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Structures Related to Morphine. IX.*[1] Extension of the Grewe Morphinan Synthesis in the Benzomorphan Series and Pharmacology of Some Benzomorphans

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2,5-Dimethyl-6:7-benzomorphan (IIIa) and the phenolic derivative (IIIb) have been synthesized in a three-step process from γ-picoline methiodide and benzylmagnesium chloride or *p*-methoxybenzylmagnesium chloride respectively. The analgesic activity and acute toxicity, in mice, of these and other closely related compounds are summarized.

The synthesis and analgesic activity of 2,5-dimethyl-6:7-benzomorphan (IIIa) have been reported in an earlier paper.[2] Two different approaches to IIIa were successful, one from β-tetralone and one from hydratroponitrile. To date neither of these approaches has proved applicable to the preparation of the 2′-hydroxy relative (IIIb), a compound one could expect to have greater analgesic potency than IIIa. The Grewe morphinan synthesis,[3] which provided a relatively facile method for obtaining 2,5,9-trimethyl-6:7-benzomorphan and the 2′-hydroxy analog, (from 3,4-lutidine),[1] has now been found to have limited utility in the synthesis of IIIa and IIIb. In this instance γ-picoline served as the starting base.

The reaction of benzylmagnesium chloride or the *p*-methoxy derivative with γ-picoline methiodide gave a good yield of the crude, very unstable dihydro derivative (I) which was distilled with considerable loss, and hydrogenated in dilute hydrochloric acid with palladium–barium sulfate. Because of little hindrance of the 3,4-double bond of the nitrogen-containing moiety, it was impossible to effect a selective reduction of I to the tetrahydro stage in contrast to experience in this laboratory with the corresponding 3,4-lutidine derivative,[1] where hydrogen absorption ceased after the 5,6-double bond was saturated. Best results were obtained with I if the reduction was interrupted after 0.7–1.0 molecular equivalent of hydrogen had been absorbed. Phosphoric or hydrobromic acid treatment of the reduction mixture containing II gave IIIa and IIIb respectively in 5.5% and 4% over-all yields based on γ-picoline methiodide. A by-product was also isolated along with IIIb. The yield of this material was very low, varying directly with the extent of hydrogen absorption of Ib. It is presumed to be 2-(*p*-hydroxybenzyl)-1,4-dimethylpiperidine resulting from complete hydrogenation of the heterocyclic ring of IIb. Compound IIIb was also prepared from IIIa *via* nitration, reduction, and diazotization, a conversion affording sufficient proof of structure of IIIb. The identity of specimens of IIIb prepared by the different methods in addition establishes the position of entry of the nitro group into IIIa.

In Table I are presented the analgesic activities and acute toxicities of the principal benzomorphans prepared to date. Similar data are given also for a few derivatives and degradation products as well as for *N*-methylmorphinan and 3-hydroxy-*N*-methylmorphinan (racemorphan). Compounds 1 and 3 are about half as potent as but less toxic than *N*-methylmorphinan (No. 9) by subcutaneous administration while 2 and 4, analogs of racemorphan, are respectively, from a tenth to a third as effective as racemorphan (No. 10) but again somewhat less toxic than the morphinan derivative. The introduction of a hydroxyl or an acetoxyl group into position 8 of compound 1 or cleavage of the nitrogen ring of 1 and 3 does not markedly alter analgesic effectiveness but does reduce toxicity (*cf.* compounds 5–8). The ratio of subcutaneous to oral dose for these benzomorphans compares favorably with that of *N*-methylmorphinan and racemorphan. Once again it can be observed that appropriate substitution of a phenolic hydroxyl is efficacious. The most interesting compound of the benzmorphan series, racemic 2′-hydroxy-2,5,9-trimethyl-6:7-benzomorphan (No. 4) with a therapeutic ratio of 1:58 is being assessed for addiction liability in the monkey.

EXPERIMENTAL

Microanalyses are by Dr. William C. Alford and staff of this institute, and infrared spectra are from William Jones also of this institute.

2,5-Dimethyl-6:7-benzomorphan (IIIa) *hydrochloride.*[2] To a vigorously stirred mixture of 15.5 g. of γ-picoline methiodide and 40 ml. of dry ether was added at 10–20° during 20–30 min., 100 ml. of 1.3*M* ethereal benzylmagnesium chloride. After 1 hr. of stirring the mixture was poured into ice water-ammonium chloride, basified with ammonium hydroxide and the ethereal layer extracted with two por-

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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

(2) E. L. May and J. G. Murphy, *J. Org. Chem.*, 20, 257 (1955).

(3) R. Grewe, *Angew. Chem.*, 59, 194 (1947).

TABLE I

PHARMACOLOGICAL RESULTS

No.	Compound Name	Toxicity, LD_{50}, Mice		Analgesic Effect, ED_{50}, Mice	
		Orally	Subcutaneously	Orally	Subcutaneously
1	2,5-Dimethyl-6:7-benzomorphan, IIIa		148 (143–153)	42.1 (39.2–45.3)	22.1 (19.3–25.2)
2	2′-Hydroxy derivative, IIIb		175 (164–186)		10.4 (9.0–11.8)
3	2,5,9-Trimethyl-6:7-benzomorphan[1]		155 (147–162)		27.3 (23.6–31.5)
4	2′-Hydroxy derivative[1]		175 (161–190)	23.9 (21.8–26.3)	3.0 (2.6–3.4)
5	8-Hydroxy-2,5-dimethyl-6:7-benzomorphan[2]		323 (307–340)		29.3 (26.5–32.3)
6	O-Acetyl derivative[2]			29.3 (26.5–32.3)	32.2 (29.4–35.2)
7	1-(2-Dimethylaminoethyl)-1-methyl-1,2,3,4-tetrahydronaphthalene[2]		362 (336–391)		24.9 (22.3–27.7)
8	1,2-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene[1]		411 (349–483)		41.0 (37.4–44.9)
9	*N*-Methylmorphinan[3,4,6]	267 (243–293)	92 (88–96)	40.9 (38.2–43.8)	11.3 (10.1–12.7)
10	3-Hydroxy-*N*-methylmorphinan (racemorphan)[4,5,6]	276 (253–301)	131 (124–138)	7.0 (5.6–8.9)	0.93 (0.84–1.03)

Compounds 1–8 were tested as hydrochlorides and 9 and 10 were tested as the phosphate and hydrobromide, respectively, by a method described previously.[7] Doses are in mg./kg. and are derived by probit analysis of the data; figures in parentheses are 1 × SE-limits.

tions of excess, cold, 10% hydrochloric acid. The combined extracts were washed with ether, basified with cold ammonium hydroxide, extracted twice with ether, and the ethereal extracts were dried over sodium sulfate in a stoppered flask at 0°. The residue (9 g.) from distillation of the ether *in vacuo* was quickly distilled, evaporatively, through a short path at 0.3 mm. in an air bath preheated to 125°. The 5.1 g. of distillate, 70 ml. of normal hydrochloric acid and 1.5 g. of 5% palladium–barium sulfate absorbed 1.0 molecular equivalent of hydrogen in 1.5 hr. when the rate of hydrogen absorption was constant at 2 ml./min. (original rate 16 ml./min.). The filtered (through Super-Cel) solution was basified with ammonium hydroxide and the liberated IIa was dried in ether and distilled as described for Ia. The 3.5 g. of distillate and 25 ml. of 85% phosphoric acid were kept at 150° for 3 days, poured into ice water, basified, and the liberated base was distilled as described before. This distillate (3.0 g.), in ether, was treated with gaseous hydrogen chloride. After cooling at 5° the ether was decanted from the viscous hydrochlorides which were dissolved in 5 ml. of warm acetone. Seeding and cooling at 5° for 1–2 days 0.85 gave g. (5.5% based on γ-picoline methiodide) of IIIa hydrochloride, m.p. 193.5–195°, indistinguishable (infrared diagram, mixed m.p.) from that described previously.[2] The picrate, m.p. 175–178°, was likewise identical with IIIa picrate reported previously.[2]

2′-Hydroxy-2,5-dimethyl-6:7-benzomorphan (IIIb). To a stirred ice-cooled mixture of 15 g. of γ-picoline methiodide and 90 ml. of dry ether was added during 10 min., 300 ml. of 0.3*M* ethereal *p*-methoxybenzylmagnesium chloride.[8] The suspension was stirred for an hour at *ca.* 25° and treated as described in the preparation of Ia except that the air bath temperature in the distillation was 150°. The 6.2 g. of reddish brown distillate (Ib), 1.5 g. of 5% palladium–barium sulfate, and 100 ml. of normal hydrochloric acid absorbed 70–75% of one molecular equivalent of hydrogen during 1 hr. when hydrogenation was proceeding at 40% of the maximum rate. The 3.6 g. of IIb distillate (distillation bath temperature 150°) obtained as described for IIa and 35 ml. of 48% hydrobromic acid were kept at 135–140° for 20 hr., poured into 300 ml. of ice water and basified with ammonium hydroxide. Insoluble material was filtered. The filtrate was extracted thrice with chloroform. The dried chloroform extracts were evaporated at reduced pressure to give 2.1 g. of amorphous material which was dissolved in 7–10 ml. of acetone to give, after cooling to 0°, 0.55 g. (4% over-all from γ-picoline methiodide) of IIIb, m.p. 206–210°; prisms from methanol, m.p. 217–218.5°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.60; H, 8.66.

The hydrochloride crystallized from absolute alcohol–ether in rods, m.p. 240–243° (dec.).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94. Found: C, 66.37; H, 8.02.

The acetone filtrate from the 0.55 g. of IIIb was acidified with dry hydrogen chloride. After a few hours the clear supernatant solution was decanted. On seeding it deposited, after 20 hr., 0.15 g.[9] of hydrochloride which appears to be *1,4-dimethyl-2-(p-hydroxybenzyl) piperidine hydrochloride* of m.p. 216–218.5°, resulting from complete reduction of the *N*-containing ring of Ib; rods from absolute alcohol–ether m.p. 219–220.5°.

(4) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(5) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(6) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).

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

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

(9) If, in the hydrogenation of IIb, hydrogenation was allowed to proceed to completion, 5–10% yields of this substance were obtained.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67. Found: C, 65.32; H, 8.77.

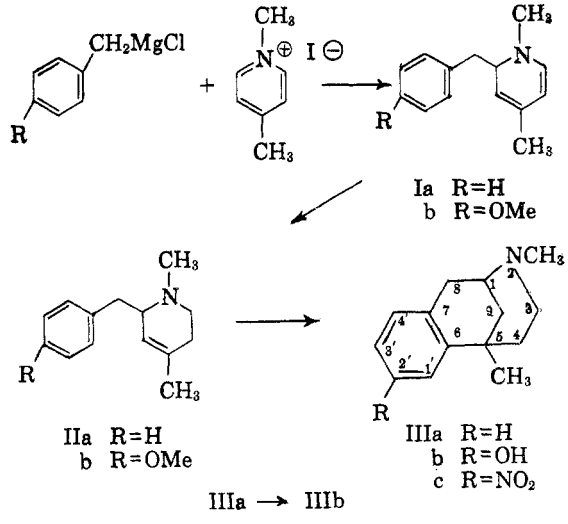
The corresponding *base* crystallized from methanol in prisms, m.p. 196–197.5°. It was dried *in vacuo* at 77° for analysis.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.64. Found: C, 76.46; H, 9.63.

2,5-Dimethyl-2'-nitro-6:7-benzomorphan (IIIc) *picrate.* To 11 ml. of nitric acid (sp. gr. 1.49–1.50) and 6 ml. of acetic acid, stirred and kept at 3–7°, was added during 2 hr. 2.3 g. of IIIa in 5 ml. of acetic acid. The solution was left for 20 hr. at *ca.* 25°, freed of acetic acid *in vacuo* at a bath temperature below 60°, and basified with ice–ammonium hydroxide. The liberated oil was dried in ether. Evaporation of the ether left 2.8 g. of base which, in 10 ml. of acetone, was added to 3.0 g. of picric acid in 30 ml. of acetone. Left at room temperature for 2 hr. and at 0° for 2 hr. the solution deposited 3.9 g. (72%) of IIIc picrate, m.p. 227–229°. The analytical sample (prisms from acetone) melted at 233–234.5° (dec.).

Anal. Calcd. for $C_{20}H_{21}N_5O_9$: C, 50.53; H, 4.45. Found: C, 50.69; H, 4.47.

Conversion of IIIc to IIIb. A mixture of 1.3 g. of IIIc (from 2.9 g. of picrate), 5 ml. of methanol, and 0.5 g. of 5% palladium–barium sulfate absorbed three molecular equivalents of hydrogen during 15 min. The filtered solution was evaporated to dryness. To the residue in 8 ml. of 3*N* sulfuric acid was added (0°, stirring) during 30 min., 0.3 g. of sodium nitrite in 2.5 ml. of water. The solution was then treated at 60–70° with a solution of 6 ml. of water and 6 ml. of water and 6 ml. of sulfuric acid, warmed to 80° during 15–20 min., poured into ice–ammonium hydroxide, and extracted with 40 ml. of chloroform in 4 portions. The dried extract was evaporated to give 0.8 g. of residue which crystallized from 8 ml. of acetone in a yield of 0.3 g. (25% from IIIc) m.p. 210–215°. A recrystallization from methanol (Norit) gave material identical with the IIIb described above. It was converted to the hydrochloride, m.p. 240–243° (dec.) whose infrared spectrum was identical with that of the IIIb hydrochloride prepared from γ-picoline methiodide.



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[CONTRIBUTION FROM THE DIVISION OF PURE CHEMISTRY, NATIONAL RESEARCH COUNCIL OF CANADA]

Lycoctonine: The "α-iso" and "Anhydro-α-iso" Compounds*[1]

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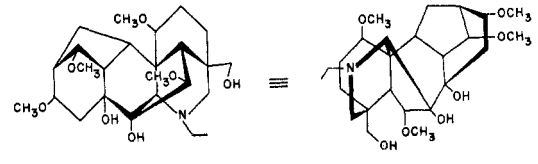
The lactam II from the *Delphinium* alkaloid lycoctonine can be oxidized by lead tetraacetate to a diketone III. This underwent internal aldol condensation to a compound IV which on heating with acid gave an isomer V. Further action of acid on V produced a pinacolic dehydration to VII. By hydrolysis of a methoxyl and lead tetraacetate cleavage, VII was converted to the γ-lactone acid IX. The properties and reactions of these compounds lend strong support to the currently accepted structure I for lycoctonine.

Structure I for lycoctonine[3] follows unambiguously[4] from the structure for des(oxymethylene)-lycoctonine determined by x-ray crystallography.[5] Most of the published chemistry of lycoctonine has been interpreted on the basis of this formula.[4]



I

The structures tentatively assigned to the transformation products of the *seco*diketone III derived from lycoctonam (II) seemed capable of chemical

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(2) National Research Council of Canada Postdoctoral Fellow.

(3) The representation showing the diterpenoid character of the structure (I) will be used in this communication.

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