with ether. Evaporation of the ether extract furnished only a very small residue.

The yellow undissolved solid was shaken with 125 ml. of 4% sodium bicarbonate for 30 min. and filtered. The filtrate was acidified and subjected to continuous extraction with ether. Removal of ether from the extract left a colorless residue which was mixed with the residue obtained above. To the total solid in absolute ethanol, excess diazomethane in ether was added and left at 0° overnight. The methyl ester was purified by two crystallizations from benzene-petroleum ether (1:1) when it came out as colorless prisms melting at 122–125°. Final purification was effected by sublimation at 0.5 mm. and the sublimate crystallized from benzene–petroleum ether (1:1), m.p. 124–125°, yield, 45 mg. The ester did not exhibit any blue color with sulfuric–nitric acid reagent.[3]

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.81; 3-OCH_3 and 1-OC_2H_5 as 4-OCH_3, 36.04. Found: C, 66.71; H, 6.05; OCH_3, 35.77.

Oxidation of O-ethyl-N-methyltiliarine dimethiodide. Two grams of *O*-ethyl-*N*-methyltiliarine dimethiodide[2] was oxidized following the procedure given above. The carboxylic acid was esterified with diazomethane and isolated as the dimethyl ester. The ester was purified by two crystallizations from benzene–petroleum ether (1:1) (solid, m.p. 122–125°) followed by vacuum sublimation at 0.5 mm. The sublimate was crystallized again from benzene–petroleum ether when the methyl ester was secured as colorless prisms, m.p. 123–125°, undepressed by the sample obtained similarly from *O*-ethyltiliacorine dimethiodide.

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Structures Related to Morphine. XIII.[1] 2-Alkyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphans and a More Direct Synthesis of the 2-Phenethyl Compound (NIH 7519)

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Starting from *p*-methoxybenzylmagnesium chloride and 1-alkyl-3,4-dimethylpyridinium iodides the 2-alkyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphane IIIb, IIIc, and IIId have been synthesized for neuropharmacological evaluation. Similarly the medically useful IIIf (NIH 7519) results from 3,4-dimethyl-1-phenethylpyridinium bromide or iodide. IIIb, IIId, and IIIe were also prepared from the known compound IIIa by standard reactions. This alternative synthesis confirms the constitution of the 2-alkyl compounds.

The potent (in mice) analgesic 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (IIIa)[1] has been found to be effective in blocking a conditioned response in mice and rats, a property not uncommon in morphine and morphine-like analgesics.[2] By varying the nitrogen substituent of III, one could expect to get a wide variation in analgesic activity which would permit to a limited extent a comparison of analgesic and other neuropharmacologic actions. We wish to report a few of the IIIa analogs studied in this connection along with a shorter synthesis for 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIf, NIH 7519.[1,3])

The most convenient route for the preparation of the 2-alkyl compounds was that described previously for IIIa.[4] *p*-Methoxybenzylmagnesium chloride and the appropriate 1-alkyl-(or aralkyl in the case of IIIf) 3,4-dimethylpyridinium iodide (I) were brought to reaction in dry ether. The resultant dihydropyridines (II) in dilute hydrochloric acid were hydrogenated to the corresponding 1,2,5,6-tetrahydro compounds, which were in turn cyclized and *O*-demethylated to III with hydrobromic acid, in 10–30% overall yields based on the starting pyridinium iodides. Because of low water solubility it was necessary to use aqueous alcoholic hydrochloric acid for the hydrogenation step in the preparation of IIIf. It is noteworthy that this synthesis for IIIf is some five steps shorter than that previously reported.[1]

The 2-ethyl (IIIb), 2-butyl (IIId), and 2-amyl (IIIe) compounds have been prepared also from IIIa by a route described earlier[1,3,5] which involves cyanogen bromide *N*-demethylation of the methyl ether of IIIa, acylation of the resultant secondary amine, reduction of the *N*-acyl derivative with ethereal lithium aluminum hydride and *O*-demethylation. This alternative synthesis provided sufficient proof of structure.

The 2-alkyl derivatives IIIb, IIIc, and IIId had no analgesic activity at sub-toxic doses. The *N*-amyl derivative (IIIe), on the other hand, was comparable to morphine in analgesic potency, somewhat more potent than IIIa. This is reasonably consistent with earlier findings[6] in the morphine series where the *N*-ethyl, -propyl, and -butyl homologs have less than one tenth the potency of morphine, and *N*-amylnormorphine is seven-tenths as effective as morphine.

(1) Communication XII, E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

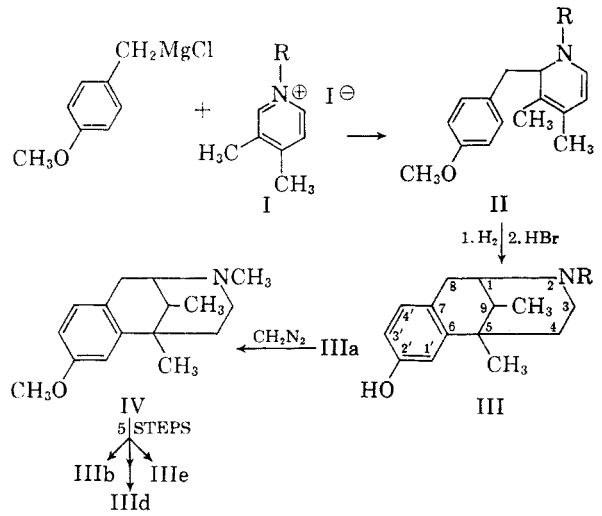
(2) Personal communication from Leonard Cook, Smith, Kline and French Laboratories.

(3) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(4) (a) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); (b) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(5) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(6) C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. Intern. Pharmacodynamie*, **110**, 186 (1957).



a) R = CH_3, b) R = C_2H_5, c) R = n-C_3H_7,
d) R = n-C_4H_9, e) R = n-C_5H_{11}, f) R = $CH_2CH_2C_6H_5$

EXPERIMENTAL

Melting points were taken by capillary using a Hershberg apparatus. Microanalyses are by Paula Parisius, Elizabeth Fath, and Byron Baer of the Institutes' service analytical laboratory, Dr. William C. Alford, Director.

1-Ethyl-3,4-dimethylpyridinium iodide (Ib). Ethyl iodide (4 ml.), 4 ml. of 3,4-lutidine,[7] 15 ml. of acetone and 15 ml. of benzene were refluxed for 2–4 hr., cooled to −5°, and filtered to give 9.4 g. (80%) of precipitate, m.p. 179–182° before and after a recrystallization from acetone.

Anal. Calcd. for $C_9H_{14}IN$: C, 41.08; H, 5.36. Found: C, 40.76; H, 5.42.

3,4-Dimethyl-1-propylpyridinium iodide (Ic). This compound was prepared from propyl iodide as described for the previous one; m.p. 104–106° (acetone-ether).

Anal. Calcd. for $C_{10}H_{16}IN$: C, 43.37; H, 5.82. Found: C, 43.00; H, 5.80.

1-Butyl-3,4-dimethylpyridinium iodide (Id). This iodide was prepared with butyl iodide as described above; m.p. 81–83.5° (acetone-ligroin, 30–60°).

Anal. Calcd. for $C_{11}H_{18}IN$: C, 45.37; H, 6.23. Found: C, 45.15; H, 6.19.

3,4-Dimethyl-1-phenethylpyridinium iodide (If). 2-Iodoethylbenzene (3.0 ml.), 2 ml. of 3,4-lutidine, 7 ml. of benzene, and 2 ml. of acetone, refluxed 3 hr. and cooled to 5° gave 4.9 g. (82%) of precipitate melting a 141–145°; plates (from acetone containing a trace of absolute alcohol) m.p. 142–144°.

Anal. Calcd. for $C_{15}H_{18}IN + 0.5H_2O$: C, 51.73; H, 5.50, H_2O: 2.36. Found: C, 51.46; H, 5.68; Loss in wt. (80°), 3.04.

The corresponding *bromide* prepared in a yield of 11.7 g. by refluxing together for 3 hr. 5 ml. of 3,4-lutidine, 9 g. of 2-bromoethylbenzene, and 15 ml. of absolute ethanol, evaporation to dryness *in vacuo* and trituration with acetone, melted at 175–176.5°; cubes from absolute ethanol-ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}BrN$: C, 61.65; H, 6.21; Br, 27.35. Found: C, 61.34; H, 6.22; Br, 27.28.

2-Ethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIIb). To a stirred suspension of 12.5 g. of Ib and 75 ml. of dry ether was added without cooling during 5–10 min., 200 ml. of 0.3*M* ethereal *p*-methoxybenzylmagnesium chloride.[8] After 1–2 hr. of stirring the two-layered mixture was poured into ice-ammonium chloride with vigorous stirring. After addition of a little aqueous ammonia, and brief shaking 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 was dried in ether. Evaporation of the ether at the water pump left 6.9 g. of II (R = C_2H_5) which was dissolved quickly in 95 ml. of cold 1*N* hydrochloric acid. This solution with 3.0 g. of 5% palladium–barium sulfate absorbed 605 ml. (88%) of hydrogen during 4 hr., when uptake had almost stopped. The suction-filtered (through Super-Cel) solution was made alkaline with ice-cold, aqueous ammonia. The liberated base was shaken into ether. The extracts were dried over sodium sulfate and distilled at the water pump. The residue was molecularly distilled at 0.2 mm. (air-bath temperature 150–175°). The distillate and 50 ml. of 48% hydrobromic acid were kept at a bath temperature of 135–140° for 20 hr., poured onto ice and made basic with concd. ammonium hydroxide. The freed IIIb was shaken into chloroform. The dried extract was distilled at the water pump. The residue crystallized from a little methanol or acetone, giving 3.5 g. (30% based on Ib) of IIIb, m.p. 158–160°; prisms from methanol-water, m.p. 163–164°.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 77.90; H, 9.19.

The *hydrobromide* crystallized from acetone in needles of m.p. 230°, after sintering at 215°.

Anal. Calcd. for $C_{16}H_{24}BrNO$: C, 58.89; H, 7.41. Found: C, 58.74; H, 7.51.

2'-Hydroxy-5,9-dimethyl-2-propyl-6,7-benzomorphan (IIIc). Essentially as described in the preparation of IIIb, 12.5 g. of Ic, 75 ml. of dry ether, and 200 ml. of ethereal *p*-methoxybenzylmagnesium chloride gave, after molecular distillation (0.1 mm., 150°) of the crude IIIc from the chloroform extracts and crystallization of the distillate from a little acetone, 2.7 g. of IIIc, m.p. 165–170°. The analytical sample (from acetone) melted at 168–170°.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71. Found: C, 78.56; H, 9.56.

The *hydrochloride* (prepared from the base in acetone with dry hydrogen chloride) crystallized from absolute ethanol-ether (charcoal) or absolute ethanol-acetone in white crystals of m.p. 240–242.5°. The analytical sample was dried for 5 hr. at 100°.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86. Found: C, 68.75; H, 8.83.

2-Butyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIId). Essentially as described before except that the IIId from the chloroform extracts was molecularly distilled at 0.1 mm. (bath temperature 175–180°), this base was obtained in 15% yield from Id, after crystallization of the distillate from ether; plates from acetone, m.p. 152–153°.

Anal. Calcd. for $C_{18}H_{27}NO$: C, 79.08; H, 9.96. Found: C, 78.87; H, 9.83.

The *hydrobromide* crystallized from absolute ethanol-ether in needles, m.p. 211–212°.

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 61.02; H, 7.96. Found: C, 61.22; H, 7.78.

2'-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIf).[1,3] To a stirred suspension of 10 g. of 3,4-dimethyl-1-phenethylpyridimium bromide[9] was added during 10–15 min. 130 ml. of 0.3*M* ethereal *p*-methoxybenzylmagnesium chloride. After 1–1.5 hr. the mixture was poured with vigorous stirring into ice-ammonium chloride solution, and a little ammonium hydroxide was added. The ethereal layer was extracted with three portions of cold 10% hydrochloric acid (in excess). The combined extracts were made alkaline

(7) Available from the Reilly Tar and Chemical Company, Indianapolis, Indiana.

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

(9) We are indebted to Dr. G. DeLaMater of the Mallinckrodt Chemical Works, Inc., for suggesting the bromide as a substitute for the iodide. The iodide crystallized as a hemihydrate and therefore required additional Grignard reagent.

with ice-cold ammonium hydroxide and the base extracted with ether. The dried (sodium sulfate) ethereal extracts gave, on evaporation to dryness at the water pump, 8.5–9.5 g. of amber-colored oil. This was treated with 80 ml. of cold 1*N* hydrochloric acid and just enough (30–40 ml.) 95% ethanol to effect complete solution of the oily material. The solution was transferred to a nitrogen-swept hydrogenation flask containing 1.2 g. of 10% palladium–barium sulfate and shaken under hydrogen. After 60–80 min. absorption had slowed from a maximum rate of 20 ml./min. to 2 ml./min. while a total of 90% of 1 molar equivalent was absorbed. Usually some oily material had separated. The mixture was filtered through Super-Cel (the flask and precipitate being washed with a little alcohol), made alkaline with cold ammonium hydroxide, and the base was shaken into ether. The combined ethereal extracts were washed with water and dried over sodium sulfate. The oil left after evaporation to dryness was molecularly distilled as rapidly as possible (boileezers, 0.1 mm., air-bath temperature 200–220°). The resultant distillate (4.7 g.), 20 ml. of 48% hydrobromic acid, and 10 ml. of 33% hydrogen bromide in acetic acid were kept at 145–150° (oil-bath temperature) for 20–24 hr., poured onto ice (in a separatory funnel), made alkaline with ammonium hydroxide and extracted with three portions of chloroform. The dried (sodium sulfate) extracts yielded (on evaporation of the chloroform *in vacuo*) a residue which was molecularly distilled as described above. The very viscous distillate crystallized from 6–8 ml. of acetone in a yield of 1.0–1.5 g. (m.p. 176–179°) after gradual cooling to −5°. The analytically pure material (from methanol) melted at 181–182° alone or in mixture with an authentic specimen.[1,3] The infrared spectra of the two were also identical.

The hydrobromide salt,[10] prepared by neutralizing the crude base (m.p. 176–179°) in acetone with 33% hydrobromic acid in acetic acid and adding an equal volume of ethyl acetate, melted at 167–171°; it gave an infrared spectrum identical with that of authentic hydrobromide.[1,3]

2-Ethyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan hydrobromide. IV (1.5 g.)[1,4b] in 10 ml. of dry chloroform was added (stirring) during 40 min. to 0.7 g. of cyanogen bromide in 5 ml. of chloroform. The solution was refluxed for 2–3 hr. and evaporated to dryness at the water pump. The residue and 20 ml. of 6% hydrochloric acid were refluxed overnight, cooled, made alkaline, and extracted with ether. The dried (sodium sulfate) ether extracts, on evaporation to dryness left 1.0 g. of crude 2′-methoxy-5,9-dimethyl-6,7-benzomorphan which was *N*-acetylated with 1 ml. of acetic anhydride (25°, 24 hr.). The mixture was shaken with ether and water, and the ethereal layer was washed with dilute hydrochloric acid, dried, and evaporated giving 1.0 g. of crude *N*-acetyl derivative. To this in 15 ml. of dry ether was added 10 ml. of 1.7*M* ethereal lithium aluminum hydride during 5–10 min. (stirring). The mixture was refluxed for 6 hr. and decomposed by careful addition of 5 ml. of water. The ethereal filtrate was dried and evaporated giving 0.9 g. of oily base which (in ether) was neutralized with 0.7 ml. of 33% hydrobromic acid in acetic acid; yield of hydrobromide 0.8 g. (45%), m.p. 232–237°; plates from acetone, m.p. 246–247°.

Anal. Calcd. for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70. Found: C, 59.81; H, 7.49.

O-Demethylation of 2-ethyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan to IIIb. By refluxing together for 30 min. 0.8 g. of this methyl ether and 5.0 ml. of 48% hydrobromic acid, evaporation to thorough dryness (*in vacuo*) and crystallization of the residue from alcohol-ether, 0.5 g. of IIIb hydrobromide identical with that prepared as described above was obtained. The free base melted at 163–164° alone or in mixture with that described above.

2-Butyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan hydrobromide. As described above, 1.0 g. of IV was *N*-demethylated with 0.5 g. of cyanogen bromide to give 0.7 g. of crude secondary amine. To this, 10 ml. of methanol, 2–3 ml. of water, and 1.0 g. of potassium carbonate, was added with stirring during 10 min., 0.5 ml. of butyryl chloride. The mixture was stirred for 2 hr., diluted with water and extracted thrice with ether. The combined extracts were washed with dilute hydrochloric acid, dried (sodium sulfate) and evaporated to dryness *in vacuo* giving 1 g. of crude butyramide derivative. It was dissolved in 10 ml. of dry ether and the solution treated gradually with 6–8 ml. of 1.3*M* ethereal lithium aluminum hydride. The mixture was refluxed overnight, treated carefully with 5 ml. of water and the ether was decanted, dried, and evaporated. This base (in dry ether) was acidified with hydrobromic-acetic acid giving a hydrobromide salt which crystallized from acetone-ether in a yield of 0.8 g.; plates, m.p. 224–225.5°.

Anal. Calcd. for $C_{19}H_{30}BrNO$: C, 62.19; H, 8.21. Found: C, 62.09; H, 7.95.

Demethylation to Id was effected as described above with boiling 48% hydrobromic acid. It was identical with the Id prepared as described above.

2-Amyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIIc). The conversion of 2 g. of IV to 1.2 g. of hygroscopic 2-amyl-2′-methoxy-5,9-dimethyl-6,7-benzomorphan hydrobromide was carried out as described for the 2-butyl homolog, using valeryl chloride as the acylating agent. This hydrobromide (0.6 g.) and 3.0 ml. of 48% hydrobromic acid were refluxed for 15–20 min., cooled, and made alkaline with aqueous ammonia. The base was dried in ether and molecularly distilled at a bath temperature of 180° (0.1 mm.) giving 0.4 g. of IIIc which crystallized from ligroin (30–60°) in prisms, m.p. 142.5–144°.

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.40; H, 10.17. Found: C, 79.55; H, 10.35.

The *hydrochloride*, prepared by acidification of the base in ether with dry hydrogen chloride crystallized from absolute alcohol-ether in needles, m.p. 204–207°.

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 70.45; H, 9.34. Found: C, 70.64; H, 9.58.

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BETHESDA 14, MD.

(10) This compound originally designated as NIH 7519 has been assigned the generic name phenazocine.