2-Diethylaminoethyl *p*-Nitrophenylpropionate.—A mixture of 10.0 g. (0.05 mole) of *p*-nitrophenylpropionic acid[10] and 25 ml. of thionyl chloride was allowed to reflux for 2 hr. The excess thionyl chloride was removed by distillation and the residue was treated with 60 ml. of dry benzene. A solution of 18.0 g. (0.15 moles) of 2-diethylaminoethanol in 60 ml. of dry benzene was slowly added to the acid chloride solution. When the addition was completed, the mixture was refluxed for 2 hr. and filtered. The filtrate, when distilled, yielded 10.0 g. (66%) of a viscous yellow oil which boiled between 167–169° (0.1 mm.). This oil, dissolved in 100 ml. of anhydrous ether, was converted to its hydrochloride by treatment with anhydrous hydrogen chloride. The salt was filtered and recrystallized from acetone by the addition of isopropyl ether. The white, crystalline product melted at 131–132°.

Anal. Calcd. for $C_{15}H_{23}ClN_2O_3$: C, 54.46; H, 7.01; N, 8.47. Found: 54.96; H, 7.19; N, 8.38.

2-Diethylaminoethyl *p*-Aminophenylpropionate.—2-Diethylaminoethyl *p*-nitrophenylpropionate hydrochloride (11.2 g., 0.034 mole) was dissolved in 30 ml. of water. Saturated sodium carbonate solution was added in sufficient quantity to raise the pH of the solution to 9. The oil that separated was extracted with three 30-ml. portions of ether. After drying with anhydrous sodium sulfate, 0.1 g. of platinum oxide, or 0.5 g. of W-2 Raney nickel catalyst was added, and the compound was reduced at a hydrogen pressure of 2.1 kg./cm.^{2} and 34° for 3 hr. After filtration, the solvent was removed by evaporation and the remaining yellow oil was distilled. The product distilled at 160–162° (0.2 mm.) and weighed 6.7 g. (75%).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 68.20; H, 9.06; N, 10.61. Found: C, 68.44; H, 9.41; N, 10.61.

Infrared Spectra.—All infrared spectra were obtained on a Beckman IR-4 infrared spectrophotometer. In the region of carbonyl absorption the frequencies were measured using a period of 8, spectral slit width 5 cm.$^{-1}$ and a gain of 100×. A speed of 0.02 μ/min. was employed.

Pharmacology.—A solution of the hydrochloride[11] or hydriodide of the test compound, in known molar concentration, and 15 μg./ml. of epinephrine hydrochloride in normal saline solution was prepared. A 0.25 ml. dose of this solution was injected intracutaneously in the anterior area of each of 2 guinea pigs whose backs had been previously clipped. An identical dose of the same solution was injected into the posterior area of each of 2 other guinea pigs. The borders of the resultant wheals were outlined with an indelible pencil. At the end of a 5 min. period, each animal was probed with a pin in the area outside the zone of the wheal. After observing the normal response of the animal to the stimulus, a total of 6 probes were applied to the area inside the wheal at intervals of 3–5 sec. The number of probes to which the guinea pig failed to respond was recorded.

The test of 6 probes to the area of the wheal was repeated on each guinea pig at 5 min. intervals for a total period of 1 hr. The number of times the probe failed to elicit a response in all 4 animals was added and the sum was divided by the total number of possible responses. The quotient, expressed in terms of per cent, was plotted on probit-logarithm graph paper against the molar concentration of the compound in the dose administered. Using the same 4 animals, a second concentration of the test compound was administered except that the injection sites (anterior-posterior) were reversed in each animal. In a similar manner additional concentrations of the test compound were employed until a well defined dose-response curve was obtained. The molar ED_{50} for each compound, the concentration at which the plotted line intersected the line of 50% response (probit 5), was then determined.

(10) F. Von Kunek and E. Pacsu, *Ber.*, **51**, 855 (1918).

(11) For those compounds isolated as the water insoluble free base, an equivalent amount of hydrochloric acid was added.

Structures Related to Morphine. XXV.[1a] 5-Propyl- and 5,9-Dipropyl-6,7-benzomorphans and a Pharmacologic Summary[1b]

J. HARRISON AGER, S. E. FULLERTON, AND EVERETTE L. MAY

National Institutes of Health, Bethesda 14, Maryland

Received January 24, 1963

Cyclization of 4-propyl- and 3,4-dipropyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridines (III) obtained in the Stevens rearrangement of the quaternary compounds (II) has produced the expected benzomorphans (IV) and (V). Compounds Va and Vb have been converted to open nitrogen analogs VIa and VIb which show significant diuretic activity in the rat. A tabular summary of the analgesic activity, acute toxicity (mice) and morphine-abstinence-suppressing capacity (monkey) of various 2′-hydroxy-2-methyl-6,7-benzomorphans is presented. In this series a pronounced, consistent separation of analgesic activity and physical dependence property has been achieved.

2′-Hydroxy-2-methyl-6,7-benzomorphans, a relatively new class of analgesic agents synthesized in our laboratory to date, include the 5-methyl[2]; 5-ethyl[3]; α- and β-5,9-dimethyl; 5,9-diethyl; 5-ethyl-9-methyl; and 5-methyl-9-ethyl derivatives.[1,4] Of the monoalkyl compounds the 5-ethyl analog was far more effective in mice than the 5-methyl. In the α-dialkyl series maximum activity was shown by the 5-methyl-9-ethyl derivative, while the 5-ethyl-9-methyl proved to be the most potent β-compound.[1,4] Thus, it appeared that a combined total of three carbon atoms in the 5 and 9 positions might be optimal for analgesic activity in this type of structure. To obtain additional information on this point, 5,9-dipropyl- and 5-propyl-2′-hydroxy-2-methyl-6,7-benzomorphane (IV and V) have been synthesized. A pharmacologic summary is also included in this report along with details of the conversion of V to corresponding open nitrogen derivatives (VI) desired for testing as diuretics.

Compounds IV and V were synthesized by the Stevens rearrangement method described previously.[1,3,5,6]

(1) (a) Paper XXIV, S. E. Fullerton, J. H. Ager, and E. L. May, *J. Org. Chem.*, **27**, 2554 (1962); (b) In honor of Dr. Erich Mosettig, deceased June, 1962.

(2) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

(3) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).

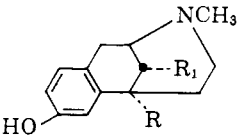
(4) For a leading reference and for details of the stereochemistry of the 5,9-dialkyl compounds, *cf.* S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(5) E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961).

(6) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962).

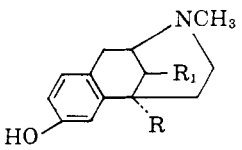
TABLE I

PHARMACOLOGY OF (±)-5-ALKYL AND (±)-5,9-DIALKYL-2-METHYL-6,7-BENZOMORPHANS



-5-Monoalkyl and α-5,9-dialkyl compounds

No.	R	R_1	ED_{50}[a]	LD_{50}[a]	Abstinence suppressant dose, mg./kg.[7]	Physical dependence capacity
VII	Me	H[f]	10.4	175	2–60, No suppression	None
VIII	Et	H[g]	2.3	170	1–16, No suppression	Low
Va	Pr	H	2.1	130	3–30, No suppression	None
IX	Me	Me[c]	3.0	175	24	Low
XI	Me	Et[e]	1.5	134	2–12, No suppression	None
X	Et[e]	Me[a]	4.9	309	>40	Low
XII	Et	Et[h]	4.2	425	2–60, No suppression	None
XII	Pr	Me[d]	2.9	>300		
Vb I	Pr	Pr	71.2	>400	3–48, No suppression	None

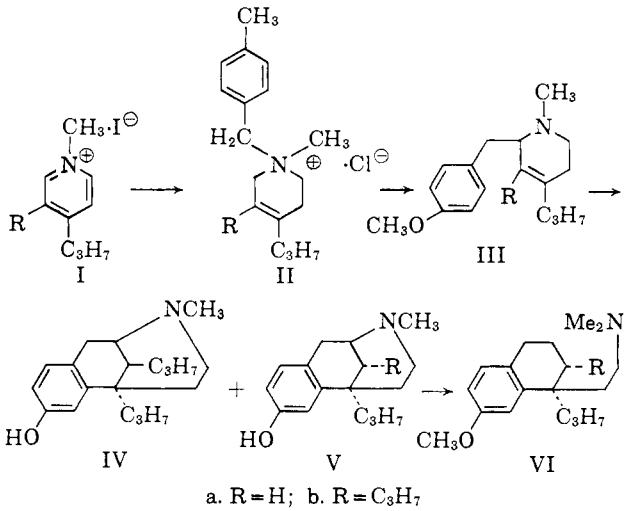


β-5,9-Dialkyl compounds

XIV	Me	Me[c]	0.44	67	>18	Low
XV	Me	Et[e]	0.47	100		
XVI	Et	Me[e]	0.27	75	1.0[b]	Intermediate
XVII	Et	Et[h]	0.28	120	0.5–12, No suppression	None
IV	Pr	Pr	0.87	55	.....	
XVIII	Morphine		2.1	550	3	High

[a] Expressed in mg./kg. (mice, subcutaneous administration); *cf.* N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Therap.*, **107**, 385 (1953). [b] All abstinence signs were not uniformly suppressed by any dose (to 12 mg./kg.) which did not produce some side effects. [c] E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959). [d] J. H. Ager, personal communication. [e] See ref. 1. [f] See ref. 2. [g] See ref. 3. [h] See ref. 6.

The yields of Va and Vb[4] (based on Ia and Ib) were *ca.* 30% and 20% respectively; IV was obtained in 3% over-all yield.[4] Cyclization of III (crude, or purified through the picrate) was effected with 48% hydrobromic acid (bath temperature 140–145°); 85% phosphoric acid gave low yields and principally decomposition products. Diastereoisomers IV and Vb were separated by fractional crystallization from acetone in which IV is much more soluble. Infrared data were valuable in following these separations (*cf.* Experimental) as were methiodide rate studies.[4]



a. R = H; b. R = C_3H_7

Conversion of Va and Vb to the open nitrogen compounds VIa and VIb was accomplished as in analogous series[6] by Hofmann degradation of the methyl ether and catalytic hydrogenation of the resultant methines. The product VIb was aromatized (5% palladium–charcoal) to 7-methoxy-1,2-dipropylnaphthalene.

In Table I are given the analgesic activity (mice), acute toxicity (mice) and physical dependence capacity[7] of 5-alkyl- and 5,9-dialkyl-2′-hydroxy-2-methyl-6,7-benzomorphans synthesized in our laboratory to date. Regarding activity, the 5-propyl derivative (compound Va) and the 5-ethyl (VIII), although racemates,[8] are equivalent to morphine (XVIII), 5 times as potent as the 5-methyl homolog (VII). The racemic α-5,9-dialkyl compounds[9] except the dipropyl derivative (Vb) are of the same order of effectiveness as morphine, maximum activity being shown by the 5-methyl-9-methyl analog (X). The first significant fall in activity is seen with the dipropyl derivative (Vb) which is

(7) G. A. Deneau and M. H. Seevers (Univ. of Mich.), personal communications, and Addenda to the Minutes of the 1959, 1960, 1961, and 1962 meetings of the Committee on Drug Addiction and Narcotics, National Research Council. Physical dependence capacity is defined as the capacity of a compound to suppress withdrawal symptoms in addicted monkeys (stabilized on 3 mg./kg. of morphine administered 4–6 times daily). Morphine (XVIII) is given as the reference compound.

(8) It is well known that in this type of structure (3-hydroxy-N-methylmorphinan, 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, etc.) almost all of the analgesic activity is due to the (−) isomer; *cf.* E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(9) The stereochemistry of the *levo*-isomers has been shown to conform to that of *levo*-3-hydroxy-N-methylmorphinan and morphine.[4]

only about 1/50 as potent as X. The β-racemates (*cf.* ref. 4 for stereochemistry) are from 7–70 times more potent than the α counterparts, maximum activity again being shown by the ethyl–methyl series. In this instance, however, it is the 5-ethyl-9-methyl (XVI) racemate showing highest potency, 30 times that of morphine. The fall in activity in going to the dipropyl derivatives is again sharp, albeit not as pronounced as in the α series. Apparently then the carbon atom total in the 5 and 9 positions should not exceed 4. The acute toxicity of the α compounds, although always lower than that of the β counterparts, does not nearly parallel analgesic activity. Thus the therapeutic index (LD_{50}:ED_{50}) of the β compounds is invariably more favorable than that of the corresponding α isomers. The highest therapeutic index (1000) is shown by β-(±) 5-ethyl-2,9-dimethyl-2′-hydroxy-6,7-benzomorphan (XVI).

As for physical dependence capacity (often equated with addiction liability), in the monkey species all compounds of this series except compound XVI either will suppress *none* of the symptoms of morphine abstinence or have *low* capacity to do so. Even the very potent compound XVI has only intermediate physical dependence capacity. It is evident, therefore, that referred to the mouse for analgesic activity and the monkey for physical dependence property, there is a uniformly good divorcement of these two phenomena in the benzomorphan series. Furthermore, in a 30-day chronic study[7] of compound XII, only mild physical dependence developed in contrast to severe withdrawal symptoms always seen in similar tests with strong analgesics such as morphine. Finally, it has been shown that in the case of XII and the *levo*-isomers of IX, these results regarding addiction liability[10] and analgesic activity[11] are to a good degree transferable to man. There can be little doubt then, that substitution of an alkyl or alkyl groups for ring C of morphine and the morphinans constitutes a step in the right direction in the dissociation of analgesic activity and addiction liability. Attention is called to compounds VIII, Va, XII and particularly XIV and XVII; the last two represent the unnatural configuration of morphine type alkaloids at positions 13 and 14 (5 and 9 of the benzomorphans). A thorough study of these compounds in man would seem warranted.

Experimental

Melting points were taken in a capillary (Hershberg apparatus, total-immersion thermometers). Microanalyses are by the Institute's service analytical unit, Harold McCann, Director. Infrared spectra (Perkin-Elmer 21) are by H. K. Miller and Mrs. Ann Wright, also of this Laboratory.

3,4-Dipropyl-1-methylpyridinium Iodide (Ib).—3,4-Dipropylpyridine (18.4 g.),[12] 28 ml. of acetone and 15 ml. of methyl iodide were mixed (heat evolution), kept at room temperature for 2–3 hr., diluted with ethyl acetate (10–12 ml.), and left at −15° for 2–3 hr. to give 31.4 g. (92%) of crystals, m.p. 98–100°; prisms from acetone or acetone–ethyl acetate, m.p. 99–100°.

Anal. Calcd. for $C_{12}H_{20}IN$: I, 47.22; H, 6.60. Found: C, 46.98; H, 6.60.

3,4-Dipropyl-1-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridinium Chloride (IIb).—To 31.4 g. of Ib, 150 ml. of *N* sodium hydroxide and 30 ml. of methanol was added 5.5 g. of sodium borohydride (stirring). The temperature rose to 65° and was maintained at 55–65° for 90 min. The mixture was diluted with cold water and extracted 3 times with ether. The combined extracts were washed once with water, dried (sodium sulfate) and evaporated at the water pump leaving 16.6 g. of crude base which was treated with 13 g. of *p*-methoxybenzyl chloride and 20 ml. acetone. After 2 hr. at −15° the material (IIb) was filtered and washed with acetone–ether (3:1); yield 31.1 g. (91%), m.p. 165–168°, after drying at 60° in a vacuum oven. It crystallized from acetone in needles, m.p. 171–173°.

Anal. Calcd. for $C_{20}H_{32}ClNO$: C, 71.08; H, 9.54. Found: C, 71.28; H, 9.45.

3,4-Dipropyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (IIIb) Picrate.—To 31.1 g. of IIb was added (vigorous, exothermic reaction) as rapidly as possible (stirring), 305 ml. of 0.9 *M* ethereal phenyllithium. The mixture was stirred for 2 hr., poured into ice water and the ethereal layer extracted 3 times with dilute hydrochloric acid in excess. The extracts were made alkaline with aqueous ammonia and the liberated base was dried in ether. Evaporation of the ether left 14.5 g. of crude IIIb which was purified through the picrate, using 50 ml. of acetone and 14.5 g. of picric acid. The yield of picrate, m.p. 132–136°, was 19.6 g. (42%); orange needles from acetone, m.p. 134–136°.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 59.54; H, 6.66; N, 10.29. Found: C, 59.40; H, 6.63; N, 10.58.

α-5,9-Dipropyl-2′-hydroxy-2-methyl-6,7-benzomorphan (Vb).—A solution of 4.5 g. of IIIb (regenerated from the picrate with aqueous lithium hydroxide and petroleum ether, b.p. 30–60°) in 48 ml. of 48% hydrobromic acid was kept at a bath temperature of 140–150° for 25 hr., poured into ice, made alkaline with ammonium hydroxide and extracted with chloroform. Evaporation of the dried extracts *in vacuo* left a residue which crystallized from 10–15 ml. of acetone (cooling eventually to −5°) in a yield of 2.6 g. (60%), m.p. 204–207°; irregular prisms from acetone or methanol, m.p. 209–211°, λ_{max}^{Nujol} 6.15 (m), 6.30 (s) μ.

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.39; H, 10.17. Found: C, 79.41; H, 10.45.

The **hydrochloride** crystallized from acetone–ether; m.p. 215–218°.[13]

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 70.45; H, 9.39; Cl, 10.95. Found: C, 70.55; H, 9.26; Cl, 10.85.

β-Isomer (IV).—The acetone filtrate from the 2.6 g. of Vb above was evaporated to dryness and the residue evaporatively distilled at 0.2 mm. (bath temperature 190–200°). The viscous distillate was dissolved in hot acetone, and the solution was concentrated to about 5 ml. On cooling to −15°, 0.56 g. (13%) of needles (IV),[14] m.p. 169–194°, separated. The base IV could be further purified through the hydrochloride salt (see below) or by recrystallization from acetone; m.p. 196.5–198°, λ_{max}^{Nujol} 6.19 (s) μ.

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.39; H, 10.17. Found: C, 79.32; H, 9.89.

The **hydrochloride** of IV (from acetone–hydrogen chloride) crystallized from methanol–acetone in prisms of m.p. 255–258°.

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 70.45; H, 9.39. Found: C, 70.35; H, 9.26.

1-Methyl-4-propylpyridinium Iodide (Ia).—4-Propylpyridine (20 ml.), 16 ml. of methyl iodide and 30 ml. of acetone were mixed (ice cooling may be necessary), kept at room temperature briefly, then cooled in Dry Ice–acetone. The crystals were collected, washed with acetone–ethyl acetate at −8°, placed in a weighed container and dried at 65° (25 mm.) for 2 hr.; yield 34 g. A small sample was recrystallized from acetone–ethyl acetate for analysis; m.p. 54–57°.

Anal. Calcd. for $C_9H_{14}IN$: C, 40.70; H, 5.36. Found: C, 40.62; H, 5.27.

2′-Hydroxy-2-methyl-5-propyl-6,7-benzomorphan (Va).—To 34 g. of Ia, 200 ml. of *N* sodium hydroxide and 10 ml. of methanol was added (stirring) 5.0 g. of sodium borohydride. The temperature rose to 52° and was kept at 55–60° for 2 hr. The re-

(10) H. F. Fraser, H. Isbell, D. E. Rosenberg, and A. D. Wolbach, Jr., personal communication.

(11) L. Lasagna and T. J. De Kornfeld, personal communication.

(12) Supplied by Dr. F. E. Cislak, Reilly Tar and Chemicals Corp., Indianapolis, Ind.

(13) Prolonged boiling of this hydrochloride in acetone converted it to a hydrochloride (ellipsoids), m.p. 261–263°, which also analyzed correctly and gave the same base (Vb) as the lower-melting hydrochloride.

(14) Occasionally the needles were contaminated with a few heavy prisms (Vb) which could be separated mechanically or by fractional crystallization from acetone in which IV is much more soluble than Vb. Infrared spectral differences in Nujol (especially in the 6–6.5 μ region) were also pronounced for IV and Vb. These and methiodide rate studies were utilized in effecting the separation and in determining the configurational assignments of IV and Vb (*cf.* ref. 1 and 4).

mainder of the procedure was essentially the same as that used in the preparation of IIb; yield of hygroscopic IIa, 28 g. (73%), m.p. 132–134°. Rearrangement of 28 g. of IIa (dried at 60° *in vacuo*) was effected as described for IIb and gave 23 g. of impure IIIa. This and 200 ml. of 48% hydrobromic were kept at a bath temperature of 140–150° for 24 hr. and the resultant Va isolated as described for Vb; yield 9.8 g. (43%) of crude Va; 6.8 g. m.p. 214–217°, after a recrystallization from acetone or methanol, λ_{max}^{Nujol} 6.14(w), 6.30(s) μ.

Anal. Calcd. for $C_{18}H_{24}ClNO$: C, 68.19; H, 8.58. Found: C, 68.42; H, 8.60.

α-5,9-Dipropyl-2′-methoxy-2-methyl-6,7-benzomorphan Methiodide.—Methanol (45 ml.), 5 g. of Vb and 80 ml. of 3% ethereal diazomethane were stirred to solution (4–6 hr.). An additional 80 ml. of diazomethane solution was added and the mixture kept at 25° for 2–3 days. Solvents were distilled finally *in vacuo* and the residue evaporatively distilled at 0.2 mm. (bath temperature 145°). The 4.3 g. of distillate and methyl iodide in acetone gave the methiodide; prisms, m.p. 245–247°.

Anal. Calcd. for $C_{21}H_{34}INO$: C, 56.88; H, 7.95. Found: C, 57.06; H, 7.85.

1,2-Dipropyl-7-methoxy-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VIb) Hydrochloride.—The above methiodide (4.3 g.), 4.3 g. of sodium hydroxide and 43 ml. of water were refluxed for 6 hr., cooled and extracted with ether. Evaporation of the ether left 2.5 g. of oil which, with 0.2 g. of platinum oxide and 30 ml. of methanol, absorbed 1 molar equivalent of hydrogen in 30 min. The filtered solution was evaporated to dryness and the residue converted to the hydrochloride (acetone–ether–dry hydrogen chloride).

Anal. Calcd. for $C_{21}H_{38}ClNO$: C, 71.3; H, 10.3. Found: C, 71.5; H, 10.4.

1,2-Dipropyl-7-methoxynaphthalene Picrate.—One gram of VIb and 1.0 g. of 5% palladium–charcoal were mixed intimately in a vented test tube which was then immersed in an oil bath, preheated to 250°. The temperature of the bath was raised to 315° during 10 min. and kept at this temperature ±5° for another 20 min. The cooled mixture was extracted 3 times with ether and these extracts were washed with dilute hydrochloric acid. Drying and evaporation of the ether and evaporative distillation at 100–110° (0.2 mm.) gave 0.6 g. of hydrocarbon which with 0.6 g. of picric acid and 3–5 ml. of ethanol (warming to solution) yielded, after cooling to −15°, the crystalline picrate; orange needles from methanol, melting at 68–69° to a melt which did not flow freely until 100°.

Anal. Calcd. for $C_{23}H_{25}N_3O_8$: C, 58.58; H, 5.35. Found: C, 58.45; H, 5.33.

Ultraviolet maxima (in ethanol) of the crude distillate above or hydrocarbon prepared from the pure picrate were at 234, 279, 288, 315 and 330 mμ. These and extinction coefficients were consistent with the 7-methoxy-1,2-dialkylnaphthalene structure.[6]

7-Methoxy-1-(2-dimethylaminoethyl)-1-propyl-1,2,3,4-tetrahydronaphthalene (VIa) Hydrochloride.—This compound was prepared essentially as described for VIb. The intermediate **2′-methoxy-2-methyl-5-propyl-6,7-benzomorphan methiodide** crystallized from acetone–methanol; m.p. 199–204°. It was dried at 100° for analysis.

Anal. Calcd. for $C_{18}H_{28}INO$: C, 53.89; H, 7.03. Found: C, 54.06; H, 7.32.

The VIa hydrochloride prepared from this methiodide crystallized from acetone in needles, m.p. 202–204°; yield from Va 70%. It was dried at 100° for analysis.

Anal. Calcd. for $C_{18}H_{30}ClNO$: C, 69.33; H, 9.70. Found: C, 69.36; H, 9.76.

Stereochemistry of the Interaction of Enantiometic 1,3-Dioxolane Analogs of Muscarone with Cholinergic Receptors[1]

B. BELLEAU AND J. PURANEN

Department of Chemistry, University of Ottawa, Ottawa, Ontario

Received November 19, 1962

Starting from D-isopropylidene glycerol, the synthesis of L(+)-*cis*-2-methyl-4-trimethylammoniummethyl-1,3-dioxolane iodide (XVI) and its enantiomer (VIII) is described as outlined in Charts 1 and 2. The relative configurations were established by direct comparison of the key intermediates VI and XIV with corresponding racemates of previously established configurations. Comparison of the cholinomimetic activity of VIII with that of XVI revealed the latter to be approximately 100 times more active than the former and 6 times more potent than acetylcholine. It is pointed out that these observations are not consistent with Waser's interpretation of the active conformation of D-muscarone. The inversion of the optical specificity of the receptors toward the enantiomers of muscarone but not toward the dioxolane analogs VIII and XVI is accounted for if the presence of an accessory nucleophilic site on the receptor is postulated.

In the first paper of this series,[1] the synthesis, stereochemistry and cholinomimetic activity of quaternary salts of the 1,3-dioxolane series (the Fourneau series[2]) was reported. The effect of optical isomerism on activity in this group was also studied in a preliminary fashion[1] and the results suggested that the enantiomers of *cis*-2-methyl-4-trimethylammoniummethyl-1,3-dioxolane iodide (*cis*-F2268) (I, R = CH_3) should be of special interest because optimum activity is associated with the *cis* configuration. Resolution experiments having produced negative results, the synthesis of the desired enantiomers (VIII) and (XVI) was approached using a starting material of known absolute configuration. We have shown[1] that the 1,3-dioxolane I (R = CH_3) referred to as F2268 in the literature[2] consists of a 60:40 mixture of *cis*- and *trans*-isomers. The synthesis of pure *dl-cis*- and *dl-trans*-F2268 was successfully accomplished and the configurations rigorously established.[1] We now wish to report the synthesis and cholinomimetic activity of the enantiomers of *dl-cis* F2268.

Starting from D-isopropylidene glycerol, the sequence described in Chart I was applied to the synthesis of optically pure D(-)(VIII) (D-*cis*-F2268). Intermediates (III) and (IV) were described in part I.[1] We had observed[1] previously that the separation of *cis*, *trans* isomers in the 1,3-dioxolane series could be accomplished best when a trichloromethyl substituent rather than a methyl group was present at position 2. As expected, the reaction of chloral with IV led to a 60-40 mixture of D-*trans*-(V) and D-*cis*-(VI) from which pure VI could be separated by crystallization albeit

(1) Published as part II of the series entitled "Studies on the Chemical Basis for Cholinomimetic and Cholinolytic Activity." For part I, see D. Triggle and B. Belleau, *Can. J. Chem.*, **40**, 1201 (1962).

(2) J. P. Fourneau, D. Bovet, F. Bovet, and G. Montézin, *Bull. Soc. Chim. Biol.*, **26**, 134, 516 (1944).