evaporated to dryness *in vacuo*. The dihydromonomethyl ester (IIIb) was recrystallized from acetone–hexane and furnished 37 mg. of pure product, m.p. 170–172°; $[\alpha]^{23}D$ +76° (*c* 0.34, alcohol); λ_{max}^{KBr} 3.05, 5.78, and 5.85 μ; n.m.r. ($CDCl_3$) τ 6.36 (OCH_3), 8.72 (4,4-dimethyl), 8.84 (19-methyl); neut. equiv. 513.

Anal. Calcd. for $C_{32}H_{54}O_5$: C, 74.09; H, 10.49; OCH_3, 5.98. Found: C, 73.93; H, 10.49; OCH_3, 6.28.

The above dihydromonomethyl ester IIIb was also obtained when the monomethyl ester IIc (50 mg.) was hydrogenated in ethanol (5 ml.) with 50 mg. of 10% Pd-on-charcoal catalyst.

3,4-Seco-$\Delta^{8,24(28)}$-eburicadien-3,4,21-triol (IVa).—A solution of 200 mg. of the 3,4-seco-$\Delta^{8,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa) in 20 ml. of freshly distilled tetrahydrofuran was added dropwise over a 15-min. period to a suspension of 200 mg. of lithium aluminum hydride in 30 ml. of tetrahydrofuran. The mixture was refluxed for 3 hr. and, after cooling, 0.5 ml. of a saturated sodium sulfate solution was added. The suspension was filtered, the precipitate washed three times with hot chloroform, and the solution evaporated to dryness *in vacuo*. The residue (197 mg.) on recrystallization from acetone gave 160 mg. of pure triol IVa, m.p. 148–149°; $[\alpha]^{23}D$ +89° (*c* 0.59, $CHCl_3$); λ_{max}^{Nujol} 3.08, 6.10, and 11.28 μ; n.m.r. ($CDCl_3$) τ 5.26 (28-CH_2), 6.33 (m 3- and 21-CH_2), 8.67 (4,4-dimethyl), 8.83 (19-CH_3).

Anal. Calcd. for $C_{31}H_{54}O_3$: C, 78.42; H, 11.47. Found: C, 78.18; H, 11.81.

The diacetate IVb was prepared in pyridine solution with acetic anhydride.

3,4-Seco-Δ^8-eburicene-4,24,28-triol-3,21-dioic Acid (V).—To a solution of 47 mg. of 3,4-seco-$\Delta^{8,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa) in 3 ml. of dioxane and 0.2 ml. of pyridine was added dropwise over a 30 min. period a solution of 26 mg. of OsO_4 in 3 ml. of dioxane. The solution was allowed to remain at room temperature for an additional hour and then decomposed with H_2S. The mixture was filtered over a Celite pad and the filtrate was evaporated to dryness *in vacuo*. The residue (58 mg.) was recrystallized from ethyl acetate with the aid of Darco G-60 affording glycol acid V, m.p. 233–235°; $[\alpha]D$ +68° (*c* 0.47, alcohol); λ_{max}^{KBr} 2.95, and 5.85 μ; neut. equiv. 269 (calcd. 268).

Anal. Calcd. for $C_{31}H_{52}O_7$: C, 69.37; H, 9.77. Found: C, 69.45; H, 9.65.

Acknowledgment.—The authors wish to thank the following members of the staff of the Squibb Institute for their contributions to this work: Mr. J. Alicino and Mr. C. Sabo for the microanalyses, Miss B. Keeler and Miss R. Karitzky for the infrared spectra, Mr. W. Bullock for the ultraviolet spectra, Dr. A. Cohen for the n.m.r. spectra, and Mr. H. Basch for the antibacterial assays.

Structures Related to Morphine. XXVII.[1] α- and β-5,9-Diethyl-2-methyl-6,7-benzomorphans

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Sodium borohydride reduction of the dihydropyridine base II obtained in the reaction of benzylmagnesium chloride and 3,4-diethylpyridine methiodide has given 2-benzyl-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (III). This is cyclized by hot hydrobromic acid mainly to α-5,9-diethyl-2-methyl-6,7-benzomorphan (VI) and (as the hydrochloride) by aluminum bromide to a mixture of VI and the β isomer IX as shown by thin film chromatography. Base IX, essentially to the exclusion of VI, resulted from aluminum bromide cyclization of *trans*-2-benzyl-3,4-diethyl-1-methyl-1,2,3,6-tetrahydropyridine hydrobromide (VIII) also synthesized from II *via* V, IV, and VII. The structure and stereochemistry of IX were proved by converting it to the known β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (X). The stereochemistry of both VI and IX was also confirmed by methiodide rate studies. Compounds VI and IX are relatively potent analgesics and VI has no addiction-sustaining capacity in morphine-addicted monkeys.

The analgesically favorable effect of a properly positioned phenolic hydroxyl in structures with a heterocyclic nitrogen (*e.g.*, the morphinans and benzomorphans)[2] has been known for some time. However, the role of this substituent in tolerance and physical dependence has not been studied, perhaps because deoxy compounds of the order of potency of morphine have not been available.[3] The high activity displayed by various 2′-hydroxy-5,9-dialkyl-6,7-benzomorphans, particularly the β-diastereomers,[4] provided hope that nonphenolic compounds[5] of morphine-like potency are not implausible. Furthermore, any such deoxy compound of possibly negligible addiction liability would not be readily convertible to a product of greater addiction potential, a hazard generally attending hydroxy compounds (*viz.*, conversion of morphine to heroin[2a] and β-*dl*-methadol to β-*dl*-acetylmethadol[2a,6]). Consequently, we have synthesized α- and β-5,9-diethyl-2-methyl-6,7-benzomorphans (VI, IX), deoxy compounds selected for study principally on the basis of comparative results reported earlier[4] in the 2′-hydroxy series.

The synthesis of the α-compound VI was achieved, as usual, by the Grewe method,[7,8] except that sodium borohydride[9] was used instead of palladium-catalyzed hydrogen in the reduction of the dihydro base II to 2-benzyl-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (III). Cyclization of III with hot hydrobromic acid gave VI in 76% yield. No β-isomer IX could be iso-

(1) Paper XXVI: J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *J. Org. Chem.*, **28**, 2470 (1963).

(2) (a) E. L. May in "Medicinal Chemistry," 2nd Ed., A. Burger, Ed., Interscience, New York, N. Y., 1960, p. 311 *et seq.*; (b) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(3) N-Methylmorphinan (ref. 2a), although one-fifth as potent as morphine and comparable to pethidine in animal screening tests, has not been further examined.

(4) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(5) Otherwise close congeners of morphine and the morphinans.

(6) H. Isbell, H. F. Fraser, M. H. Seevers, and G. A. Deneau, private communications.

(7) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948).

(8) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

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

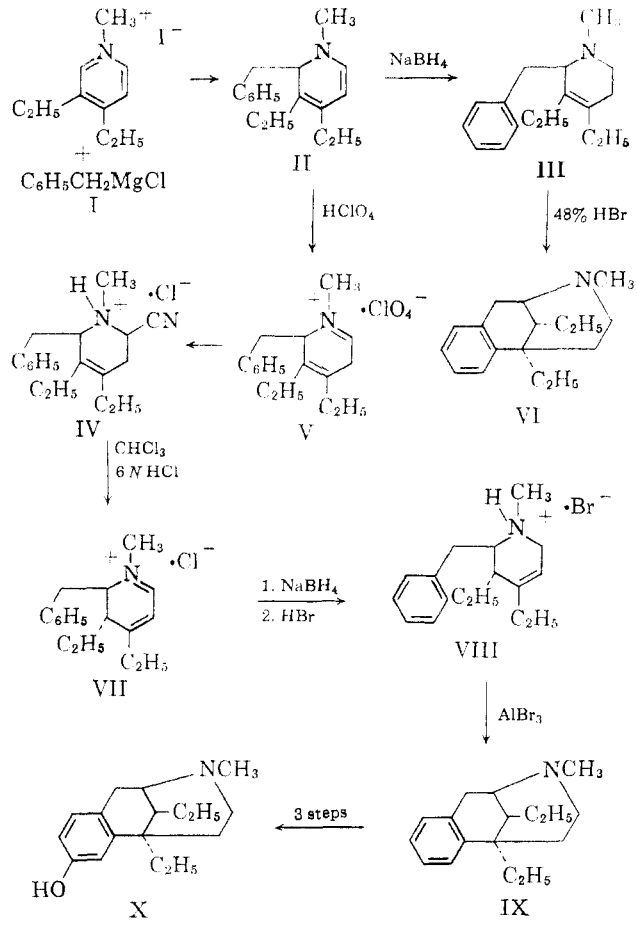
lated in contrast to experience in the hydroxy series where 3–6% yields of β-compounds could always be detected, and in contrast with the only other deoxy compound investigated in this manner.[1] However, treatment of III-hydrochloride in carbon disulfide with aluminum bromide led to a mixture of VI and IX in a ratio of 1:2, in conformity with the dimethyl deoxy series.

For the synthesis of IX to the exclusion of VI, we applied the elegant series of transformations recently reported by Fry[10] for the lower homologous β-2,5,9-trimethyl-6,7-benzomorphan. In this sequence the perchlorate V of dihydro base II was treated with sodium cyanide giving 2-benzyl-6-cyano-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (IV) isolated as the hydrochloride salt. Boiling chloroform in the presence of 6 *N* hydrochloric acid caused migration of the Δ^3-double bond of IV to the Δ^4-position and expulsion of hydrogen cyanide to give the hydrochloride of 2-benzyl-3,4-diethyl-1-methyl-2,3-dihydropyridine (VII) with the benzyl and 3-ethyl groups presumably in *trans*-juxtaposition.[10] This uncharacterized compound was reduced to 2-benzyl-3,4-diethyl-1-methyl-1,2,3,6-tetrahydropyridine, isolated as the hydrobromide VIII, which could be cyclized to β-5,9-diethyl-2-methyl-6,7-benzomorphan (IX) in a 50% yield of distilled (pure) base.

The structure of VI was assigned by analogy[1] while that of IX was confirmed by its conversion to the 2′-hydroxy analog X,[11] *via* nitration, reduction, and nitrous acid oxidation of the resulting amine.[8] Further confirmation of the stereochemistry of VI and IX was obtained from data on their rate of reaction with methyl iodide.[12] Thus the methiodide of VI was formed at least ten times more rapidly than that of IX as has been observed in the 2′-hydroxy series.[12] Mixtures of VI and IX could be analyzed by thin layer and gas chromatography.

The analgesic activities of VI and IX were determined by the mouse–hotplate method,[13] along with acute toxicities (mice)[13] and physical dependence capacity (in monkeys[14]) which is the capacity of a substance to suppress abstinence symptoms in morphine-addicted monkeys. Similar data for the 2′-hydroxy relatives, morphine, N-methylmorphinan, and 3-hydroxy-N-methylmorphinan are given for comparison.[14] The α-deoxy compound VI is nearly as potent an analgesic as the 2′-hydroxy relative,[11] whereas the β-isomer IX, only a little more active than VI, is one-fifteenth as potent as its 2′-hydroxy congener X, more nearly in line with expectations. Racemates VI and IX are more than twice as potent as (±)-N-methylmorphinan and are comparable to (*levo*) morphine, if one considers that the activity of VI and IX is, in each case, probably due to the *levo* antipode. The acute toxicities of VI and IX are, like analgesic potency, nearly identical, again somewhat surprising. In the 2′-hydroxy series the β isomers were invariably more toxic and more potent than their α counterparts.[4]

Scheme I



Notwithstanding the relatively high analgesic effectiveness of VI and IX, they have negligible capacity to substitute for morphine in an established addiction in monkeys. (±)-N-Methylmorphinan and (−)-3-hydroxy-N-methylmorphinan, on the other hand, are potent suppressors (5.3 and 0.9 mg., respectively, ≅ 3 mg. of morphine) of morphine abstinence relative to their analgesic potency.

However, on chronic administration of VI during a 31-day period while gradually increasing the dose to a total of 16 mg./kg. four times daily, abstinence signs on withdrawal were of intermediate intensity and persisted for 3 weeks, rather long lasting. In comparison with the 2′-hydroxy relative of VI,[4] slightly more potent and much less acutely toxic than VI, this is an unfavorable result; the 2′-hydroxy compound produced only mild withdrawal symptoms after 31 days of chronic administration while a dosage of 30 mg./kg. four times daily was reached. There is a hint then that the phenolic hydroxy, known to enhance potency and reduce toxicity,[2] also has a detoxifying effect with regard to drug dependence.

Experimental

Melting points were taken in a capillary (Hershberg apparatus, total immersion thermometers). Microanalyses are by Paula Parisius and Alice Wong of this laboratory.

2-Benzyl-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (III).—3,4-Diethyl-1-methylpyridinium iodide (I, 69 g., 0.25 mole)[11]

(10) E. M. Fry, *J. Org. Chem.*, **28**, 1869 (1963).

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

(12) S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(13) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). We are indebted to Dr. Nathan Eddy, Mrs. Louise Atwell, Mrs. Josephine Goodwin, and Mrs. Wendy Ness for these data which have been derived by probit analysis.

(14) M. H. Seevers and G. A. Deneau, Addenda to the Minutes of the Committee on Drug Addiction and Narcotics, National Academy of Sciences, National Research Council (1958–1962); see also H. Halbach and N. B. Eddy, *Bull. World Health Organ.*, **28**, 139 (1963); G. A. Deneau and M. H. Seevers, personal communications.

TABLE I

PHARMACOLOGICAL COMPARISON OF (±)-α- AND -β-5,9-DIETHYL-2-METHYL-6,7-BENZOMORPHANS, 2′-HYDROXY RELATIVES, MORPHINE, CODEINE, AND MORPHINANS

Compound	ED_{50} (s.c.)[a]	LD_{50} (s.c.)[a]	Abstinence[a] suppressant dose	Physical dependence capacity
VI[b]	5.0	83	No suppression to 16[e]	None
2′-Hydroxy derivative[b]	4.2	425	2–60, no suppression	None
IX[b]	4.2	115	2–16, slight suppression[c]	Very low
2′-Hydroxy derivative[b]	0.3	120	0.5–12, no suppression	None
N-Methylmorphinan[c]	11.3	92	5.3	High
(−)-3-Hydroxy derivative[d]	0.5	365	0.9	High
Morphine[b]	2.0	576	3.0	High

[a] Expressed in mg./kg. [b] HCl salt, see ref. 11. [c] Phosphate salt, see ref. 2a. [d] HBr salt, see ref. 2a. [e] Convulsant dose in one monkey.

and 100 ml. of dry ether were stirred vigorously as 200 ml. (0.27 mole) of 1.4 *M* ethereal benzylmagnesium chloride was added rapidly. The mixture, stirred for about 6 hr., gave two liquid layers and was poured, with vigorous stirring, into ice–water containing ammonium chloride and a little aqueous ammonia. The ether layer was shaken three times with excess, cold hydrochloric acid. The acid extracts were made alkaline with cold, aqueous ammonia and extracted quickly with ether to give, after drying over magnesium sulfate and evaporation of the ether *in vacuo*, 40 g. of dark brown oil II which was immediately dissolved in 250 ml. of methanol. The stirred solution was treated with 150 ml. of 1 *N* sodium hydroxide, then gradually with 9 g. (0.25 mole) of sodium borohydride. The mixture was stirred overnight at 50–60°, diluted with water, and extracted three times with ether. The combined extracts were washed once with water, dried (magnesium sulfate), and evaporated at the water pump leaving 37 g. (61% from I) of III, b.p. 105° (200 μ).

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.80; H, 10.17.

The **picrate** was prepared and recrystallized from ethanol; m.p. 130.5–132.5°.

Anal. Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.46; H, 5.97. Found: C, 58.59; H, 5.53.

The **hydrobromide** was prepared and recrystallized several times from acetone–ether; m.p. 165–166°.

Anal. Calcd. for $C_{17}H_{26}BrN$: C, 62.96; N, 8.08. Found: C, 63.18; H, 7.97.

α-5,9-Diethyl-2-methyl-6,7-benzomorphan (VI).—The tetrahydropyridine hydrobromide (III·HBr, 7 g., 0.22 mole) was dissolved in 100 ml. of 48% hydrobromic acid and stirred at 135–140° for about 2 days, to give a clear, brown solution. The product was cooled and poured into ice–water. Concentrated ammonium hydroxide was added until the mixture was basic, and it was then extracted with ether. The organic solution was washed with water, dried over magnesium sulfate, and filtered. The solvent was removed *in vacuo* to give a brown oil (4.9 g., 93%). The oil was distilled at 108° (150 μ) to give a colorless oil (4 g., 76%).

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 84.02; H, 10.17.

The oil was converted to the **hydrochloride** and crystallized from acetone–ether. It was sublimed at 170° (90 μ) and recrystallized, m.p. 250–251°.

Anal. Calcd. for $C_{17}H_{26}ClN$: C, 72.96; H, 9.37. Found: C, 73.02; H, 9.70.

A **picrate** was prepared and crystallized in ethanol. Large crystals formed during recrystallization from acetone; m.p. 176–179°.

Anal. Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.46; H, 5.97; N, 11.86. Found: C, 58.68; H, 5.77; N, 11.80.

2-Benzyl-3,4-diethyl-1-methyl-2,5-dihydropyridinium Perchlorate (V).—Ethereal benzylmagnesium chloride (275 ml., 0.44 mole) was added in a slow stream to a vigorously stirred mixture of pyridinium iodide (I, 100 g., 0.36 mole) in ether (200 ml.). The reaction mixture separated into the two liquid layers previously noted, during a 5-hr. stirring period. The mixture was poured into ice-cold 60% perchloric acid (150 ml.), giving a vigorous reaction. The mixture was separated, and the reddish upper layer was washed several times with hexane. Most of the solvent was removed from the red solution *in vacuo*, to give an oil mixed with water. This was allowed to stand at room temperature for 2 days, during which time a solid formed. The yellow solid was filtered and recrystallized from acetone–ether, to give 42 g. (34% from the pyridinium iodide I) of product, After several further recrystallizations from acetone–ether. colorless to pale yellow crystals, m.p. 128–129°, were obtained.

Anal. Calcd. for $C_{17}H_{24}NClO_4$: C, 59.73; H, 7.08. Found: C, 59.61; H, 6.72.

2-Benzyl-6-cyano-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride (IV).—The perchlorate (V, 43 g., 0.125 mole) and sodium cyanide (10 g., 0.2 mole) were stirred in a mixture of water (100 ml.) and ether (100 ml.) for about 4 hr. The yellow organic solution was separated from the pale yellow aqueous phase, washed with water, and dried over magnesium sulfate. The product was filtered and the solvent removed *in vacuo* to give a brown oil (29 g., 85%). The oil was converted to its **hydrochloride** (yellow solid, 26 g.) which was recrystallized from acetone–ether, m.p. 104–106°.

Anal. Calcd. for $C_{18}H_{25}ClN_2$: C, 70.93; H, 8.25. Found: C, 71.11; H, 8.38.

***trans*-2-Benzyl-3,4-diethyl-1-methyl-1,2,3,6-tetrahydropyridine Hydrobromide (VIII).**—The 6-cyanotetrahydropyridine hydrochloride (IV, 25 g., 0.082 mole) was dissolved in a mixture of chloroform (200 ml.) and 6 *N* hydrochloric acid (100 ml.). The mixture was refluxed and stirred overnight. The condenser was then removed and the chloroform was allowed to evaporate. The product was cooled, and most of the residual water was removed *in vacuo* to give solid VII. This solid was dissolved in a mixture of water (75 ml.) and methanol (75 ml.). Sodium borohydride (10 g., 0.27 mole) was added in small portions to the stirred mixture. The reaction was vigorous, gas being evolved during each addition of the borohydride. The mixture was then heated to 60° and stirred for about 4 hr. to give a mixture of a brown oil and a pale yellow aqueous solution. The oil was separated, and the aqueous solution was washed with ether. The combined oil and ether extracts were dried over magnesium sulfate. The product was filtered and the solvent removed *in vacuo;* the residual reddish oil was distilled at 96° (170 μ) to give the desired colorless product.

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.97; H, 10.18.

It was found that better yields could be obtained by converting the dry ethereal solution of the base to its hydrobromide directly, without the intermediate distillation. The over-all yield from the 6-cyanotetrahydropyridine (IV) through dihydropyridinium chloride VII, which need not be isolated, to the recrystallized tetrahydropyridine hydrobromide VIII was 31%.

The **hydrobromide** was recrystallized from acetone–ether; m.p. 214.5–215.5°.

Anal. Calcd. for $C_{17}H_{26}BrN$: C, 62.96; H, 8.08. Found: C, 63.14; H, 8.08.

β-5,9-Diethyl-2-methyl-6,7-benzomorphan (IX) Hydrochloride.—Aluminum bromide (10 g., 0.038 mole) was added in small portions to a cold mixture of tetrahydropyridine hydrobromide (VIII, 8.2 g., 0.025 mole) in carbon disulfide (40 ml.). The mixture was stirred at room temperature for about 6 hr. to give an orange, liquid, lower layer. The upper, carbon disulfide layer was decanted, and the residual material was washed with ether several times. Water was added and the cold solution made basic with 9% ammonium hydroxide. The mixture was ether extracted, and the ethereal solution was dried over magnesium sulfate. Filtration and removal of solvent *in vacuo* gave a yellow oil (5.4 g., 88%). The product was distilled, and a hydrochloride

was prepared from the colorless oil and recrystallized several times from acetone–ether; m.p. 234–235°.

Anal. Calcd. for $C_{17}H_{26}ClN$: C, 72.96; H, 9.37. Found: C, 73.11; H, 9.71.

A **picrate** was prepared and recrystallized several times from ethanol; m.p. 209–210°.

Anal. Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.46; H, 5.97. Found: C, 58.67; H, 5.97.

β-5,9-Diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (X).[11]—The benzomorphan IX was converted *via* the 2′-nitro and 2′-amino derivatives to the known 2′-hydroxy X according to the general procedure of May and Fry.[8] The 2′-hydroxy compound was found to be identical with the known compound[11] in its melting point, mixture melting point (no depression), infrared spectrum, and thin layer chromatography.[15]

Vapor Phase Chromatography.—A Research Specialties vapor phase chromatograph was used with a 1.83-m. glass column, 6.3 mm. in diameter, silanized and packed with 1.5% SE 30 on 100–140 Chromosorb W. It was equipped with a flame ionization detector. The α-5,9-diethyl-2-methyl-6,7-benzomorphan hydrochloride (VI), β-5,9-diethyl-2-methyl-6,7-benzomorphan hydrochloride (IX), and β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (X) could be identified. A 9:1 mixture of α-VI and β-IX was identifiable. The reverse was not true. At least 25% of VI is needed in the mixture to discern it. The chromatograph was run isothermally at a column temperature of 132° for VI and IX. The α-benzomorphan VI had a somewhat longer retention time (21 min.) on the column than the β-IX (16 min.) and therefore gave a broader, more widespread band. No attempt was made to sharpen the peak since the two compounds could be easily differentiated. The 2′-hydroxybenzomorphan X was chromatographed using a column temperature of 190°. The retention time for this compound was 4 min.

Rate Studies.—The general procedure of Fullerton, May, and Becker[12] was used. In Table II are given the results which show that the reaction of VI with methyl iodide is ten times faster than the reaction of IX with this reagent, and leaves no doubt about the stereochemistry of VI and IX.

TABLE II

RATES OF REACTION OF METHYL IODIDE WITH BENZOMORPHANS

Compound	Reaction time, hr.	% Benzomorphan converted to methiodide
α-5,9-Diethyl-2-methyl-6,7-benzomorphan (VI)	2.5	29.8
	5.0	55.9
β-5,9-Diethyl-2-methyl-6,7-benzomorphan (IX)	2.5	3.8
	5.0	4.3
	24.0	9.7

(15) All of the products from the various reactions were examined by thin layer chromatography, using the general method of J. Cochin and J. W. Daly [*Experientia*, **18**, 294 (1962)]. The plates were coated with silica gel G (Merck, Darmstadt). The solvent system consisted of ethanol–dioxane–benzene–ammonium hydroxide, 5:40:50:5. The products were detected by spraying with potassium iodoplatinate reagent. In the case of VI and IX it was found that β-compound IX ran faster than α-compound VI. The R_f values were 0.81 for IX and 0.58 for VI, compared with 0.85 for a simultaneously chromatographed standard test mixture provided by the Brinkmann Instrument Co. (a mixture of 0.01% each of 4-dimethylaminobenzene, indophenol, and sudan red G in benzene).

Analgetics Based on the Pyrrolidine Ring. III.

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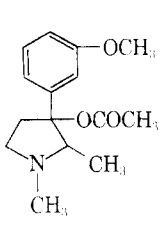
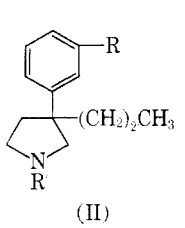
Received January 3, 1964

The pyrrolidine analgetic, *m*-(1-methyl-3-propyl-3-pyrrolidinyl)phenol (II, R = OH; R′ = CH_3), is described, having activity superior to meperidine by a parenteral route in rats and with no morphine-like addiction liability in monkeys. Various analogs and congeners have been synthesized.

In continuance of our work on pyrrolidines of possible value as analgetics we have prepared a series of 3,3-disubstituted pyrrolidines (II, R′ = CH_3; R = OCH_3, OH, and $OCOCH_3$) which are more active than the 1,2-dimethyl-3-phenyl-3-propionoxypyrrolidine (I) described earlier.[1]



(I)



(II)

Chemistry.—The 3,3-disubstituted pyrrolidines (II) were prepared by chemical reduction of the corresponding succinimides. *m*-Methoxybutyrophenone was prepared by the reaction of *m*-methoxybenzoyl chloride with dipropylcadmium (a method we found more convenient than that described by McElvain[2]) and treated with ethyl cyanoacetate to give the substituted ethyl cinnamate (III), following the conditions given by Cope[3] and Cragoe.[4] Potassium cyanide readily added across the olefinic linkage in this molecule to give the succinonitrile (IV) which on acid hydrolysis was converted into the succinic acid (V). With methylamine, this furnished the succinimide[5] (VI) which, with lithium aluminum hydride, gave the pyrrolidine (II, R = OCH_3; R′ = CH_3).

(1) J. F. Cavalla, R. A. Selway, J. Wax, L. Scotti, and C. V. Winder, *J. Med. Pharm. Chem.*, **5**, 441 (1962).

(2) S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

(3) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *ibid.*, **63**, 3452 (1941).

(4) E. J. Cragoe, Jr., C. M. Robb, and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).

(5) C. A. Miller and L. M. Long, *J. Am. Chem. Soc.*, **75**, 6265 (1953).