

prisms: mp 212–213 °C; $[\alpha]_D^{20}$ -149.6° (*c* 1.0, CHCl₃); IR (CHCl₃) 3500 (OH), 1685 (C=O), and 1620 cm⁻¹ (C=C); NMR (CDCl₃) 2.40 (s, 3, N-CH₃), 3.68 (s, 3, C₆-OCH₃), 3.86 (s, 3, C₃-OCH₃), 6.73 (s, 1, C₅-H), and 7.03 ppm (s, 1, C₂-H); mass spectrum *m/e* (rel intensity) 409 (90, M⁺), 407 (91, M⁺), 394 (100), 392 (100), 323 (34), and 321 (33). Anal. (C₁₉H₂₂BrNO₄·0.5MeOH) C, H, N, Br.

(-)-1-Bromosinomeneine (4). Bromine (99%, 4.01 g, 25.0 mmol) in HOAc (50 mL) was added, dropwise, over 15 min at 20 °C to a stirred solution of **2** (10.2 g, 25.0 mmol) in HOAc (150 mL) containing HBr-HOAc (30%, 7.0 mL). After 1.5 h, the solution was evaporated in vacuo, and the residue was treated with MeOH (50 mL), made alkaline with 33% NaOH, diluted with H₂O, and extracted with CH₂Cl₂. The extracts were washed with H₂O and dried (MgSO₄) to give, after removal of the solvent in vacuo, **4**. Recrystallization from EtOH gave **4** as colorless needles: mp 217 °C; $[\alpha]_D^{23}$ -85.6° (*c* 1.0, CHCl₃) [lit.⁹ for (+) enantiomer of **4**] mp 217 °C; $[\alpha]_D^{23}$ $+83.08^\circ$ (*c* 3.89, CHCl₃); IR (CHCl₃) 1690 (C=O) and 1622 cm⁻¹ (C=C); NMR (CDCl₃) 2.46 (s, 3, N-CH₃), 3.50 (s, 3, C₇-OCH₃), 3.85 (s, 3, C₃-OCH₃), 4.80 (s, 1, C₅-H), 5.55 (d, 1, *J* = 2 Hz, C₈-H), and 6.90 ppm (s, 1, C₂-H); mass spectrum *m/e* (rel intensity) 407 (98, M⁺), 405 (100, M⁺), 392 (31), 390 (36), 364 (24), and 362 (24). Anal. (C₁₉H₂₀BrNO₄) C, H, N.

(-)-1-Bromo-7-methoxycodeine (5). A THF (50 mL) solution of **4** (1.02 g, 2.5 mmol) was added, over 10 min, to a stirred suspension of LiAlH₄ (0.3 g, 7.9 mmol) in THF (20 mL) at 0 °C. After stirring for 30 min at 0 °C, the excess LiAlH₄ was decomposed with aqueous THF. The resultant mixture was filtered and the precipitate washed with THF. The filtrate was dried (MgSO₄) and the solvent removed in vacuo to give **5** (1.0 g), which was recrystallized from EtOH to give colorless needles (0.84 g, 82%); mp 170–171 °C; $[\alpha]_D^{23}$ -56.1° (*c* 1.0, MeOH) [lit.¹² for (+) enantiomer of **7**] mp 171 °C, $[\alpha]_D^{23}$ $+53.5^\circ$ (*c* 2.055, MeOH); IR (CHCl₃) 3550 (OH) and 1640 cm⁻¹ (C=C); NMR (CDCl₃) 2.43 (s, 3, N-CH₃), 3.32 (s, 3, C₇-OCH₃), 3.80 (s, 3, C₃-OCH₃), 4.90 (d, 1, *J* = 6.2 Hz, C₅-H), and 6.83 ppm (s, 1, C₂-H); mass spectrum *m/e* (rel intensity) 409 (100, M⁺), 407 (100, M⁺), 393 (35), 391 (43), 365 (24), and 363 (24). Anal. (C₁₉H₂₂BrNO₄) C, H, N.

(-)-7-Methoxycodeine (6). A THF (10 mL) solution of **4** (0.3 g, 0.73 mmol) was added, over 5 min, to a stirred suspension of LiAlH₄ (0.05 g, 1.3 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred for 18 h at 20 °C. An additional amount of LiAlH₄ (0.05 g, 1.3 mmol) in THF (5 mL) was then added to the reaction mixture, and stirring was continued for 2 h at 20 °C. The workup procedure was identical with that in **5** and gave a colorless oil. Purification by TLC (CHCl₃-MeOH, 9:1) gave **6** as a solid (0.2 g, 85%). Recrystallization from Et₂O gave colorless needles: mp 138–140 °C; $[\alpha]_D^{23}$ -18.9° (*c* 0.8, MeOH); IR (CHCl₃) 3540 (OH)

and 1640 cm⁻¹ (C=C); NMR (CDCl₃) 2.45 (s, 3, N-CH₃), 3.32 (s, 3, C₇-OCH₃), 3.83 (s, 3, C₃-OCH₃), and 4.91 ppm (d, 1, *J* = 6.2 Hz, C₅-H); mass spectrum *m/e* (rel intensity) 329 (43, M⁺), 314 (17), 286 (11), 83 (100). Anal. (C₁₉H₂₃NO₄) C, H, N.

(-)-Sinomeninone (7). A solution of **6** (0.04 g, 0.12 mmol) in 5.0 M HCl (2 mL) was allowed to stand at room temperature for 24 h. It was made alkaline with 0.5 M Na₂CO₃ and extracted with CHCl₃. The extracts were dried (Na₂SO₄) and the solvent was removed in vacuo to give **7** (0.043 g). Purification by preparative TLC (CHCl₃-MeOH, 9:1) gave pure **7** (0.036 g, 90%), mp 139–140.5 °C. The IR was identical with that of an authentic sample prepared from 7-bromodihydrocodeinone dimethyl ketal.¹⁰

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2,6-Methano-3-benzazocine-11-propanols. Lack of Antagonism between Optical Antipodes and Observation of Potent Narcotic Antagonism by Two *N*-Methyl Derivatives

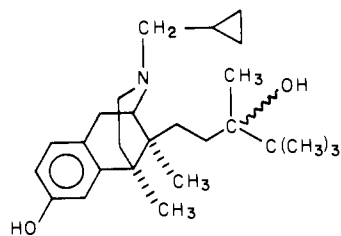
William F. Michne

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. Received June 21, 1978

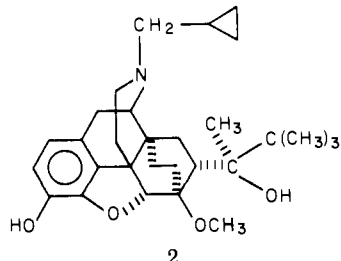
Resolution of a 2,6-methano-3-benzazocine-11-propanol analogue of buprenorphine showed that the biological activity resides in the *levo* antipode. An attempt to enhance agonist activity by preparation of *N*-methyl derivatives resulted in two compounds three and five times as potent as nalorphine as antagonists of phenazocine. These compounds are the most potent *N*-methyl narcotic antagonists reported to date.

We recently reported the synthesis and narcotic agonist-antagonist evaluation of some 2,6-methano-3-benzazocine-11-propanols analogous to the ring C bridged oripavine-7-methanols.¹ Because the effects on biological activity of identical changes in peripheral substituents on the 2,6-methano-3-benzazocine and 4,5-epoxymorphinan ring systems in general are of similar magnitude and direction,²⁻⁴ we were surprised to find major differences in the structure-activity profiles of ours and the parent series.

In particular, when compared with buprenorphine (**2**), neither **1a** nor **1b** showed very much agonist activity (Table I), while **1a** showed considerably more antagonist activity than either **1b** or **2**. Our NMR data suggested that the relative configurations of the alcohol-bearing carbons of **1b** and **2** were the same. If one assumes that the antagonist activity of **1a** is largely or totally confined to the (-) antipode,² one might expect **1c**, the (+) antipode of isomer II, to show some antagonist activity since the absolute



1a, (±) isomer I⁵
 b, (±) isomer II
 c, (+) isomer II
 d, (-) isomer II

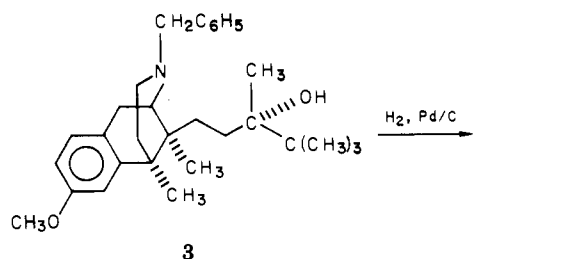


2

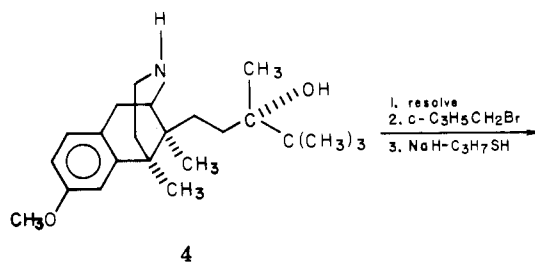
configurations of the alcohol-bearing carbons of (-)-**1a** and **1c** are identical, and it has been shown that the alcohol functionality of the bridged oripavines may be capable of interacting with the opiate receptor after the aromatic ring has been destroyed.⁶ Thus, antagonism of **1d** by **1c** could explain the poor agonist activity of the racemate **1b**. The optical antipodes **1c** and **1d** were obtained as shown in Scheme I. The *N*-phenylmethyl intermediate **3**¹ was hydrogenolyzed over palladium on carbon to give **4** as a syrup. This compound was resolved by crystallization of its mandelic acid salts, and the resulting bases were converted to **1c** and **1d** by alkylation with cyclopropylmethyl bromide, followed by cleavage of the methyl ether with sodium hydride-propanethiol. The test results (Table I) for these antipodes clearly show the incorrectness of our hypothesis; **1c** is inactive as an antagonist and **1d** is twice as active as the racemate in both test systems.

Another possible explanation for the lack of agonist activity in **1b** is that in this molecule the combination of the nitrogen- and alcohol-bearing carbon substituents favors antagonist activity and a different combination of these two substituents might be found to favor agonist activity. The *N*-methyl-19-(4-methylbutyl) derivative **5** (Scheme II) is the most potent bridged oripavine-methanol agonist reported, approximately 9200 times as potent as morphine.⁷ We therefore prepared **7a** and **7b** by reaction of **6**⁸ with methyllithium, followed by separation of isomers using high-pressure liquid chromatography, and finally cleavage of the methyl ether. The test results (Table I) for these isomers show that each of these compounds is an even poorer agonist than **1b**, but both are very potent antagonists whose activity, unlike that observed for **1a** and **1b**, is independent of alcohol-bearing carbon stereochemistry. These two compounds, three and five times as potent as nalorphine, are the most potent *N*-methyl narcotic antagonists reported to date.⁹ We conclude that these compounds probably bind to the receptor in a manner different from that proposed for the oripavine-methanols,¹⁰ perhaps as a result of the conformational freedom of the propanol side chain. We are extending our investigations in an effort to find more potent and perhaps even pure narcotic antagonists among these *N*-methyl derivatives. Such compounds, if they can be shown to exist, would be of interest because they would violate the structure-activity "rules" regarding opiate agonism and antagonism while at the same time possibly shedding some

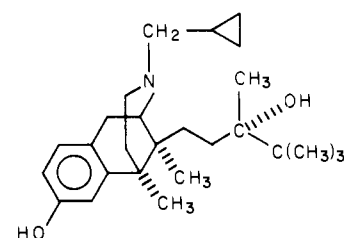
Scheme I



3

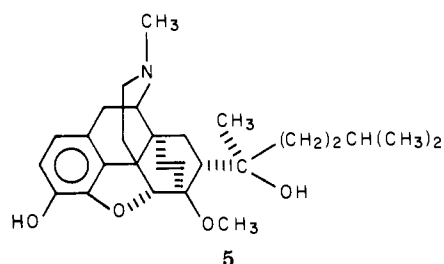


4

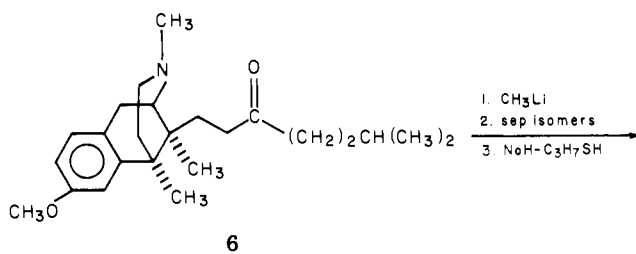


1c, (+) isomer
 d, (-) isomer

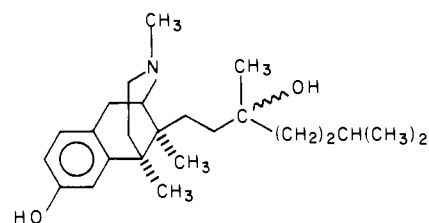
Scheme II



5



6

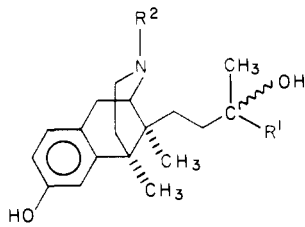


7a, (+) isomer I
 b, (±) isomer II

light on the biochemical mechanisms of these phenomena.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. IR, NMR, and mass spectra substantiated the structures of all new compounds. Rotations were measured using

Table I. Biological Activities of Some 2,6-Methano-3-benzazocine-11-propanols^a


compd	R ¹	R ²	isomer	ED ₅₀ ^b	AD ₅₀ ^c
1a ^d	C(CH ₃) ₃	CPM ^e	(±)-I	>25 ^g	0.022 (0.015-0.033)
1b ^d	C(CH ₃) ₃	CPM	(±)-II	8.9 (6.7-11)	0.71 (0.47-1.1)
1c	C(CH ₃) ₃	CPM	(+)-II	>25 ^g	inactive ^f
1d	C(CH ₃) ₃	CPM	(-)-II	3.8 (2.2-6.8)	0.34 (0.22-0.53)
2	buprenorphine			0.058 (0.031-0.095)	0.11 (flat)
7a	(CH ₃) ₂ CH(CH ₃) ₂	CH ₃	(±)-I	22 (14-30)	0.032 (0.019-0.054)
7b	(CH ₃) ₂ CH(CH ₃) ₂	CH ₃	(±)-II	14 (3.4-50)	0.020 (0.014-0.029)
	nalorphine			2.8 (1.5-7.7)	0.1 (0.07-0.14)

^a All compounds were administered as aqueous solutions of their salts. ^b Acetylcholine writhing test (mouse),¹¹ mg (base)/kg sc (95% confidence limits). ^c Phenazocine antagonism (rat tail flick),¹² mg (base)/kg sc (95% confidence limits). ^d Data from ref 1. ^e CPM = cyclopropylmethyl. ^f At the screening dose of 80 mg/kg. ^g ED₅₀ values were not calculated for compounds showing less than 50% protection at 25 mg/kg.

a Rudolph Research Autopol III automatic polarimeter. Where analyses are indicated by the symbols of the elements, analytical results are within ±0.4% of the theoretical values.

(2α,6α,11S*)-(+)- and (-)-3-(Cyclopropylmethyl)-α-(1,1-dimethylethyl)-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11,α-trimethyl-2,6-methano-3-benzazocine-11-propanol Methanesulfonate (1c and 1d). A suspension of 11.1 g (0.023 mol) of 3-HCl¹ and 3.0 g of 10% Pd/C in 200 mL of DMF was shaken under 50 psi of H₂ until uptake ceased. The catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between dilute NH₄OH and CHCl₃. The CHCl₃ layer was washed with H₂O, dried and charcoaled, and filtered and evaporated to give 8.2 g (100%) of 4 as a syrup. A 6.4-g (0.018 mol) portion of this syrup in 46 mL of warm EtOAc was treated with 1.4 g (0.009 mol) of *l*-mandelic acid and cooled to deposit a crop of *l*-mandelate salt. The mother liquor was washed with dilute NH₄OH, dried, and evaporated to give 5.3 g of syrup which in 20 mL of EtOAc was treated with 1.4 g (0.009 mol) of *d*-mandelic acid and cooled to deposit a crop of *d*-mandelate salt. This mother liquor was washed with dilute NH₄OH, dried, and filtered to give 3.1 g of syrup which in 15 mL of EtOAc was treated with 1.0 g (0.0066 mol) of *l*-mandelic acid and cooled to give a second crop of *l*-mandelate salt. The *l*- and *d*-mandelates were purified by recrystallization from EtOAc; the *l*-acid salt (2.3 g, 50%) had mp 162–165 °C and the *d*-acid salt (1.6 g, 35%) had mp 163–166 °C. The *d*-acid salt was converted to the base with dilute NH₄OH and dried in CHCl₃, and the solvent was evaporated. The residue (1.1 g, 3.05 mmol) in 25 mL of DMF was treated with 0.7 g (5.2 mmol, 70% excess) of cyclopropylmethyl bromide and 0.5 g (5.95 mmol) of NaHCO₃. The reaction mixture was warmed on a steam bath for 1 h and then distilled until the head temperature reached 150 °C. The mixture was cooled and 0.7 g (15.2 mmol) of NaH (57% dispersion in oil) added. Under N₂, 1.4 mL (15.2 mmol) of propanethiol was added dropwise and the mixture refluxed 4 h. After cooling, the mixture was poured into 70 mL of 0.05 M CH₃SO₃H and washed with Et₂O. The aqueous layer was made basic with NH₄OH and extracted with Et₂O, and the Et₂O layer was washed with H₂O, dried, filtered, and evaporated to give 1.1 g of a foam. This was dissolved in 11 mL of MeOH, acidified with CH₃SO₃H, and diluted with 22 mL of Et₂O to give 0.9 g of solid. After recrystallization from MeOH-Et₂O there was obtained 0.6 g (40%) of 1c·CH₃SO₃H: mp 279–282 °C; [α]_D²⁵ +61.0° (c 1.0, EtOH). Anal. (C₂₆H₄₁NO₂·CH₃SO₃H) C, H, N.

Treated similarly, the *l*-acid salt gave 1d·CH₃SO₃H (43%): mp 281–285 °C; [α]_D²⁵ -61.3° (c 1.0, EtOH). Anal. (C₂₆H₄₁NO₂·CH₃SO₃H) C, H, N.

(2α,6α,11S*)-(±)-1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11,α-tetramethyl-α-(3-methylbutyl)-2,6-methano-3-benz-

azocine-11-propanol (7a and 7b). To 200 mL (0.1 mol) of 0.5 M CH₃Li-Et₂O under N₂ was added with stirring and ice cooling a solution of 20.4 g (0.055 mol) of 6⁸ in 200 mL of C₆H₆. The reaction was allowed to come to room temperature over 1 h and then was quenched by shaking with 200 mL of saturated NH₄Cl. The organic layer was dried and evaporated to give 20.8 g of syrup. This was separated in two passes through 700 g of silica gel on a Waters Associates System 500 preparative high-pressure liquid chromatography apparatus using a 60:40 (v/v) hexane-EtOAc solvent mixture. There was obtained 5.3 g (25%) of isomer I and 10.6 g (50%) of isomer II, each a syrup pure by TLC. Treatment of these pure isomers with NaH-propanethiol, as described for 1c above, gave respectively 7a·CH₃SO₃H (71%) [mp 204–206 °C (from MeOH-Et₂O)]. Anal. (C₂₄H₃₉NO₂·CH₃SO₃H) C, H, N] and 7b·HCl (45%) [mp 238–241 °C (from EtOH-Et₂O)]. Anal. (C₂₄H₃₉NO₂·HCl) C, H, N].

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- For a given structure such as 1, the I and II isomers differ only in the configuration of the alcohol-bearing carbon atom relative to the chirality of the ring system.
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- The preparation of 6 and related ketones will form the subject of a separate publication.
- Previously the most potent *N*-methyl antagonist compound of which we are aware is a 6-methyl-6-azabicyclo[3.2.1]octane derivative, equipotent to nalorphine in inhibition of morphine-induced respiratory depression in rabbits: M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, S. Saito, K. Aoe, T. Date, S. Nurimoto, and G. Hayashi, *J. Med. Chem.*, **20**, 221 (1977).
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