of the ether left 1.8 g. of oil which gave (from acetone–HCl gas) 1.5 g. (38% over-all after recrystallization from acetone) of hydrochloride, m.p. 202–203°.

Anal. Calcd. for $C_{21}H_{34}ClNO$: C, 71.7; H, 9.7. Found: C, 71.6; H, 9.9.

2-Hexyl-2′-hydroxy-α-5,9-dimethyl-6,7-benzomorphan (IIIa).—The preceding hydrochloride (1.5 g.) and 15 ml. of 48% HBr were refluxed for 15 min. The mixture was cooled and made alkaline with NH_4OH, and the liberated base was extracted with chloroform. Drying and distillation of the solvent *in vacuo* left a residue which was evaporatively distilled (0.5 mm., 170–180°). The distillate crystallized from acetone in a yield of 0.27 g. (20%), m.p. 130–132°, with bubbling. Analysis indicated a molecule of acetone of solvation, not removed on prolonged heating at 80° *in vacuo*.

Anal. Calcd. for $C_{20}H_{31}NO \cdot CH_3COCH_3$: C, 76.8; H, 10.4. Found: C, 76.3; H, 10.6.

The solvate-free IIIa was obtained by heating the solvated compound to its melting point.

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79.7; H, 10.2. Found: C, 79.9; H, 10.5.

The **hydrochloride** of IIIa, prepared from acetone-HCl, crystallized from acetone containing a little methanol in short rods, m.p. 205–207°.

Anal. Calcd. for $C_{20}H_{32}ClNO$: C, 71.1; H, 9.5. Found: C, 71.3; H, 9.8.

5-Hexyl-2′-methoxy-2-methyl-6.7-benzomorphan Methiodide.—Methanol (5 ml.), 0.75 g. of IIc, and 35 ml. of 3% ethereal diazomethane were stirred for 46 hr. A 15-ml. portion of CH_2N_2 was then added. After another 22 hr., solvents were distilled, and the residue was evaporatively distilled (bath temperature 140–150°, 0.1 mm.). The distillate in acetone was treated with 0.5 ml. of methyl iodide to give 1.2 g. (90%) of crystals, m.p. 225–226°.

Anal. Calcd. for $C_{21}H_{34}INO$: C, 56.8; H, 7.4; I, 28.9. Found: C, 56.9, H, 7.7; I, 28.9.

1-Hexyl-7-methoxy-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene Hydrochloride.—The above methiodide (1.2 g.) and 12 ml. of 10% NaOH were refluxed for 2–3 hr. The resultant oil was dried (Na_2SO_4) in ether and hydrogenated (0.1 g. of platinum oxide) in alcohol with absorption of 1 *M* equiv. of hydrogen. The product was converted to the hydrochloride (ethereal HCl) which was recrystallized from acetone-ether; over-all yield from methiodide 0.7 g. (75%), m.p. 195–196°.

Anal. Calcd. for $C_{21}H_{36}ClNO$: C, 71.3; H, 10.2. Found: C, 71.0; H, 10.2.

Structures Related to Morphine. XXXII.[1] α- and β-2,9-Dimethyl-5-propyl-6,7-benzomorphan from 3-Methyl-4-propylpyridine

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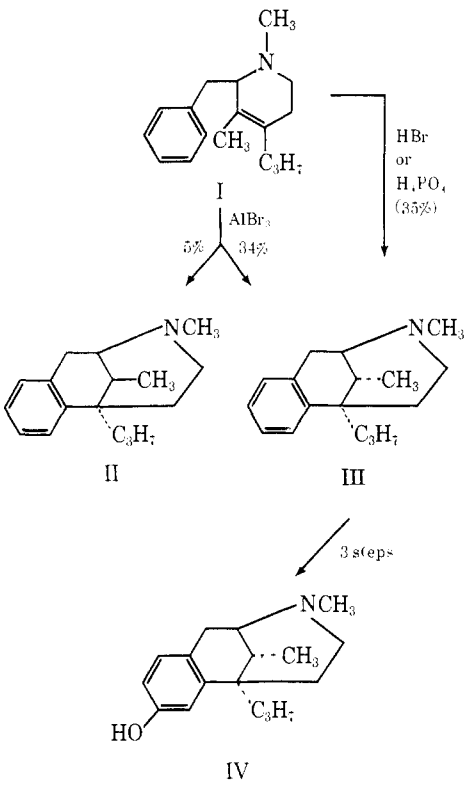
In the synthesis of two relatively strong analgesics, α- and β-2,9-dimethyl-5-propyl-6,7-benzomorphan (III and II, respectively), from 3,4-dihydro-2(1H)-naphthalenone (β-tetralone) by stereo-controlled reactions, the yields are very low.[3] In order to provide sufficient material for pharmacological study of II and III and to further confirm their structure we have effected a three-step synthesis from 3-methyl-4-propylpyridine and have converted the α-compound (III) into the also known α-2,9-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan (IV). This establishes the structure of II and III beyond reasonable doubt.

The cyclization of 2-benzyl-1,3-dimethyl-4-propyl-1,2,5,6-tetrahydropyridine (I) (prepared by sodium borohydride reduction of 2-benzyl-1,2-dihydro-1,3-dimethyl-4-propylpyridine in turn prepared by the Freund reaction using benzylmagnesium chloride and 3-methyl-4-propylpyridine)[4] with aluminum bromide in carbon disulfide gave a mixture of II (34%) and III (5%) (see Scheme I).[5] With either 48% hydrobromic acid or 85% phosphoric acid, the α-isomer (III) was isolated in 30–35% yield, no β-isomer (II) being detected. Nitration of III followed by hydrogenation and nitrous acid oxidation of the resultant 2′-amino derivative[4] gave the known 2′-hydroxy relative (IV).[6] Analgetic activities of II and III are comparable to morphine and codeine, respectively.[3]

SCHEME I



Experimental

2-Benzyl-1,3-dimethyl-4-propyl-1,2,5,6-tetrahydropyridine (I) Hydrochloride.—To an ice-cooled, stirred suspension of 50 g. of 1,3-dimethyl-4-propylpyridinium iodide[5] was added, during 15–20 min., freshly prepared benzylmagnesium chloride (from 32 g. of $C_6H_5CH_2Cl$, 6 g. of Mg turnings, and 150 ml. of ether). The mixture was stirred for 1.5 hr. without cooling and poured

(1) Paper XXXI: A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

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(3) C. F. Chignell and E. L. May, *J. Med. Chem.*, **8**, 385 (1965).

(4) For a leading reference see A. E. Jacobson and E. L. May, *ibid.*, **7**, 400 (1964).

(5) This is a less favorable ratio of β-isomer and a lower yield of each isomer than had hitherto been obtained with lower homologs: J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *J. Org. Chem.*, **28**, 2470 (1963).

(6) C. F. Chignell, J. H. Ager, and E. L. May, *J. Med. Chem.*, **8**, 235 (1965).

into ice–water–NH_4Cl and treated with a little NH_4OH. The ether was separated and extracted three times with excess 8–10% HCl. The combined extracts were made basic with NH_4OH and the liberated base was shaken into ether. Drying and evaporation of the ether left 36.5 g. of crude 2-benzyl-1,2-dihydro-1,3-dimethyl-4-propylpyridine which was dissolved in 35 ml. of methanol and 150 ml. of 10% aqueous NaOH. To the stirred solution was added **7.7 g.** of $NaBH_4$. After the initial vigorous reaction had subsided, the solution was refluxed for 1.5 hr., cooled, poured into ice–water, and extracted three times with ether. The dried (Na_2SO_4) ethereal extracts were evaporated to dryness, and the residue was subjected to short-path distillation at 0.5 mm. (bath temperature 135–140°); yield 30 g. It gave 31 g. (62% based on starting methiodide) of hydrochloride (from ether with dry HCl), m.p. 124–127°; needles from ethyl acetate, m.p. 134–135°, after drying at 65° (80 mm.).

Anal. Calcd. for $C_{17}H_{26}ClN$: C, 73.0; H, 9.3. Found: C, 73.1; H, 9.5.

The **picrate** of I (yellow needles from acetone) melted at 149–150°.

Anal. Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.5; H, 6.0. Found: C 58.3; H, 5.7.

Cyclization of I. A. With HBr.—A solution of 3.6 g. of I in 35 ml. of 48% HBr was kept at a bath temperature of 135–140° for 26 hr., poured into ice–water, made alkaline with NH_4OH, and extracted with ether. Evaporative distillation (bath temperature 150–155°) of the residue from the dried ether extracts gave 2.7 g. of impure **α-2,9-dimethyl-5-propyl-6,7-benzomorphan (III)** which, from acetone–ether–dry HCl gave 1.4 g. (32%) of the **hydrochloride** salt, m.p. 194–195°, identical (melting point and infrared data) with that prepared from β-tetralone.[3] No β-isomer (II) could be found. When 85% H_3PO_4 (48 hr., bath temperature 180°) was used instead of 48% HBr, the results were essentially the same.

B. With $AlBr_3$.—To 20 ml. of carbon disulfide and 1.9 g. of I·HCl, 2.0 g. of $AlBr_3$ was added. The mixture was stirred for 3 hr. at room temperature. Carbon disulfide was decanted from a thick syrup which was dissolved with cold water. The solution was made basic with NH_4OH, and the suspension was extracted several times with ether. Drying and evaporation of the ether left an oil which was distilled as described in the previous experiment; yield 1.4 g. It was converted to the hydrochloride with acetone–HCl, and the solution was evaporated to dryness *in vacuo*. The syrup resulting was dissolved in a little warm acetone. Ether was added to incipient turbidity and after seeding with III·HCl,[2] the solution was left at room temperature depositing 0.64 g. (34%) of the hydrochloride of III during 24 hr. The filtrate and acetone–ether washings, seeded with II·HCl (β-isomer),[3] deposited 0.09 g. of crystals identical with the II·HCl (infrared and melting point data) prepared from β-tetralone.[3]

Conversion of III to α-2,9-Dimethyl-2'-hydroxy-5-propyl-6,7-benzomorphan (IV).—To an ice-cold mixture of 16 ml. of fuming HNO_3 and 10 ml. of glacial acetic acid was added dropwise during 1 hr., 0.8 g. of III in 10 ml. of acetic acid. The solution was stirred overnight at room temperature. Most of the acetic acid was evaporated at reduced pressure (bath temperature about 60°). The resulting mixture was made alkaline with 9% NH_4OH and extracted three times with chloroform. The extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue in 0.5 ml. of acetone was treated with 0.5 g. of picric acid to give 1.3 g. (60%) of **α-2,9-dimethyl-2'-nitro-5-propyl-6,7-benzomorphan picrate**, m.p. 202–203°.

Anal. Calcd. for $C_{23}H_{27}N_5O_9$: C, 53.4; H, 5.2. Found: C, 53.5; H, 5.4.

The base (0.62 g., prepared from 1.2 g. of picrate with aqueous LiOH–ligroin) was hydrogenated in 5–10 ml. of methanol with 0.5 g. of 5% Pd–$BaSO_4$ to absorb 3 *M* equiv. of hydrogen. The residue from the filtered mixture was evaporated to dryness and dissolved in 8 ml. of 10% H_2SO_4, and the solution was treated during 0.5 hr. with 0.28 g. of $NaNO_2$ in 2 ml. of water. The reaction flask was then placed in an oil bath at 60°. Several drops of concentrated H_2SO_4 was added, and the mixture was stirred at 65–75° for 1 hr., filtered, ice cooled, made alkaline with NH_4OH, and extracted ($CHCl_3$). The extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was evaporatively distilled at 0.5 mm. (bath temperature 170–180°). Crystallization of the residue from a little acetone gave 0.1 g. (10% over-all from III) of IV, indistinguishable from that prepared by two alternative methods described previously.[6]

1-(3-Phenylpropyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline, a Pharmacologically Active Narcotine Derivative

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Opium, depending on its source, is known to contain from 3–10% of an isoquinoline alkaloid called narcotine (noscapine, I). While several other alkaloids obtained from opium have been of great value in medicine, little use has been found for narcotine despite its apparent efficacy as a nonaddictive antitussive.[1]

Influenced by the nonaddictiveness and ready availability of narcotine, we have been examining this compound as part of our program to develop improved medicinal agents, especially those affecting the central nervous system. We have prepared derivatives based on the total narcotine skeleton, as well as several compounds derived from a fragmentation product, cotarnine (II). While our work was in progress, we learned from Kaneko[2] that most of our experiments had been anticipated by his group in Japan. There is, however, one new compound of interest which they do not mention. This compound, 1-(3-phenylpropyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III), is easily obtained in 60–70% yield by treating II with 3-phenylpropylmagnesium bromide.

In Table I are given the analgetic activity and acute toxicity of III and those of meperidine and codeine (subcutaneous administration, mouse hot plate assay).[3] Compound III is comparable to codeine in potency and it has about the same therapeutic index as meperidine or codeine.

TABLE I

PHARMACOLOGICAL COMPARISON OF III, MEPERIDINE, AND CODEINE

Compd.	ED_{50}, mg./kg.[b]	LD_{50}, mg./kg.
III[a]	9.1	232
Meperidine[a]	4.5	180
Codeine[a]	7.5	270

[a] HCl salt. [b] Based on new values for morphine, codeine, meperidine, etc., obtained with more senstive mice: A. E. Jacobson and E. L. May, submitted for publication.

In addition, preliminary antimicrobial screening[4] has

(1) H. A. Bickerman, *Med. Clin. N. Am.*, **45**, 805 (1961), and references therein.

(2) H. Kaneko, Y. Nagai, and M. Isogaki, *Yakugaku Zasshi*, **84**, 988 (1964); *ibid.*, **84**, 1094 (1964). We would like to thank Dr. Kaneko for a copy of the manuscript in advance of publication.

(3) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). We are indebted to Dr. Nathan Eddy, Mrs. Louise Atwell, and Mrs. Wendy Ness for these data. During the course of testing for analgesia, Mrs. Atwell observed that III caused considerable diuresis in the mice; morphine-like analgetics, in general, tend to produce the opposite effect.

(4) Antimicrobial screening was carried out in the Smith Kline and French Laboratories, Philadelphia, Pa. We are indebted to Dr. M. Gordon for these data.