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.

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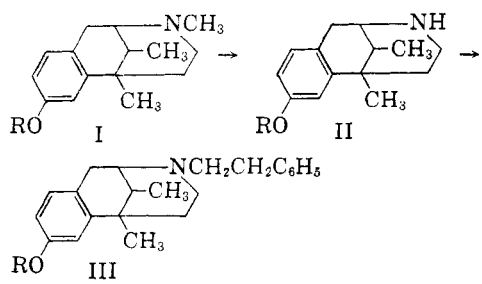
(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Ia) and its optical isomers have been converted to analogous *N*-phenethyl compounds (IIIa) in 40% overall yield. The (±)-IIIa (NIH 7519) appears to be a promising agent for the relief of both acute and chronic pain.

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.

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

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TABLE I

PHARMACOLOGICAL RESULTS

NIH No.		LD_{50} Mice Subcutaneously	Analgesic Effect[a] ED_{50} Mice Orally	Analgesic Effect[a] ED_{50} Mice Subcutaneously
	Morphine sulfate	576	3.7	2.1
7410	(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan.HCl.H_2O (Ia)[1,7]	175	23.9	3.0
7569	(−)-Ia.HBr	>400	14.1	1.7
7571	(+)-Ia.HBr	Convulsant at 20	—	Inactive
7519	(±)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan.HBr (IIIa)	332	6.4	0.25
7613	(−)-IIIa.HBr	147	3.9	0.11
7614	(+)-IIIa.HBr	201	12.9	7.6
7550	(±)-2′-Methoxy-2,5,9-trimethyl-6,7-benzomorphan.HBr (Ib)[1]		21.7	9.8
7625	(±)-2′-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan.HBr (IIIb)		10.6	6.5

[a] For the method of determining analgesic effect see reference (5). All doses are in mg./kg. of substance as administered and are the result of statistical (probit) analysis of the data.

camphor-8-sulfonic acid[6] (5.0 g.), 4.4 g. of Ia hydrochloride[1,7] and 35 ml. of water were kept warm until crystallization began, cooled very gradually to room temperature, then kept at 5° for 3 hr. and filtered. The 6.3 g. of precipitate was dissolved in 200 ml. of boiling water; the solution was concentrated to 150 ml. and kept at −5° overnight to give 3.8 g. of the pure sulfonate salt of (−)-Ia, m.p. 285–288° (dec.). The filtrate, combined with that from the 6.3 g. above was made alkaline with a large excess of concentrated NH_4OH to give 1.7 g. of base of m.p. 178–180° (turbid melt, clear at 212°). This was dissolved in 10 ml. of boiling absolute alcohol and 2–3 ml. of water was added. The solution was seeded with (±)-Ia and kept at −5° for 20 hr. Filtering and washing the crystals with 2:1 alcohol-water gave 0.36 g. of (−)-Ia, m.p. 231–235°. The combined filtrate and washings were warmed and diluted to about 30 ml. with water to give, after cooling gradually to 5°, then at −5° for 24 hr. or more, 1.1 g. (60%) of (+)-Ia, m.p. 181–183°. It crystallized from 1:1 acetone-water in rods of m.p. 183–184.5°, $[\alpha]_D^{20}$ +84.3° (*c* 0.83, abs. ethanol).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.75; H, 9.25.

The *hydrobromide* of (+)-Ia, recrystallized from absolute ethanol–ether, melted at 238–242° (dec.) and had $[\alpha]_D^{20}$ +52.1° (*c* 1.46, water).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.93; H, 7.15.

The 3.8 g. of pure sulfonate of Ia above was dissolved in 150 ml. of boiling water and treated with excess concd. NH_4OH to give, after 15 hr. at −5°, 1.5 g. (80%) of (−)-Ia, m.p. 183–184.5°, $[\alpha]_D^{20}$ −84.8° (*c* 0.09, absolute ethanol); rods from aqueous acetone.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.91; H, 8.97.

The hydrobromide of (−)-Ia had m.p. 238–241° and $[\alpha]_D^{20}$ −52.0° (*c* 2.00, water).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.66; H, 7.34.

(±)-2′-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIb) *hydrobromide.* A solution of 1.4 g. of Ib[1] in 10 ml. of chloroform was added during 1 hr. to a stirred solution of 0.7 g. of cyanogen bromide in 5 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residue and 30 ml. of 6% HCl were refluxed for 5–8 hr., the solution was made alkaline and the liberated oil was shaken into ether. Drying and evaporation of the ether left 1.3 g. of crude IIb to which was added 20 ml. of methanol, 6 ml. of water, and 1 g. of K_2CO_3. The mixture was stirred while adding during 10 ml. 1.0 min. of phenylacetyl chloride. After 2 hr. of stirring water was added, and the oil was shaken into ether. The ethereal extracts were washed with dilute HCl then bicarbonate solution, dried, and evaporated to give 1.8 g. of crude phenylacetamide derivative. This in 15 ml. of dry ether was treated gradually (stirring) with 15–20 ml. of 1.6*M* ethereal $LiAlH_4$. The mixture was refluxed 6–8 hr. and treated dropwise with 5–8 ml. of water. The ethereal layer was dried and evaporated to dryness giving 1.7 g. of residue. This in 1:1 acetone-ether was acidified to Congo Red with 33% HBr–AcOH giving 1.2 g. (50%) of IIIb hydrobromide, m.p. 244–245.5°; square plates from acetone.

Anal. Calcd. for $C_{23}H_{30}BrNO$: C, 66.34; H, 7.26. Found C, 66.12; H, 7.19.

(±)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIa) *hydrobromide* (NIH 7519). (a) From (±)-Ia. Acetic anhydride (10 ml.) and 10 g. of (±)-Ia were kept on the steam bath for 30–45 min., cooled and poured into ice water. After 5 min. the mixture was made alkaline (while keeping ice cold) with 50% aqueous KOH. The freed base was shaken quickly into ether and dried over Na_2SO. Evaporation of the ether left 11.5 g. of Ic which, in 35 ml. of chloroform, was added during 30–45 min. to a stirred solution of 5 g. of cyanogen bromide in 25 ml. of chloroform. The solution was then refluxed for 3 hr. and evaporated to dryness. The residue and 150 ml. of 6% HCl were refluxed 6–8 hr. The cooled solution was made alkaline with concentrated NH_4OH. The base was shaken into 2:1 1-butanol-benzene to give, after drying, 8.8 g. of crude IIa.[8] This IIa, 100 ml. of methanol, 15–20 ml. of water, and 10 g. of K_2CO_3 were stirred and treated during 15 min. with 10 ml. of phenylacetyl chloride. After an additional 3 hr. of stirring 300 ml. of water was added and the mixture extracted thrice with 2:1 1-butanol–benzene. The combined extracts were washed with dilute HCl, then water, dried and solvents were evaporated *in vacuo*. The residue (12 g.) and 100 ml. of dry ether were stirred while adding dropwise 60 ml. of 1.5*M* ethereal $LiAlH_4$. The mixture was refluxed overnight, cooled in ice, and treated carefully with 60 ml. of 48% HBr Addition of an equal volume of water, filtration, washing with cold water then ether, and drying the precipitate gave 10.5–12 g. of crude IIIa hydrobromide which crystallized from 11 ml. of acetone and 10 ml. of ethyl acetate in a yield of 7 g. (40% based on Ia) m.p. 166–170°; rods from acetone or absolute ethanol–ether.

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.40; H, 7.00.

The *base*, prepared from the hydrobromide with aqueous

(6) Aldrich Chemical Company, Inc., Milwaukee, Wis.

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

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

methanol–NH_4OH crystallized from methanol in rods, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.27; H, 8.48.

(b) *From* IIIb. A mixture of 10 ml. of 48% HBr and 1.3 g. of IIIb hydrobromide was refluxed vigorously for 20 min. The solid gradually changed to a fluid, dark oil. The mixture was ice cooled, and the aqueous layer was decanted. The residue was dried *in vacuo* then dissolved in 4 ml. of acetone. The solution was again evaporated to dryness *in vacuo*. The residue crystallized from 4 ml. of acetone in a yield of 1.0 g. (after cooling at −5°). It melted at 165–168° and was identical with the (±)-IIIa hydrobromide described above.

(−)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. This levorotatory IIIa was prepared from (−)-Ia as described above for the conversion of (±)-Ia to (±)-IIIa. It melted at 284–287° and had $[\alpha]_D^{20}$ −84.1° (*c*, 1.12, 95% ethanol).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.82; H, 7.02.

The *base* (prepared from the hydrobromide with aqueous methanolic NH_4OH) crystallized from aqueous methanol or absolute methanol in needles, m.p. 159–159.5°, $[\alpha]_D^{20}$ −122° (*c* 0.74, 95% ethanol).

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 81.94; H, 8.44.

(+)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. As described in the conversion of (±)-Ia to (±)-IIIa above, (+)-Ia yielded (+)-IIIa hydrobromide, m.p. 284–287°, $[\alpha]_D^{20}$ +84.4° (*c* 1.47, 95% ethanol).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.65; H, 7.15.

The *base* crystallized from methanol in needles, m.p. 159–160°, $[\alpha]_D^{20}$ +120° (*c*, 0.60, 95% ethanol).

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.35; H, 8.41.

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2,2′,2″-Tripyrrylmethenes[1,2]

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The potassium permanganate oxidation of 2,2′,2″-tripyrrylmethanes yields the corresponding methenes in varying yields. Di-2-(3,5-dimethyl-4-carbethoxy)pyrryl ketone was isolated as a by-product from the oxidation of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane. 2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethene forms an inclusion compound with isooctane. Spectral properties of the methenes and prodigiosin are compared and differences noted.

2,2′,2″-Tripyrrylmethenes constitute a relatively unexplored class of organic compounds. Further interest in such compounds stems from Wrede and Rothhaas[4] suggestion that prodigiosin is 2,2′,2″-(4-*n*-amyl-4′-methoxy-5-methyl)tripyrrylmethene. Fischer and Gangl[5] reported the synthesis of two 2,2′,2″-tripyrrylmethenes by oxidation of the corresponding tripyrrylmethanes with lead dioxide in acetic acid. The tripyrrylmethanes can be synthesized by several procedures.[6–8] More recently, Treibs and Hintermeier[9] described the preparation of five other 2,2′,2″-tripyrrylmethenes through the condensation of an α,α′-dipyrryl ketone, or an α-carbo-t-butoxypyrrole, and an α-free pyrrole promoted with phosphorous oxychloride in chloroform. An attempt on our part to oxidize 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane to the methene by the procedure of Fischer and Gangl gave only a low yield of the methene, as attested by a microscopic examination of the reaction product. Hydrogen peroxide in aqueous acetic acid and oxygen in benzene gave a slight color change to the reaction mixture, indicative of only a small degree of oxidation. Since Corwin and Brunings[10] found that 2,2′-(3,3′,5,5′-tetramethyl-4,4′-dicarbethoxy)dipyrrylmethane can be oxidized to the corresponding dipyrrylmethene in a good yield with potassium permanganate, we were led to try the conversion of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane to the tripyrrylmethene by this method. We have tried the oxidation at

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