tion of 50 ml. of water, 9.0 g. of silver oxide, and 4.5 g. of bicyclo[4.4.0]decane-1-thianium bromide.

A 3.5-g. sample of the hydroxide was heated for 6 hr. at 150°. The product was taken up in hexane, the solution was dried and freed of solvent. Distillation of the residual oil gave a mobile, colorless liquid, b.p. 100° (15 mm.), believed to be *2-(3-butenyl)tetrahydrothiopyran.*

Anal. Calcd. for $C_9H_{16}S$: C, 69.16; H, 10.32. Found: C, 68.94; H, 10.44.

Bicyclo[4.4.0]decane-1-thianium iodide (V, $X = I$). The iodide was prepared by titrating a sample of the sulfonium hydroxide with 47% hydriodic acid, followed by removal of water at 80° (20 mm.), and crystallization of the residue from absolute alcohol. The iodide was a white crystalline, relatively nonhygroscopic solid which sublimed at 264–265° with decomposition. Treatment with a solution of the iodide with picric acid gave the picrate, identical with that described herewith in a mixed melting point determination.

STANFORD, CALIF.

[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. XI.[1] Analogs and a Diastereoisomer of 2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan

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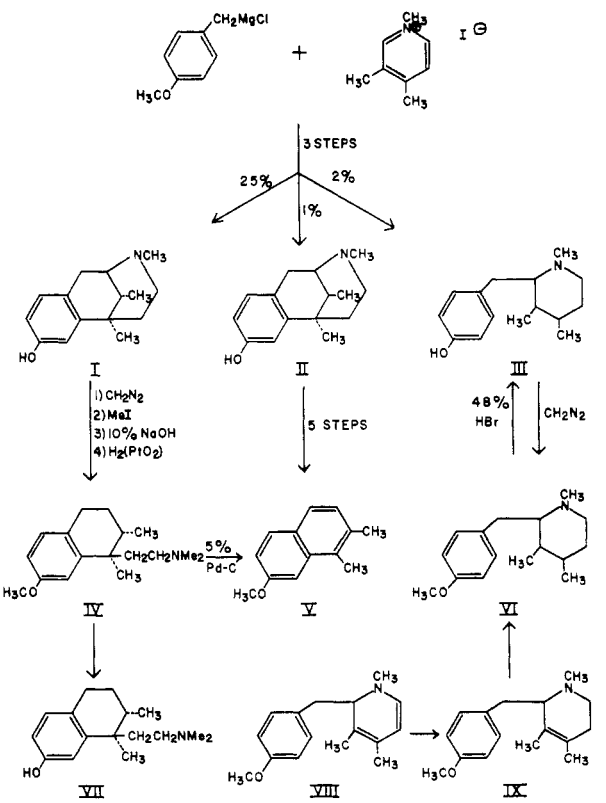
2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) has been degraded to 7-methoxy-1,2-dimethylnaphthalene (V) *via* 7-methoxy-1,2-dimethyl-1-(2-di-methylaminoethyl)-1,2,3,4-tetrahydronaphthalene (IV). Similar degradation of an isomeric by-product (II) obtained in 1% yield in the synthesis of I also gave V proving diastereoisomerism for I and II at carbon 9. Another by-product isolated in 2% yield appears to be the piperidine derivative (III). Hydrobromic acid treatment of IV yielded the phenolic base (VII) which is practically devoid of analgesic activity, paralleling results obtained in another series (*cf.* reference 3).

It has been amply demonstrated[2–4] that the introduction of a phenolic hydroxyl *meta* to the quaternary carbon in a number of synthetic compounds containing a phenyl- or benzo-azabicyclo structure characteristic of morphine, markedly improves analgesic behavior. On the other hand in the one published instance of similar substitution in an open nitrogen counterpart[3] there was an increase in acute toxicity and a fourfold decrease of analgesic potency unless the phenolic hydroxyl was protected by methyl. To determine whether this would be true in another series, 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) has been converted to 7 - hydroxy - 1,2 - dimethyl - 1 - (2 - dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VII) for comparison with the corresponding methoxy (IV) and deoxy[4] compounds. The transformation of I to VII was effected by exhaustive methylation of the methyl ether of I, hydrogenation of the resulting methine to the methyl ether (IV), and *O*-demethylation of IV with aqueous hydrobromic acid. Either the methine or the corresponding hydrogenated base (IV) could be aromatized to 7-methoxy-1,2-dimethylnaphthalene (V) which was used as a reference compound as described here.



In synthesizing larger amounts of I[4a] not only was an improved procedure developed but, in

(1) Communication X, E. L. May, *J. Org. Chem.*, **23**, 947 (1958).

(2) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949); O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949); O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(3) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955).

(4) (a) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); (b) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

addition, two phenolic by-products[5] were isolated from the residues of several combined preparations. One of these proved to be a diastereoisomer (II, 1% yield from 3,4-lutidine methiodide) of I as shown by its degradation to V in a manner identical to that described for I. Since the 5,8-iminoethano system is constrained to a *cis*-fusion, I and II can differ only at carbon 9. For this reason and for reasons stated previously,[4a] the methyl of carbon 9 is tentatively placed *trans* (equatorial) to the *quasi*-equatorial methyl of carbon 5 for the hydroaromatic ring.[6]

The other by-product from the synthesis of I appears to be 2-(*p*-hydroxybenzyl)-1,3,4-trimethylpiperidine (III). This compound would be produced by complete hydrogen saturation of the *N*-containing ring of the dihydro base (VIII)[7] and *O*-demethylation of the resultant VI under the conditions used to cyclize and *O*-methylate the major product (IX) to I and II.

By deliberate over-reduction of VIII in two stages, the second involving the use of palladium-charcoal and the *base* (IX) a 40% yield of VI could be obtained along with 25–30% of an isomeric product. The two are presumed to be diastereoisomers corresponding to VI. The predominant isomer VI and the III isolated as a by-product were interconvertible; diazomethane methylation of III gave VI and 48% hydrobromic acid treatment of VI (15 min. reflux) yielded III.

As for analgesic activity, the diastereoisomer II has a subcutaneously effective dose in mice of 0.4 mg./kg.[8] compared to 3.0 mg./kg. for I and 2.1 for morphine. Therefore, one can predict reasonably that the *levo*-isomer of II is 9–10 times as potent as (*levo*-) morphine. The piperidine derivative (III), without a quaternary carbon, and the methyl ether of I produced analgesia in mice at *ca.* 15 and 10 mg./kg. respectively. The phenolic open nitrogen analog (VII) of I was ineffective at doses up to 100 mg./kg. while the corresponding methyl ether (IV) and the deoxy analog[4b] were active at 25–30 mg./kg. This is at least the second example[3] of the detrimental effect of a free phenolic hydroxyl situated *meta* to the quaternary carbon in an analgesic possessing an aliphatic tertiary nitrogen. As stated before there is a favorable effect when the nitrogen is heterocyclic. Perhaps there is intramolecular interference of the free-swinging aliphatic nitrogen with the phenolic hydroxyl which prevents each from exercising its function *in vivo*. Molecular models and hydrogen ion titration curves for I and VII are consistent with this postulate. Further studies and publication of data along these lines are planned.

(5) These same by-products have been independently isolated and characterized by the Smith Kline and French Laboratories (personal communication).

(6) These assignments appear consistent with data obtained from infrared spectral comparisons of I and II with 3-hydroxy-*N*-methylmorphinan[2] and 3-hydroxy-*N*-methylisomorphinan.[8]

(7) The hydrogenation of VIII, formed in the first step in the preparation of I, never proceeded beyond the absorption of 0.9 molar equivalent even on prolonged shaking, in the presence of dilute hydrochloric acid and palladium-barium sulfate. Reaction was essentially complete after 4–5 hr.

(8) Compare this also with (±)-3-hydroxy-*N*-methylisomorphinan of M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958). The pharmacological data for our compounds are from Dr. N. B. Eddy, Chief, Section on Analgesics, and staff.

EXPERIMENTAL

Microanalyses were performed by Paula M. Parisius, Elizabeth Fath, and Byron Baer of the Institutes service analytical laboratory, Dr. William C. Alford, director. Melting points (Hershberg apparatus) are corrected.

2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I).[4a] A stirred suspension of 50 g. of 3,4-lutidine methiodide and 75 ml. of dry ether was treated during 15–20 min. with 700 ml. of 0.3–0.35*M* ethereal *p*-methoxybenzylmagnesium chloride. The mixture was stirred for an additional 60–90 min. and poured with vigorous stirring into 250 ml. of ice water containing 50 g. of ammonium chloride. The ethereal layer was extracted 3–4 times with a total of 250 ml. of 2*N* hydrochloric acid. The combined extracts were made alkaline with ice–ammonium hydroxide and the liberated base was extracted with 250 ml. of ether in three portions. The combined, dried (Na_2SO_4) extracts were evaporated at the water pump leaving 42–45 g. of oil (VIII) which was dissolved quickly in 200 ml. of ice cold *N* hydrochloric acid (nitrogen atmosphere) and the solution shaken under hydrogen with 8 g. of 5% palladium–barium sulfate. After 10–15 hr. 0.8–0.9 molar equivalent of hydrogen had been absorbed and reaction had almost ceased. The mixture was filtered through Super-Cel and made alkaline with ice cold ammonium hydroxide. The liberated material was shaken into ether. The dried extracts were distilled, the residue at a bath temperature of 125–140°/0.1 mm., to give 20–24 g. of tetrahydro base (IX) which, with 175 ml. of 48% hydrobromic acid, was kept at 135–140° for 20–25 hr. The resultant solution was poured into ice water and made alkaline with concentrated ammonium hydroxide. Extraction with 250–300 ml. of chloroform followed by drying and evaporation of the chloroform gave a residue which crystallized on trituration with 25 ml. of cold methanol. After 10–20 hr. at −5° the yield of I was 10–12.5 g.; m.p. 228–233°.

Distillation of the methanol from the filtrates of 2 of the above preparations gave a residue which was evaporatively distilled at 180°/0.5 mm. The viscous distillate[9] was dissolved in about 25 ml. of methanol. On cooling for 2 hr. at 5°, 2.1 g. of solid, m.p. 195–220°, separated. It was dissolved in 20 ml. of methanol and acidified with gaseous hydrogen chloride. After an hour at −10° 0.5 g.[10] of the hydrochloride of II, m.p. 268–271°, was obtained. It crystallized from 95% ethanol-ether in needles of m.p. 269–272° (dec.).

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28. Found: C, 67.02; H, 8.41.

The *base* II crystallized from alcohol in prisms, m.p. 215–217.5°.

(9) Attempts at chromatographic separation were not particularly promising.

(10) An additional 0.3–0.4 g. of II could be obtained through the difficultly soluble (in methanol) hydrochloride salt by combining all mother liquors and adding gaseous hydrogen chloride. Furthermore the 12 g. of I, m.p. 228–232°, above usually contained about 0.3 g. of II which was separated in the same fashion (hydrochloride salt from methanol).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.13; H, 9.15.

2-(*p-Hydroxybenzyl*)-*1,3,5-trimethylpiperidine* (III). The filtrate from the 2.1 g. of solid of m.p. 195–220° (above) was concentrated to 10–15 ml. and kept at −5°. After 15–20 hr. 2.1 g. of crystals, m.p. 160–174° were obtained. A recrystallization from 10 ml. of methanol gave 1.5 g. of m.p. 176–179°. The analytical sample melted at 178–179.5°; rectangular plates.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.23; H, 9.94. Found: C, 77.53; H, 9.83.

The *hydrochloride* crystallized from alcohol-ether in square plates, m.p. 220–222°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97. Found: C, 66.75; 66.63; H, 8.86, 8.98.

2-(*p-Methoxybenzyl*)-*1,3,4-trimethylpiperidine* (VI) *picrate*. (a) *From* III. Ethereal diazomethane methylation of III in methanol-ether as described for I below gave a 90% yield of VI isolated as the picrate. It crystallized from alcohol-acetone in yellow rods of m.p. 175–176°.

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92. Found: C, 55.57; H, 5.90.

(b) *From* IX. Two g. of distilled IX, 1.0 g. of 5% palladium-charcoal and 15 ml. of alcohol absorbed 0.9 molar equivalent of hydrogen during 3.5 hr. The mixture was filtered through Super-Cel and the combined filtrate and washings (*ca.* 25 ml.) were treated with 2.3 g. of picric acid. On warming to solution and keeping at 25° for 1.5–2 hr., 1.9 g. (45%) of picrate, m.p. 157–165°, separated. After two careful recrystallizations from acetone or acetone-alcohol it melted at 170–173° and was undepressed by picrate prepared in the diazomethane methylation of III.

The filtrate from the 1.9 g. of picrate, m.p. 157–165° deposited rapidly 1.2 g. (35%) of another (isomeric)[11] picrate, m.p. 158–162°. Two recrystallizations from acetone made the melting point constant at 166.5–168.5°; yellow prisms.

Anol. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92. Found: C, 55.51; H, 5.72.

Conversion of VI *to* III. The base VI (0.5 g. from 1.0 g. of picrate, m.p. 171–173.5°, prepared from IX) and 4 ml. of 48% hydrobromic acid were refluxed for 30 min., cooled, diluted with water, and made alkaline with ammonium hydroxide. On addition of a few ml. of ether, the base gradually crystallized. It was kept at 5° overnight and filtered; yield 0.4 g. (80%), m.p. 173–177°. Upon recrystallization from 2–3 ml. of methanol the m.p. was 178–179.5° alone or in mixture with III isolated from the residues of the preparation of I. The infrared spectra of the two were also identical.

2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide. Three g. of I, 30 ml. of methanol, and 45 ml. of 3% ethereal diazomethane were stirred to solution (30–45 min.). After 4 hr., 45 ml. additional diazomethane solution was added and the mixture kept for 2–3 days at *ca.* 25°. Solvents were distilled *in vacuo* and the methyl ether evaporatively distilled at 130° (bath temperature) and 0.1–0.5 mm. to give 3.0 g. (94%). The hydrobromide salt (from ether–33% HBr–acetic acid) crystallized from acetone in flakes, m.p. 234–236.5°.

Anal. Calcd. for $C_{16}H_{24}BrNO$: C, 58.90; H, 7.41. Found: C, 58.74; H, 7.63.

The *methiodide* (from acetone) melted at 177–180°.[12]

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.71; H, 6.76. Found: C, 52.47; H, 6.64.

7-Methoxy-1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (IV) *hydrobromide*. The methiodide above (2.4 g.) and 30 ml. of 10% sodium hydroxide were refluxed for 3 hr. The oily base was dried (sodium sulfate) in ether and evaporatively distilled (150°/0.5 mm.). The 1.3 g. of distillate, 20 mg. of platinum oxide, and 10 ml. of methanol absorbed one molar equivalent of hydrogen in 20 min. The filtered solution was evaporated to dryness *in vacuo*, the oil was dissolved in ether and acidified with 33% hydrogen bromide in acetic acid; yield of IV hydrobromide 1.3 g. (62%), m.p. 187–190°; flakes from acetone, m.p. 192–193.5°.

Anal. Calcd. for $C_{17}H_{28}BrNO$: C, 59.64; H, 8.24. Found: 59.49; H, 8.22.

7-Hydroxy-1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VII). One g. of IV and 10 ml. of 48% hydrobromic acid were refluxed for 30 min., cooled, made alkaline with ammonium hydroxide, and extracted with ether. Evaporation of the dried ethereal solution left 0.6 g. (84%) of VII; plates from ether, m.p. 132–136°.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.70; H, 10.19. Found: C, 77.87; H, 10.36.

The *picrate* (containing 2 molar equivalents of picric acid)[13] crystallized from alcohol (containing a little picric acid) in prisms, m.p. 142–142.5°.

Anal. Calcd. for $C_{16}H_{25}NO \cdot 2[C_6H_2(NO_2)_3OH]$: C, 47.66; H, 4.43; N, 13.90; mol. wt., 705.6. Found: C, 47.69; H, 4.31; N, 13.76; mol. wt.,[13] 710, 724.

The *hydrochloride* (from acetone) was hygroscopic but became a stable powder melting at 187–189°.

Anal. Calcd. for $C_{16}H_{26}ClNO \cdot 1/2\ H_2O$: Cl, 12.10. Found: Cl, 12.16.

There was no weight loss on drying the hydrochloride at 100° without vacuum. The base VII could be regenerated from either the hydrochloride or dipicrate.

7-Methoxy-1,2-dimethylnaphthalene (V) *picrate*. (a) *From* I. The methiodide of 2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan (methyl ether of I), 0.5 g., and 5 ml. of 10% sodium hydroxide were refluxed for 2 hr. and the resultant methine[14] isolated and hydrogenated as described above. The resultant 0.3 g. of base IV and 0.3 g. of 5% palladium-charcoal were intimately mixed in a test tube fitted with an air vent. The tube was then immersed in a 250° bath. The temperature of the bath was raised to 315° during 10 min. and kept at 305–320° for 20 min. The cooled mixture was extracted thrice with ether. The ether extracts were washed with dilute hydrochloric acid, dried and evaporated leaving a residue which was evaporatively distilled at an air-bath temperature of 100–110° (0.1 mm.). The distillate (0.1 g.), 0.1 g. of picric acid, and 4 ml. of 95% ethanol were warmed to solution, then cooled gradually to −15° to give 80–130 mg. (15–25% based on starting methiodide) of the picrate of V, m.p. 132–134°; orange needles from methanol.

Anal. Calcd. for $C_{19}H_{17}N_3O_8$: C, 54.93; H, 4.13. Found: C, 55.16; H, 4.01.

(b) *From* II. Methylation of 0.4 g. of II as described for I gave 0.65 g. of the *methiodide* of the methyl ether of II; needles from absolute alcohol–ether, m.p. 217–218°, plates from acetone, m.p. 232–234°. The needles were analyzed.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.72; H, 6.77. Found: C, 52.60, 52.83, H, 6.83, 6.64.

This *methiodide* (0.6 g.), 0.6 g. of potassium hydroxide and 6 ml. of water were kept on the steam bath for 2 hr. and the oily base dissolved in ether. The dried ethereal extracts were evaporated. The resulting base was aromatized with 0.4 g. of 5% palladium-charcoal as described above. The picrate (90 mg., 14% based on methiodide) melted at 131–133° and was undepressed when mixed with that prepared from I. The infrared spectra of the two were also identical.

(11) We believe this picrate is a diastereoisomer corresponding to VI. Its melting point was depressed by the isomeric picrate and the IR spectra of the two showed some differences.

(12) E. M. Fry and E. L. May, *J. Org. Chem.*, 24, 116 (1959).

(13) Determined by absolute alcoholic sodium methoxide titration (Thymol Blue) by Dr. A. Patchornik, Visiting Scientist from the Weizmann Institute of Science, Rehovoth, Israel.

(14) Palladium-charcoal treatment of this base also gave a 15% yield of the picrate of V as described in the aromatization of IV.

7-Methoxy-1,2-dimethylnaphthalene. The picrate (0.3 g.) from several combined aromatization experiments was converted to the hydrocarbon (alkali-ether) which was distilled evaporatively (115°/0.5 mm.). It crystallized from methanol in somewhat hygroscopic needles, m.p. 48–49.5°; λ_{max}^{EtOH} 234, 273, 283, 291, 316, (ε 70, 400, 4,070, 4,710, 3,930, 1,430, 2,000).[15] For analysis a sample was dried at 117°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.33; H, 7.78.

Acknowledgment. We wish to thank Dr. Harry Saroff of this Institute for titration curves and helpful discussions.

BETHESDA 14, MD.

(15) Ultraviolet and infrared data are due respectively to Mrs. Ann Wright and Mr. William Jones, both of this Institute.

[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. XII.[1] (±)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (NIH 7519) and Its Optical Forms

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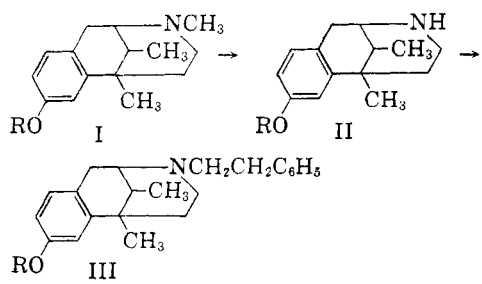
(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia) and its optical isomers have been converted to analogous *N*-phenethyl compounds (IIIa) in 40% overall yield. The (±)-IIIa (NIH 7519) appears to be a promising agent for the relief of both acute and chronic pain.

In a recent communication[2] we reported the conversion of (±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia) and the optical isomers thereof to the corresponding 2-phenethyl analogs (III). In the present report details of these conversions and of the optical resolution of Ia are presented along with additional pharmacological data.

Cyanogen bromide treatment of Ib or Ic in chloroform yielded, after acid hydrolysis, the secondary amines IIb and IIa respectively. Treatment of the crude IIa and IIb with phenylacetyl chloride (aqueous methanol–potassium carbonate medium) afforded the phenylacetamides which, without purification, were reduced to IIIa and IIIb with ethereal lithium aluminum hydride. Refluxing hydrobromic acid was used to convert IIIb to IIIa.



a, R = H; b, R = CH_3; c, R = $COCH_3$

(+)-3-Bromo-8-camphorsulfonic acid [(+)-α-bromo-camphor-π-sulfonic acid] formed crystalline salts of the optical isomers of Ia which could be readily separated on recrystallization from water. The salt of the (−)-isomer of Ia was the less soluble of the two.

Analgesic and toxicity data are given in Table I as specified. It is of interest that the *levo*-isomer of (±)-Ia (NIH 7410) not only contains all of the analgesic activity of the latter but is also much less toxic than the racemate. The *levo*-isomer of (±)-IIIa (20 times more potent than morphine) is about seventy times as potent as the *dextro*-isomer, which nevertheless shows fairly good activity. The methoxy derivatives Ib and IIIb are between morphine and codeine in analgesic effectiveness. Finally, (±)-IIIa has only one sixth the physical dependence potency of morphine in monkeys[3] and appears to be a promising agent for the relief of both acute and chronic pain in man at about one seventh the optimal dose of morphine; its use appears to be attended with fewer and less objectionable side-effects.[4]

EXPERIMENTAL

Melting points are corrected. Microanalyses were performed by Paula M. Parisius and Byron Baer of the Institute's service analytical laboratory, Dr. William C. Alford, Director.

Optical resolution of (±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia).[1] The ammonium salt of (+)-3-bromo-

(1) Paper XI of this series. E. L. May and J. Harrison Ager, *J. Org. Chem.*, **24**, 1432 (1959). Ia is the predominant isomer obtained in the synthesis from 3,4-lutidine methiodide.

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

(3) G. Deneau, University of Michigan, personal communication.

(4) J. E. Eckenhoff, *Anesthesiology*, **30**, 355 (1959).

(5) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).