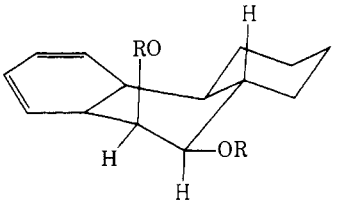
Received December 26, 1973

Mephenesin was the first modern psychopharmacological agent developed for its central muscle relaxant effects. In contrast to curare type skeletal muscle relaxants which act upon the myoneural junction, mephenesin was shown to act primarily by selective retardation or blockade of nerve impulses in internuncial pathways of the spinal cord.[2] As such, this drug has little or no effect upon the normal knee jerk but promptly reduces the exaggerated knee jerk, has little effect upon respiration, antagonizes the effects of strychnine, and relieves tetanic spasms. The short duration of action of mephenesin has limited its clinical usefulness. Attempts to prolong the action of this drug resulted in the preparation of various esters and carbamates, eventually leading to meprobamate, which possesses actions similar to mephenesin but is more potent, particularly in its ability to block the convulsive effects of pentylenetetrazole.

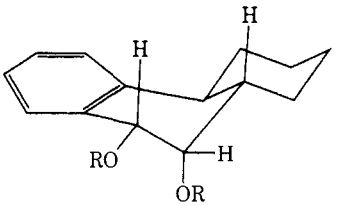
Although a vast amount of work has been accumulated and reviewed concerning structure–activity relationships of muscle relaxant diols and carbamate esters,[2,3] to date no conformational aspects of their varied activities have been examined. To approach a possible stereochemical evaluation of these drugs, the isomeric 9,10-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes 1–4[4]‡ and their carbamate esters **9–12** were prepared and screened for anticonvulsant activity.

Use of the *trans*-octahydrophenanthrene nucleus as a conformationally semirigid carrier for the pharmacophoric groups of medicinal agents such as norephedrine analogs has been reported.[5] Recently, the isomeric 9,10-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10)-octahydrophenanthrenes 1–4 were prepared by a variety of stereoselective methods utilizing electrophilic reagents.[4] These isomeric diols, 1–4, were converted to intermediate bis(phenylcarbonate) esters, 5–8, and subsequently to the dicarbamates 9–12.

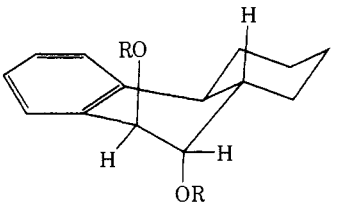
Although several methods are available for the conversion of alcohols to carbamates, some have serious limitations when applied to vicinal diols. For example, a very facile single-step method for preparing monocarbamates by reaction of the alcohol with sodium isocyanate and trifluoracetic acid is reported to give a significant amount of cyclic carbonate with the related vicinal diol phenaglycodol and its *p*-trifluoromethyl analog.[6] Following completion of our work, a similar method was used for conversion of a series of 4-phenyl-1-alkynylcyclohexanols to their respective carbamates.[7] Our studies demonstrate the applicability of the use of phenyl chloroformate followed by liquid ammonia for the high-yield production of dicarbamates from vicinal diols, even in cases where cyclic carbonates would be expected to present difficulties.



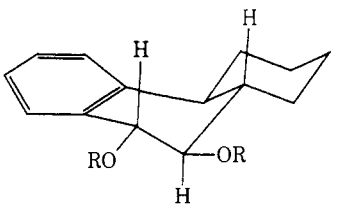
1, R = H
5, R = CO_2Ph
9, R = $CONH_2$



2, R = H
6, R = CO_2Ph
10, R = $CONH_2$

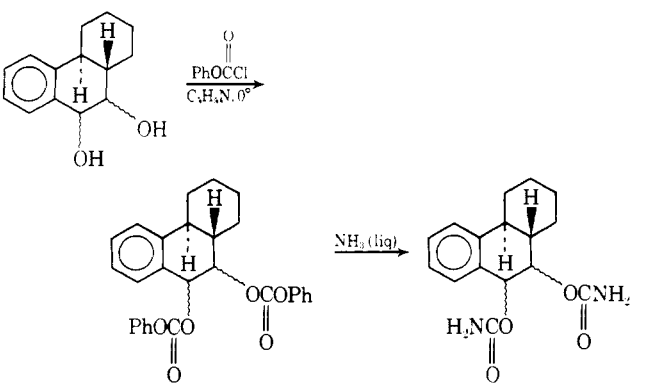


3, R = H
7, R = CO_2Ph
11, R = $CONH_2$



4, R = H
8, R = CO_2Ph
12, R = $CONH_2$

To support the structural assignments, high-resolution mass spectral data were gathered for each of the isomeric



†Taken in part from the Ph.D. Thesis of B. E. Sherwood, submitted to the Graduate School, University of Washington, Feb 1973. A preliminary account of this work was presented.[1]

‡All compounds are racemic although only a single isomer is drawn. The central ring is arbitrarily assigned the half-chair conformation where equatorial (e) and axial (a) substituents at C-9 are in fact pseudoequatorial and pseudoaxial, respectively.

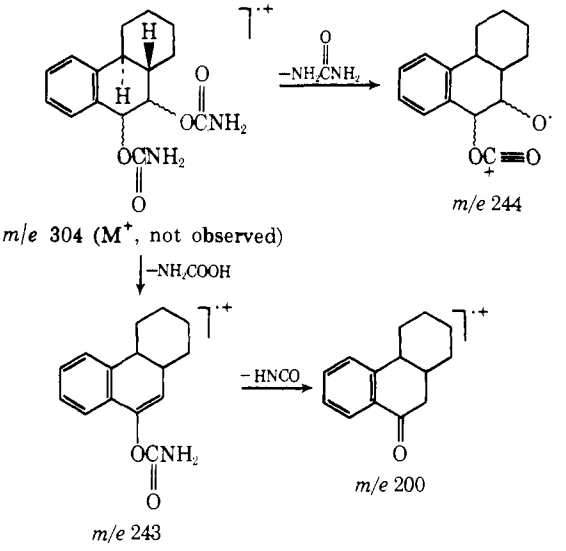
Table I. Anticonvulsant Activity and Partition Coefficient Data

Compound	Configuration of 9,10 substituents	Approx ED_{50} (mg/kg) for protection against tonic convulsions: Supramaximal electroshock	Approx ED_{50} (mg/kg) for protection against tonic convulsions: Pentylenetetrazole	Log $P_{o,w}$[a]
Alcohols				
1	9a,10e	150	150 (0.69 mmol/kg)	2.32
2	9e,10a	150	50 (0.23 mmol/kg)	2.57
3	9a,10a	125	100 (0.46 mmol/kg)	2.01
4	9e,10e	150	>150	2.47
Carbamate esters				
9	9a,10e	>300	>300	2.39
10	9e,10a	>300	>300	2.19
11	9a,10a	>300	>300	2.17
12	9e,10e	>300	>300	2.17
Meprobamate		75 (0.34 mmol/kg) 75[b]	75 (0.34 mmol/kg) 80[b,c]	−0.52[d]
Mephenesin		80 (0.42 mmol/kg) 85[c]	>400 (>2.1 mmol/kg) >400[b,c]	

[a]Partition coefficient data (1-octanol–H_2O) were determined as described in the Experimental Section. [b]G. Maffii, E. Testa, and R. Ettorre, *Farmaco, Ed. Sci.*, **13**, 187 (1958); pentylenetetrazole dose, 140 mg/kg. [c]G. Maffii and E. Socin, *Brit. J. Pharmacol.*, **13**, 357 (1958); 5% acacia suspension. [d]Reference 10.

dicarbamates which showed fragmentary loss of the carbamate groups consistent with the assigned structures. The molecular ions are not stabilized sufficiently to allow detection of a parent peak using EIMS. Rapid loss of the carbamate moieties occurs by at least two means including loss of the elements of urea, one or more molecules of carbamic acid, and/or by loss of carbamic acid and isocyanic acid, similar to other carbamates[8] (Scheme I). Loss of the elements of urea occurs to a small extent in each of the four dicarbamates giving a peak at *m/e* 244. The fragment lost was shown not to be the carbamate radical (NH_2COO) by accurate mass measurements at *m/e* 244. Fragmentation of the molecular ion to liberate carbamic acid (NH_2COOH) occurs in each of the isomers to give a peak at *m/e* 243 (1-4%), one of the possible olefinic carbamate esters. This ion further fragments by loss of isocyanic acid (HNCO) yielding a fragment of *m/e* 200 ($C_{14}H_{16}O$) base peak for **9** and **12** and commanding a relative intensity of 78 and 60%, respectively, for **10** and **11**. The structure of *m/e* ion 200 is supported by the fragmentation pattern of 1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydro-9-oxophenanthrene (**13**).[9] Major fragments observed in spectra of the dicarbamates are the same as those observed in spectra of ketone **13**.

Scheme I. Suggested Mass Fragmentation Scheme for Dicarbamates



Pharmacology. The determination of central muscle relaxant activity is a complex problem requiring several assay techniques, since some CNS depressant procedures do not always correlate with useful antianxiety effects.[10,11] One of the screening systems useful for this activity is the anticonvulsant assay and observation of other central depressant effects. The results of the anticonvulsant activity assay are presented in Table I.

These data show some muscle relaxant effects for the diols as demonstrated by the protection against pentylenetetrazole, including diol **2** which is approximately 1.5 times as effective as meprobamate (on a molar basis) in a similar assay, and at least ten times as potent as mephenesin, a related diol. Other observations recorded were loss of righting reflex and ataxia for **1** at 300 mg/kg and decreased muscle tone for compound **3** at this dose.

The results are very preliminary but suggest some central depressant effects of the diols similar to the muscle-relaxant tranquilizer mephenesin or meprobamate. Insufficient data are presently available to demonstrate a similar selectivity of these compounds.

The difference in activity of the individual diols may be related to differences in distribution or metabolism (rates and/or pathways) and not necessarily related to a drug-receptor interaction. The distribution coefficient data show that probably more than the partition effects must be considered. Although the most lipid-soluble compound, **2**, is most active, there seems to be no simple correlation with partition coefficient, since the most water-soluble compound, **3**, is the next most potent. Further interpretation of these pharmacological results must await additional experimentation.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on Beckman IR-5 and IR-20 spectrometers. Ultraviolet spectra were obtained on a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded on 60-MHz Varian A-60 and T-60 spectrometers in the solvent stated with tetramethylsilane (TMS) as an internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectral data were recorded on an AEI MS-9 mass spectrometer at a probe temperature of 175°. A Digital Equipment Corp. PDP-12 computer equipped with programs available from the Mass Spectrometry Laboratory, Department of Chemistry, University of Washington, Seattle, Wash. 98195, was used for

data collection and mass spectral fragment determinations. Peaks given in the mass spectral fragmentations are within 5.0 millimass units from calculated values. Elemental microanalyses were performed by Dr. F. B. Strauss, Microanalytical Laboratories, Oxford, England, and Huffman Laboratories, Wheatridge, Colo. Unless otherwise stated, anhydrous sodium sulfate was used to dry solutions in organic solvents. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of theoretical values.

O,O'-**Di(phenoxycarbonyl)-9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8).** To a suspension prepared by adding dropwise phenyl chlorocarbonate, 5.8 g (37 mmol), to 70 ml of pyridine being stirred at 0° (pink color) was added dropwise a solution of 9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (4), 2.0 g (9.2 mmol), in 50 ml of pyridine over a 30-min period. The suspension was stirred at 0° for 1 hr, allowed to warm to room temperature, and stirred an additional 7 hr. Water was added dropwise to destroy excess phenyl chlorocarbonate and the solution was diluted with water and extracted with several portions of ether. The ether solution was washed with 10% aqueous hydrochloric acid, followed by 10% aqueous sodium hydroxide and water, then dried, and evaporated. The remaining oil solidified upon standing and was recrystallized from ether to yield *O,O'*-di(phenoxycarbonyl)-9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8): 2.97 g (71%); mp 148–149.5°; nmr ($CDCl_3$) δ 6.23 (d, 1, $J_{9,10}$ = 8.0 Hz, H_9), 5.23 (dd, 1, $J_{10,10a}$ = 10.5 Hz, H_{10}).

O,O'-**Di(phenoxycarbonyl)-9(a),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (5).** Compound 5 was prepared in 95% yield from 1, mp 122.5–123.5° (hexane–ether), by the procedure described for preparation of 8: nmr ($CDCl_3$) δ 6.32 (d, 1, $J_{9,10}$ = 3.5 Hz, H_9), 5.01 (dd, $J_{10,10a}$ = 11.0 Hz, H_{10}).

O,O'-**Di(phenoxycarbonyl)-9(e),10(a)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (6).** Compound 6 obtained as an oil was prepared in 94% yield from 2 by the procedure described for preparation of 8: nmr ($CDCl_3$) δ 6.08 (d, 1, $J_{9,10}$ = 4.0 Hz, H_9), 5.55 (d, 1, $J_{10,10a}$ ~ Hz, H_{10}).

O,O'-**Di(phenoxycarbonyl)-9(a),10(a)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (7).** Compound 7 was prepared in 91% yield from 3 by the method given for preparation of 8: mp 134–136° (benzene–hexane 1:1); nmr ($CDCl_3$) δ 6.02 (d, 1, $J_{9,10}$ = 2.5 Hz, H_9), 5.22 (m, 1, H_{10}).

9(e),10(e)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene Dicarbamate (12). *O,O'*-Di(phenoxycarbonyl)-9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8), 2.46 g (5.37 mmol), was added in small portions over a 20-min period to 130 ml of liquid ammonia and the solution was stirred and allowed to reflux using a dewar condenser filled with a Dry Ice–acetone mixture. After 6 hr the condenser was removed and the ammonia allowed to evaporate. The white solid residue was dissolved in ethyl acetate and the solution was washed with water, followed by 10% aqueous hydrochloric acid, 10% aqueous sodium bicarbonate, and water, dried, and evaporated. The white solid remaining was washed with warm hexane, affording 9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene dicarbamate (12): 1.35 g (83%); mp 244–246° dec; λ_{max} (H_2O) 210 nm (ϵ 7370); λ_{max} (1-octanol) 264 nm (ϵ 268); nmr (DMSO-d_6) δ 5.87 (d, 1, $J_{9,10}$ = 9.0 Hz, H_9), 4.83 (t, broadened, 1, $J_{10,10a}$ ~ 10.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 244 (1, M − CH_4ON_2), 243 (4, M − CH_3O_2N), 200 (100, M − $C_2H_4O_3N_2$), 185 (18, $C_{13}H_{13}O$), 182 (55, $C_{14}H_{14}$), 171 (23, $C_{12}H_{11}O$), 158 (52, $C_{12}H_{14}$), 157 (80, $C_{11}H_9O$; 8, $C_{12}H_{13}$), 154 (27, $C_{12}H_{10}$), 145 (23, $C_{10}H_9O$), 141 (56, $C_{11}H_9$), 131 (12, C_9H_7O), 129 (55, $C_{10}H_9$), 115 (42, C_9H_7), 105 (16, C_7H_5O), 91 (36, C_7H_7), 77, (20, C_6H_5). *Anal.* ($C_{16}H_{20}N_2O_4$) C, H, N.

9(a),10(e)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene Dicarbamate (9). The procedure described for the 9(e),10(e) isomer 12 was used to prepare this isomer, affording 9 in 83% yield: mp 206–210° dec (benzene–ethanol 2:1); λ_{max} (H_2O) 210 nm (ϵ 8260); λ_{max} (1-octanol) 265 nm (ϵ 280); nmr (DMSO-d_6) δ 5.97 (d, 1, $J_{9,10}$ = 3.0 Hz, H_9), 4.75 (dd, 1, $J_{10,10^a}$ = 11.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 244 (7, M − CH_4ON_2), 243 (3, M − CH_3O_2N), 200 (100, M − $C_2H_4O_3N_2$), 185 (32, $C_{13}H_{13}O$), 184 (25, $C_{14}H_{16}$), 182 (15, $C_{14}H_{14}$), 158 (20, $C_{12}H_{14}$), 157 (14, $C_{11}H_9O$; 14, $C_{12}H_{13}$), 145 (62, $C_{10}H_9O$), 141 (61, $C_{11}H_9$), 131 (10, $C_{10}H_{11}$; 5, C_9H_7O), 129 (58, $C_{10}H_9$), 115 (37, C_9H_7), 105 (10, C_8H_9; 3, C_7H_5O), 91 (22, C_7H_7), 77 (13, C_6H_5). *Anal.* ($C_{16}H_{20}N_2O_4$) H, N; C: calcd, 63.14; found, 62.72.

9(e),10(a)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene Dicarbamate (10). The procedure described for the preparation of the 9(e),10(e) isomer 12 was used for the synthesis of this isomer, affording 10 in 83% yield: mp 219–220.5° (hexane–ethyl acetate 1:1); λ_{max} (H_2O) 210 nm (ϵ 7250); nmr (DMSO-d_6) δ 5.83 (d, 1, $J_{9,10}$ = 4.0 Hz, H_9), 5.17 (d, 1, $J_{10,10a}$ ~ 0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 244 (1, M − CH_4ON_2), 243 (3, M − CH_3O_2N), 200 (78, M − $C_2H_4O_3N_2$), 185 (24, $C_{13}H_{13}O$), 184 (44, $C_{14}H_{16}$), 182 (40, $C_{14}H_{14}$), 158 (13, $C_{12}H_{14}$), 157 (31, $C_{11}H_9O$; 6, $C_{12}H_{13}$), 145 (21, $C_{10}H_9O$), 141 (100, $C_{11}H_9$), 131 (15, C_9H_7O; 7, $C_{10}H_{11}$), 129 (49, $C_{10}H_9$), 128 (40, $C_{10}H_8$), 115 (37, C_9H_7), 105 (7, C_7H_5O; 10, C_8H_9), 104 (7, C_8H_8), 91 (27, C-27, C_7H_7), 77 (19, C_6H_5). *Anal.* ($C_{16}H_{20}N_2O_4$) C, H, N.

9(a),10(a)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene Dicarbamate (11). The procedure described for the preparation of the 9(e),10(e) isomer 12 was used for the synthesis of this isomer, affording 11 in 89% yield: mp 199–201° (ethyl acetate); λ_{max} (H_2O) 210 nm (ϵ 6590); λ_{max} (1-octanol) 265 nm (ϵ 268); nmr (DMSO-d_6) δ 5.55 (d, 1, $J_{9,10}$ = 2.0 Hz, H_9), 4.80 (dd, 1, $J_{10,10a}$ = 1.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 244 (1, M − CH_4ON_2), 243 (1, M − CH_3O_2N), 200 (60, M − $C_2H_4O_3N$), 185 (20, $C_{13}H_{13}O$), 184 (50, $C_{14}H_{16}$), 182 (22, $C_{14}H_{14}$), 158 (12, $C_{11}H_{10}O$; 6, $C_{12}H_{14}$), 157 (18, $C_{11}H_9O$; 6, $C_{12}H_{13}$), 145 (35, $C_{10}H_9O$), 142 (45, $C_{11}H_{10}$), 141 (100, $C_{11}H_9$), 131 (9, C_9H_7O), 129 (55, $C_{10}H_9$), 128 (20, $C_{10}H_8$), 115 (39, C_9H_7), 105 (5, C_8H_9; 1, C_7H_5O), 104 (6, C_8H_8), 91, (22, C_7H_7), 77 (15, C_6H_5). *Anal.* ($C_{16}H_{20}N_2O_4$) C, H, N.

1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-Octahydro-9-oxophenanthrene (13).[9] This ketone was prepared by the method of Gutsche and Johnson,[12] mp 95° (lit.[12] mp 95–96°). Deuterium exchange was accomplished as previously described:[9] mass spectrum (70 eV) *m/e* (rel intensity, fragment) 201 (16, M + 1), 200 (100, $C_{14}H_{16}O$), 185 (32, $C_{13}H_{13}O$), 182 (19, $C_{14}H_{14}$), 158 (60, $C_{12}H_{14}$), 157 (15, $C_{11}H_9O$), 145 (15, $C_{10}H_9O$), 141 (13, $C_{11}H_9$), 131 (48, C_9H_7O), 129 (22, $C_{10}H_9$), 128 (20, $C_{10}H_8$), 115 (31, C_9H_7), 105 (30, C_7H_5O), 91 (18, C_7H_7), 77 (23, C_6H_5). The deuterated ketone gives a very similar spectrum with major differences at 201 and 202 corresponding to parent ions of the deuterated compounds with one and two deuteriums, respectively, as expected.[13,14]

Octanol–Water Partition Studies. To 10.0 ml of distilled water in a 15-ml screw-capped centrifuge tube was added about 40 mg of a diol and the mixture was inverted on a submersion rotator (Scientific Industries, Inc., Queens Village, N. Y.) at 29 rpm for 30 min at room temperature. Octanol (1-octanol, Eastman Organic Chemicals), 0.50 ml, was added and the inversion continued for an additional 30 min at 29 rpm. The two-phase solution was then separated after centrifugation at 2000 rpm for 10 min. The concentrations of diol in the aqueous phase and in the octanol phase (100 λ diluted to an appropriate volume) were determined by uv methods (measured at 263 and 264 nm, respectively) utilizing a standard curve (absorbance *vs.* concentration) in each solvent. All experiments were done in duplicate. The $P_{o,w}$ for the dicarbamates were determined in a similar fashion (uv, 210 nm in H_2O and 264 nm in octanol) using a previously prepared stock solution of each dicarbamate in 1-octanol (about 3 mg/ml). Variations were consistently less than 5%.

Pharmacological Testing. Protection against tonic convulsion of supramaximal electroshock was determined by the method of Berger,[15] with slight modification. Corneal electrode stimulation, 150% of threshold, was applied 30 min after ip administration of test compounds (1% acacia suspension) to groups of four male 14–20-g mice. Protection against pentylenetetrazole-induced convulsions was done by the method of Berger,[16] with slight modification. Pentylenetetrazole (100 mg/kg) was administered 30 min after ip administration of test compounds (1% acacia suspension) to groups of four male 14–20-g mice.

Acknowledgments. Partial support of this research was provided by a Career Development Award (5-K4-GM-70,023) to W. L. N. from the National Institute of General Medical Sciences. Funds for partial support of the mass spectrometry facility were provided by the National Science Foundation. The authors wish to express their gratitute to Dr. Milton Kletzkin, Wallace Laboratories, for screening the experimental compounds in anticonvulsant assays.

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Communications to the Editor

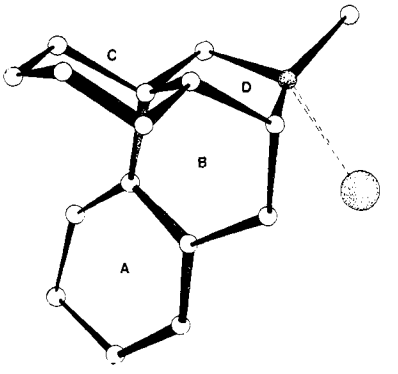
Importance of the Nitrogen Lone Electron Pair Orientation in Stereospecific Opiates

Sir:

In recent years, important new information has accumulated concerning the stereochemical basis of structure–activity relationships at the analgesic receptor level.[1] Elegant methods now appear to be available for the localization and isolation of the receptor through the work of Snyder and coworkers.[2] However, the actual nature of the forces controlling agonist and antagonist binding at this level is still poorly understood. Absolute optical specificity of the receptor is displayed toward conformationally rigid agonists and antagonists of the morphinan series[1] but rarely toward flexible structures which may exhibit bimodal[3] and perhaps polymodal binding.[4] The unimodal binding of the morphinans may thus allow a study of conformational effects at the specific active site proper in the absence of possible complications from exo binding,[5] bimodal binding,[3] or binding on peripheral control sites[4] (polymodal binding). One aspect of conformation–activity relationships which appears to have escaped attention until now concerns stereoelectronic effects about the basic nitrogen of morphinans as opposed to stereoisomerism about chiral carbons. We now wish to present concrete evidence that the relative spatial orientation of the N lone electron pair (with or without an attached proton) in morphinans is of critical importance for productive interaction with the opiate receptor.

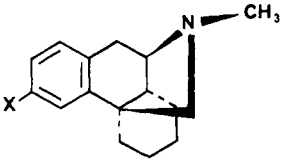
Our recently developed total synthesis of 14-substituted (hydroxyl) morphinans and isomorphinans[6] as based on earlier explorations[7] has allowed after appropriate modification the synthesis of the five-membered ring D analogs Ia and Ib of *N*-methylmorphinan and 3-hydroxyl-*N*-methylmorphinan (racemorphan), respectively.† The pure racemates Ia and Ib proved completely inactive as analgesics in the usual laboratory mouse tests. They were also totally devoid of antagonist activity and none of the common side effects characteristic of narcotics were observed. Only general CNS stimulation preceded by ataxia was produced in mice and rats at 5–20 mg/kg.

The complete inability of Ia and Ib to interact with the morphine receptor led us to an X-ray analysis of the three-dimensional structure of Ia whose crystal habit as the hydrobromide salt proved ideal for this purpose. The detailed X-ray work will be published separately when refinement of the atomic parameters is completed.‡ The



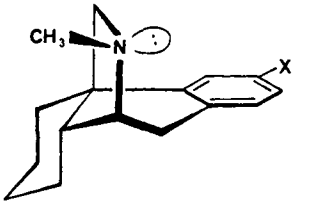
IIa

Figure 1. Stereoview of the crystal structure of *N*-methyl-D-normorphinan hydrobromide. The shaded atoms are nitrogen and bromine, respectively.

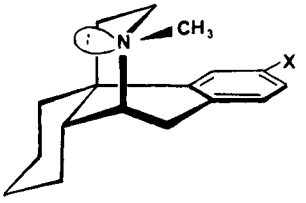


Ia, X=H

Ib, X=OH



IIb



III

†B. Belleau, T. Conway, and T. Doyle, unpublished results.

‡F. R. Ahmed and A. D. Hardy, unpublished results.