Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 66.0; H, 6.38; N, 3.38. Found: C, 65.6; H, 6.46; N, 3.11.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XIX.[1] Benzomorphans from 3,4-Diethylpyridine

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3,4-Diethylpyridine has been converted to 5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IV) and a diastereoisomer (V) (in low yield) by either the Grewe synthesis or a method based on the Stevens rearrangement. Hofmann cleavage of the methyl ether of IV followed by palladium-charcoal aromatization produced a nitrogen-free compound whose spectral, chemical, and analytical behavior are accommodated by the structure of 1,2-diethyl-7-methoxynaphthalene (X). The analgesic activity (mouse) and physical dependence capacity (monkey) of IV, V, and the *N*-phenethyl analog of IV have been determined.

The use of 3,4-lutidine[2] in the Grewe morphinan synthesis has provided a group of compounds—benzomorphans—possessing interesting central nervous system effects. In this class as a whole it is apparent that a marked separation of analgesic action and morphine abstinence-suppressing ability (often equated with addiction liability)[3] has been achieved with respect to the mouse and monkey species; one member of this group, 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan,[2a,4] has been shown to have clinical utility. The substitution of 3,4-diethylpyridine for 3,4-lutidine as a starting material could be expected to produce homologous benzomorphans such as IV, V, and XI, which are also very close relatives of the powerful analgesic, 3-hydroxy-*N*-methylmorphinan (VI).[5] This report is concerned with the conversion of 3,4-diethylpyridine to 5,9-diethyl-6,7-benzomorphans by the Grewe synthesis or by a more versatile alternative synthesis,[6] the latter based on the Stevens rearrangement of 1-benzyl-1,2,5,6-tetrahydropyridines.

When 3,4-diethylpyridine methobromide or methiodide (II) and *p*-methoxybenzylmagnesium chloride (I) were brought together in the Freund reaction, a good yield of the dihydropyridine derivative (III) resulted. Reduction of III in aqueous methanol with sodium borohydride afforded the tetrahydro compound (IX) which was obtained also, albeit in lower yield, by hydrogenation of III (dilute hydrochloric acid, palladium on barium sulfate). Treatment of IX with hot 48% hydrobromic acid gave 5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IV) in 10–30% over-all yields, depending on the procedure used for the conversion of III to IX, and about 3% of a diastereoisomer (V) in analogy with the 5,9-dimethyl series.[2]

Compound IV was also prepared in 25% over-all yield[6] by sodium borohydride reduction of II to 3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (VII), isolated as the *p*-methoxybenzyl chloride quaternary (VIII) rearrangement of VIII to IX with phenyllithium[6] and treatment of the crude IX with 48% hydrobromic acid.

The benzomorphan IV was converted to the *N*-phenethyl analog (XI) in the standard way[2] and to 1,2-diethyl-7-methoxynaphthalene by Hofmann degradation of the methiodide of IV methyl ether, and palladium-charcoal aromatization of the product.

Compounds IV and XI are somewhat less potent in mice (subcutaneous administration)[7] than the

(1) Paper XVIII, S. Saito and E. L. May, *J. Org. Chem.*, **26**, 4536 (1961).

(2) (a) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959); (b) J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960); (c) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959); (d) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(3) G. A. Deneau and M. H. Seevers, Addendum 1, Minutes of the 21st Meeting of the Committee on Drug Addiction and Narcotics, National Research Council, January 1960, and personal communications.

(4) Generic name phenazocine, trade names Prinadol, Narphen; *cf.* H. F. Fraser and H. Isbell, *Bulletin on Narcotics*, **12**, 15 (1960) for a leading reference.

(5) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955); R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949); O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949). Compound IV is simply the open (at the 6,7-bond of VI) analog of VI. We are of the opinion (*cf.* ref. 2a and 2d) that the 9-ethyl substituent is oriented away from nitrogen (axial for the hydroaromatic ring) in IV and toward it in V. Preliminary NMR data appear to confirm this.

(6) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

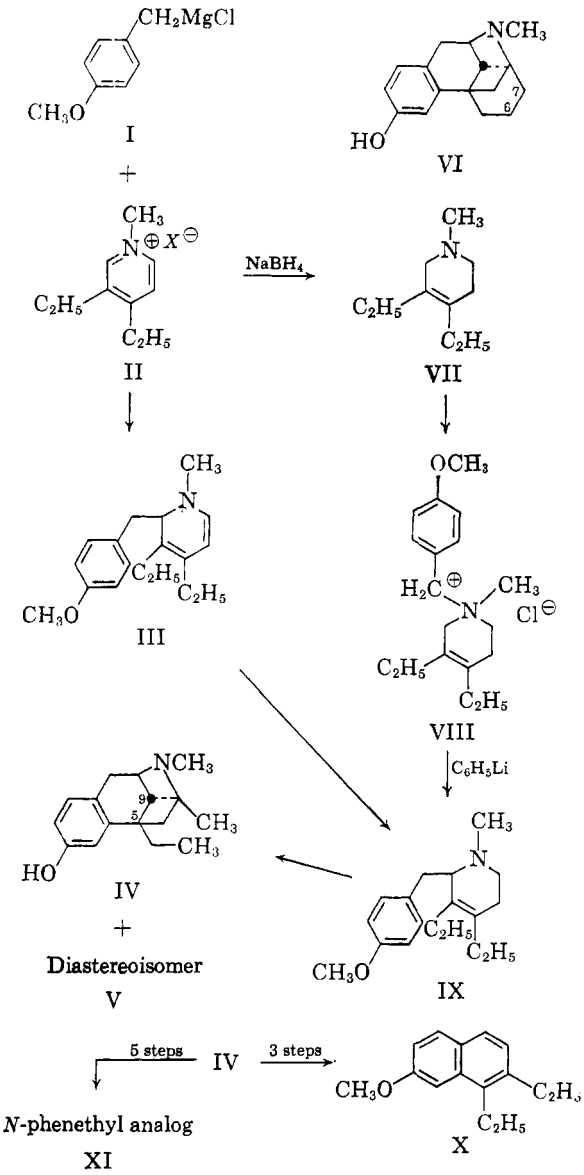

Figure 1

respective 5,9-dimethyl analogs. The racemate V is fifteen times as potent as IV, eight times as active as morphine. As it is almost certain that the *levo*-isomer corresponding to V exerts virtually all of the analgesic effect due to V, it may be regarded as about fifteen times as potent as morphine. To our best knowledge this is the most potent analgesic with a morphine-like structure reported to date when the substituent on the nitrogen is methyl. (−)-3-Hydroxy-*N*-methylisomorphinan[8] is about nine times as potent as morphine. Compound IV and V, when substituted for morphine in addicted monkeys stabilized on 3 mg./kg. of morphine, failed to suppress any of the abstinence signs at doses of 2,4,8, and 16 mg./kg., and IV did not suppress vegetative signs and tenderness at doses of 24 and 40 mg./kg. Thus they are considered to have no physical dependence capacity in the monkey by these tests,[3] rather remarkable for compounds of such potency and chemical structure. The ability of IV to relieve clinical pain is being assessed. Replacement of methyl on the nitrogen of IV by phenethyl resulted in merely a two-fold increase in activity, lower than usually observed for such a change. Thus XI is only about one-eighth as potent as its 5,9-dimethyl counterpart, phenazocine.

EXPERIMENTAL

Melting points were taken in a capillary (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 Ann Wright also of this laboratory.

3,4-Diethyl-1-methylpyridinium iodide (II. X=I). 3,4-Diethylpyridine (5 g.),[9] 10 ml. of acetone, and 3.0 ml. of methyl iodide were kept at room temperature (heat evolution) for 2–3 hr., diluted with 2–3 ml. of ethyl acetate, and left at −15° overnight to give 9.3 g. (91%) of crystals, m.p. 106–108°; prisms from acetone or acetone–ethyl acetate, m.p. 112–114°.

Anal. Calcd. for $C_{10}H_{16}IN$: C, 43.33; H, 5.82. Found: C, 43.60; H, 5.85.

The *bromide* (II. X=Br) crystallized from ethanol-ethyl acetate as the hemihydrate, m.p. 61–65°.

Anal. Calcd. for $C_{10}H_{16}BrN + 1/2\ H_2O$: C, 50.21; H, 7.17; H_2O, 3.92. Found: C, 49.68; H, 7.38; loss (65°), 4.06.

The dried (at 65°) sample gave correct C,H values for anhydrous material.

Anal. Calcd. for $C_{10}H_{16}BrN$: C, 52.19; H, 7.01. Found: C, 52.54; H, 7.13.

3,4-Diethyl-1-(p-methoxybenzyl)-1-methyl-1,2,5,6-pyridinium chloride (VIII).[6] To 24.4 g. of II (X = I), 4.5 g. of sodium hydroxide, 50 ml. of water, and 30 ml. of methanol was added 3.8 g. of sodium borohydride (stirring). The temperature rose to 68° and was maintained at 55–65° for 75–90 min. The mixture was diluted with cold water and extracted thrice with ether. The combined extracts were washed once with water, dried (sodium sulfate), and evaporated at the water pump leaving 12.7 g. of crude VII which was treated with 15 g. of *p*-methoxybenzyl chloride and 25 ml. of acetone. After 2 hr. at room temperature and 2 hr. at −15°, the hygroscopic VIII[6] was filtered and washed with acetone-ether (3:1), yield 19.0 g. (68%), m.p. 157–160°.

5,9-Diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan (IV). (a) *From* VIII. To 19.0 g. of VIII hemihydrate (dried at 60°/25 mm.) was added as rapidly as possible (stirring) 150 ml. of 0.9*M* ethereal phenyllithium. The brisk refluxing subsided after a few minutes. The mixture was stirred for 4 hr., poured into ice water and the ethereal layer extracted thrice with excess, dilute hydrochloric acid. The acid extracts were made alkaline with aqueous ammonia, and the liberated base was dried in ether. Evaporation of the ether left 16.3 g. of base (crude IX). This and 125 ml. of 48% hydrobromic acid were kept at 140–150° (bath temperature) for 20–24 hr., poured onto ice, made alkaline with concentrated ammonium hydroxide, and extracted with chloroform. Evaporation of the dried chloroform extracts at the water pump left a residue which crystallized from 10–15 ml. of acetone (cooling eventually to −5°) in a yield of 6.2 g. (40% based on VIII, a marked improvement over

(7) Pharmacological results are from Mrs. Ethel Atwell of this laboratory, Dr. Nathan Eddy, Consultant.

(8) M. Gates and M. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).

(9) Generously supplied by Dr. F. E. Cislak, Reilly Tar and Chemicals Corp., Indianapolis, Ind.

that previously reported[6]), m.p. 243–246°; rods from ethanol, m.p. 248–249°, λ_{max}^{Nujol} 6.15 (m), 6.31(s) μ.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71. Found: C, 78.90; H, 9.91.

The *hydrochloride* of IV crystallized from absolute ethanol or methanol-acetone in long, thin plates of m.p. 256–258° dec.; λ_{max}^{Nujol} 3.1, 4.0 μ.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86. Found: C, 68.89; H, 9.08.

The acetone filtrate from the 6.2 g. of IV above was evaporated to dryness and the residue evaporatively distilled (bath temperature 190–200°) at 0.2 mm. The viscous distillate crystallized from 3–5 ml. of acetone; yield of base (V) 0.4 g. (2.7% based on VIII), m.p. 203–206°. The *hydrochloride* of V crystallized from methanol-ether in plates of m.p. 253–255° or from methanol-acetone in small octahedra, m.p. 247–249° dec. The octahedra (hemihydrate, λ_{max}^{Nujol} 2.87, 2.94, 3.12 μ) were analyzed.

Anal. Calcd. for $C_{17}H_{25}ClNO + 1/2\ H_2O$: C, 66.97; H, 8.92; Cl, 11.62. Found: C, 67.29; H, 8.62; Cl, 11.39.

The *anhydrous hydrochloride* was obtained after drying for 5 hr. at 100° *in vacuo*.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86. Found: C, 69.03; H, 8.82.

The V *base*[10] prepared from the hydrochloride in aqueous methanolic ammonia crystallized from alcohol in needles or long plates, m.p. 214–215°, λ_{max}^{Nujol} 6.2 μ.[11]

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71. Found: C, 78.72; H, 9.82.

(b) *From* I *and* II. To a stirred suspension of 23 g. of II (X = Br) and 75 ml. of dry ether was added during 5–10 min. 370 ml. of 0.35*M* *p*-methoxybenzylmagnesium chloride.[12] After 1–2 hr. the two-layered mixture was poured (with vigorous stirring) into ice water containing ammonium chloride. After addition of a little aqueous ammonia, the ethereal layer was extracted thrice with excess, cold, dilute hydrochloric acid. These extracts were made alkaline with cold, aqueous ammonia and the liberated base dried in ether. Evaporation of the ether at the water pump left 24.1 g. of crude III to which was added 70 ml. of methanol, 45 ml. of *N* sodium hydroxide, and 3.0 g. of sodium borohydride.[13] The temperature rose to 59° and was maintained at 50–60° for 2 hr. The mixture was diluted with water, extracted with ether, and the ether washed twice with water and dried. Evaporation left 22.6 g. of crude IX which was treated as described under (a) above to give (on crystallization of the residue from the chloroform extracts from methanol) 7.6 g. (30% based on II) of IV, m.p. 244–246° and 0.3 g. (2.5%) of V, m.p. 187–200°.

5,9-Diethyl-2'-hydroxy-6,7-benzomorphan. Acetic anhydride (10 ml.) and 2.5 g. of IV were kept on the steam bath for 30–45 min., cooled and poured into ice water. After 5 min., 50% potassium hydroxide in slight excess (ice-cooling) was added and the liberated base shaken quickly into ether. Drying and evaporation of the ether left 2.7 g. of oily *O*-acetyl derivative which, in 15 ml. of chloroform, was added during 20–30 min., to a stirred solution of 1.5 g. of cyanogen bromide in 8 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residual *N*-cyano compound and 45 ml. of 6% hydrochloric acid were refluxed for 6–8 hr., cooled, made alkaline with concentrated ammonium hydroxide, and extracted with 1-butanol-benzene (2:1). Evaporation of the extracts *in vacuo* and trituration of the residue with methanol gave 1.8 g. (77%) of secondary base, m.p. 259–261°; plates from ethanol, m.p. 264.5–265.5°.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.44. Found: C, 78.59; H, 9.63.

5,9-Diethyl-2'-hydroxy-2-phenethyl-6,7-benzomorphan (XI) *hydrobromide.* The nor-base above (2.6 g.), 30 ml. of dimethylformamide, 6 ml. of water, and 3 g. of potassium carbonate were stirred at 100° (bath temperature) and treated with 3.0 ml. of phenylacetyl chloride during 15 min. The bath temperature was then kept at 120–125° for 3 hr. The mixture was diluted with 60 ml. of water and extracted thrice with 1-butanol-benzene (2:1). The combined extracts were washed with dilute hydrochloric acid, then water. Evaporation of the organic layer *in vacuo* gave 2.8 g. of crude phenylacetamide derivative (λ_{max}^{Nujol} 6.24, μ, m.p. 259–261°). To this amide (2.2 g.) in 25 ml. of dry ether was added dropwise (stirring) 25 ml. of 1.5*M* ethereal lithium aluminum hydride. The mixture was refluxed overnight, cooled in ice, and treated gradually with 20 ml. of 48% hydrobromic acid in 20 ml. of water. The precipitated hydrobromide salt of XI was filtered, washed with water, then ether; yield of crude material, 1.5–2 g. It crystallized from ethanol in rods of m.p. 249–250°.

Anal. Calcd. for $C_{24}H_{34}BrNO$: C, 66.65; H, 7.92. Found: C, 66.43; H, 7.67.

The XI *base* (prepared from the hydrobromide with aqueous methanolic ammonia) crystallized from methanol in rods of m.p. 200–202°.

Anal. Calcd. for $C_{24}H_{33}NO$: C, 82.00; H, 9.46. Found: C, 81.76; H, 9.26.

5,9-Diethyl-2'-methoxy-2-methyl-6,7-benzomorphan methiodide. Methanol (20 ml.), 2 g. of IV, and 34 ml. of 3% ethereal diazomethane were stirred to solution (4–6 hr.). An additional 34 ml. of the diazomethane solution was added and the mixture kept at 23–25° for 2–3 days. Solvents were distilled *in vacuo* and the residue evaporatively distilled (bath temperature 135–145°) at 0.2 mm. The 2.3 g. of distillate gave readily the crystalline methiodide (acetone as solvent) which was recrystallized from ethanol; needles, m.p. 241–242°.

Anal. Calcd. for $C_{19}H_{32}INO$: C, 54.67; H, 7.75. Found: C, 54.86; H, 7.56.

Degradation of IV *to 1,2-diethyl-7-methoxynaphthalene* (X) *picrate.* The above methiodide (2.3 g.), 2.3 g. of sodium hydroxide, and 23 ml. of water were refluxed for 4 hr., cooled, and extracted with ether. The resultant methine (0.9 g.) and 0.9 g. of 5% palladium on 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., where it was kept for 20 min. The cooled mixture was extracted thrice with ether. The extracts were washed with dilute hydrochloric acid, dried, and evaporated leaving a liquid which was evaporatively distilled at 100–110°/0.2 mm. The 0.4 g. of distillate, 0.4 g. of picric acid, and 5 ml. of alcohol were warmed to solution, then cooled gradually to −15° to give 0.35 g. (15% based on starting methiodide) of picrate; orange needles from alcohol, m.p. 100–101°.

Anal. Calcd. for $C_{21}H_{21}N_3O_8$: C, 56.88; H, 4.79. Found: C, 56.62; H, 5.01.

The *free* hydrocarbon (X) prepared from the picrate with aqueous lithium hydroxide–petroleum ether (b.p. 30–60°) was a liquid which was evaporatively distilled (100–110°/0.2 mm.) for analysis; $\lambda_{max}^{C_2H_5OH}$ 234, 271, 280, 292, 315, 330 (ϵ 67,000, 4,500, 5,100, 4,300, 1,500, 2,000).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.47. Found: C, 83.78; H, 8.36.

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(10) The structure of V has been deduced by analogy with the 5,9-dimethyl series (*cf.* ref. 2c and 5) and the high analgesic potency of the hydrochloride salt.

(11) The differences in absorption in the phenyl region are distinct for IV (6.15, 6.31 μ) and V (6.2 μ only). These differences are useful in estimating the content of each in a mixture of the two and in following their separation, which has been achieved chromatographically on Florisil (chloroform-ethanol) or by a careful fractional crystallization of their hydrochlorides from absolute ethanol.

(12) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, **70**, 2296 (1948).

(13) Reduction of III in *N* hydrochloric acid with 5% palladium–barium sulfate ultimately gave IV in only 11% over-all yield (from II).