

57324-57-9; 9, 103818-48-0; 10, 103818-49-1; 13, 103818-50-4; 14, 100551-53-9; 15, 103818-51-5; 16, 103818-52-6; 18, 103818-53-7; 19, 103818-54-8; 20, 103818-55-9; 22, 103818-56-0; 23, 103818-57-1; Z-Gly-L-Leu, 1421-69-8; Bz-L-Leu, 1466-83-7; Gly-L-Leu, 869-19-2; Beoc-Gly-L-Leu, 103818-58-2; ethanol, 64-17-5; pivaloyl chloride, 3282-30-2; sodium cyanamide, 19981-17-0; *n*-butyryl chloride, 141-75-3; palmitoyl chloride, 112-67-4; 1-adamantoyl chloride, 2094-72-6; stearoyl chloride, 112-76-5; cyanamide, 420-04-2; carbobenzoxy chloride, 501-53-1; *N*-carbobenzoxyglycine succinimido

ester, 2899-60-7; *N*-hydroxysuccinimide, 6066-82-6; *N*-phthaloylglycine *N*-hydroxysuccinimide ester, 3397-29-3; sodium cyanamide, 19981-17-0; hippuric acid, 495-69-2; 2-bromoethyl chloroformate, 4801-27-8; L-pyroglutamyl-L-leucine benzyl ester, 103818-59-3; L-pyroglutamic acid succinimido ester, 59850-85-0; L-leucine benzyl ester, 1738-69-8; L-pyroglutamyl-L-leucine, 21282-11-1; L-pyroglutamyl-L-phenylalanine, 21282-12-2; Z-L-pyroglutamic acid succinimido ester, 40291-26-7; phenylacetyl chloride, 103-80-0.

Preparation and Analgesic Activity of (-)-11 α -Substituted 1,2,3,4,5,6-Hexahydro-6 α ,7-(methyleneoxy)-2,6-methano-3-benzazocines¹

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Dihydrocodeinone oxime (1) under Beckmann rearrangement conditions gave a product (2) that facilitated the preparation of (-)-11 α -substituted 1,2,3,4,5,6-hexahydro-6 α ,7-(methyleneoxy)-2,6-methano-3-benzazocines, a hitherto little-examined series of morphine partial structures. Compounds 7a and 12 gave good levels of agonist antinociceptive activity. Masking of the 8-oxygen function, as in 6 and 8, dramatically reduced mouse hot-plate activity, as did its loss (9).

Derivatives of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (the benzomorphans) constitute a class of opiate analgesics with a broad spectrum of pharmacological actions.^{3,4} They include agents with μ or κ agonist and mixed agonist/antagonist properties. Numerous variants have been synthesized not only in an attempt to develop a potent analgesic with minimal undesired properties but also as a means of exploring the nature of the opiate receptor.

(-)-1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines are configurationally related to morphine and as such are responsible predominantly for the antinociceptive properties of the racemate. Some (-)-benzomorphans lack a physical dependence capacity (PDC) in rhesus monkeys, and in addition, they may precipitate or exacerbate the abstinence syndrome.⁵⁻⁷ In particular, the demonstration⁸ that (-)-3,6-dimethyl-8-hydroxy-11 α -propyl-2,6-methano-3-benzazocine and the corresponding 11 β -propyl derivative appeared to have minimal PDCs and the latter also exhibited antagonist properties led us to investigate stereospecific routes to related series.⁹

During the course of the study we synthesized (-)-1,2,3,4,5,6-hexahydro-8-hydroxy-6 α ,7-(methyleneoxy)-3-methyl-11 α -propyl-2,6-methano-3-benzazocine (7) and a series of related compounds that we report here. Previously Sargent and Ager¹⁰ had converted codeine via *N*-phenethyl-7,8-dihydroxydihydrodesoxycodine into a 6 α ,7-(methyleneoxy)-2,6-methano-3-benzazocine analogue of phenazocine that had twice the mouse hot-plate antinociceptive potency of morphine. In addition, the ozonolysis of thebaine¹¹ afforded a low yield of furanobenzomorphan, but no biological data were presented. More recently¹² an oxide-bridged 5-(*m*-hydroxyphenyl)morphinan was reported to lack *in vivo* opiate activity.

The main structural difference between 1,2,3,4,5,6-hexahydro-6 α ,7-(methyleneoxy)-2,6-methano-3-benzazocines and 4,5-epoxymorphinans (morphine and related compounds) is the absence of a C ring in the former. A vestigial C ring together with an intact furan moiety has

been shown in a furanobenzomorphan analogue of phenazocine¹⁰ to maintain good analgesic properties. Reden et al.¹³ have indicated that in morphine series, although a phenolic hydroxyl group aids receptor binding, it is not a prerequisite. Masking of the 3-OH as in codeine or heroin, however, does reduce receptor affinity considerably.

Morphinan-6-ones do not require an oxygen function in the aromatic ring to elicit analgesic responses, but oxygen at C-3 or C-4 enhanced both receptor binding and antinociceptive activity.¹⁴ *N*-Methyl-4-methoxymorphinan-6-one, however, is a more potent analgesic than its phenolic counterpart (cf. levorphanol and its methyl ether¹⁵).

The investigation of furanobenzomorphans such as those described here may shed further light on the role of both the C ring and aromatic oxygenation in opiate antinociceptive responses.

- (1) The correct nomenclature for this ring system is 3*H*-2a,6-methano-2*H*-furo[4,3,2-*f*,*g*][3]benzazocine, but for purposes of comparison with other benzomorphan studies, the 2,6-methano-3-benzazocine name and numbering have been adopted in this paper.
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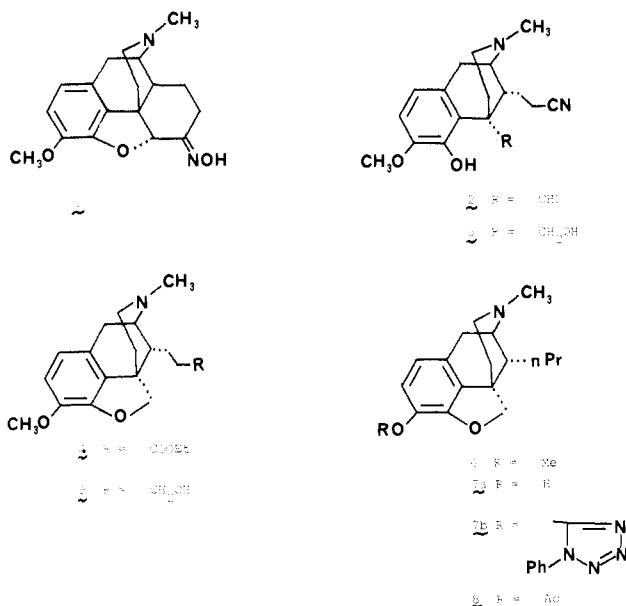
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Table I. Analgesic Activities of (-)-11 α -Substituted 1,2,3,4,5,6-Hexahydro-6 α ,7-(methyleneoxy)-2,6-methano-3-benzazocines

compound ^a	MHP: ^b ED ₅₀ , mg/kg	MTF: ^c ED ₅₀ mg/kg	PPO: ^d ED ₅₀ , mg/kg	MTF vs. morphine: ^e AD ₅₀ , mg/kg
4	IA ^f (50)	IA ^f (30)	g	IA ^f (30)
5	IA ^f (20)	IA ^f (10)	IA ^f (30)	g
6	IA ^f (20)	8.1 (2.3-28.2)	0.8 (0.3-2.8)	IA ^f (30)
7a	1.8 (1.3-2.6)	0.4 (0.2-0.8)	0.1 (0.06-0.2)	IA ^f (30)
8	g	0.7 (0.5-1.0)	0.2 (0.1-0.3)	IA ^f (30)
9	IA ^f (20)	20.7 (14.3-30.1)	2.9 (1.3-6.3)	IA ^f (30)
11	IA ^f (20)	IA ^f (30)	g	0.4 (0.1-1.0)
12	1.7 (1.4-2.1)	1.4 (0.9-2.4)	0.2 (0.1-0.4)	IA ^f (30)
morphine sulfate	1.2	5.8 (5.7-5.9)	0.23 (0.2-0.25)	
codeine phosphate	9.3 (6.7-12.8)	14.5 (8.1-20.0)	1.1 (0.5-2.5)	IA ^f (30)
naloxone hydrochloride	IA	IA	IA	0.035 (0.010-0.093)

^aTested as hydrochlorides (sc) in water. ^bMouse hot-plate test²⁰ employing Cesarian-derived general-purpose mice at N.I.H., Bethesda. ^cMouse tail-flick antinociceptive assay.^{21,22} ^dPhenylquinone antinociceptive assay.^{21,22} ^eMouse tail-flick analgesic antagonist assay vs. morphine.^{21,22} ^fInactive at the dose level (milligram/kilogram) indicated. ^gLow level of activity exhibited, which did not follow a dose-response relationship.

Chemistry. Schöpf,¹⁶ during work on the structure of morphine, subjected dihydrocodeinone oxime (1) to Beckmann rearrangement conditions and isolated (-)-11 α -(2-cyanoethyl)-6 α -formyl-1,2,3,4,5,6-hexahydro-7-hydroxy-8-methoxy-3-methyl-2,6-methano-3-benzazocine (2) as the major product. Such substituents in the 6- and 11-positions offered the opportunity, through appropriate transformations, of preparing optically pure (-)-6,11-dialkylbenzomorphans in reasonable yields.⁹

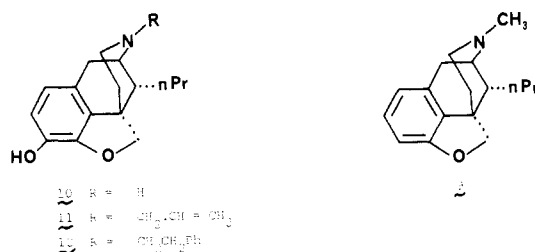


Reduction of the aldehyde group of 2 with NaBH₄ proceeded in high yield (88%) to the 6-hydroxymethyl derivative, 3. Alcoholysis of the nitrile function of 3 with absolute EtOH and concentrated H₂SO₄ not only effected the transformation of nitrile to ester but in addition protonation of the hydroxymethyl group occurred and cyclization of the furan ring resulted to give the (-)-6 α ,7-(methyleneoxy)-2,6-methano-3-benzazocine (4), the key intermediate for this series. The ¹H NMR of 4 showed the furan ring methylene proton signal as an AB quartet centered at δ 4.41 (J = 8 Hz).

The ester 4 was readily reduced with LAH in THF to the hydroxypropyl compound 5, and this was converted to 6 by a modification of the previously published method.¹⁷ Methyltriphenoxyphosphonium iodide in dry

THF converted 5 to the corresponding iodide, which, without isolation, was treated with sodium cyanoborohydride to give 6. BBr₃ in chloroform¹⁸ O-demethylated 7 to (-)-1,2,3,4,5,6-hexahydro-8-hydroxy-6 α ,7-(methyleneoxy)-3-methyl-11 α -propyl-2,6-methano-3-benzazocine (7a) in 83% yield. Acetylation of 7a in the presence of triethylamine gave 8.

Conversion of 7a to (-)-1,2,3,4,5,6-hexahydro-6 α ,7-(methyleneoxy)-3-methyl-11 α -propyl-2,6-methano-3-benzazocine (9) was effected in high yield by its conversion to the 8-phenyltetrazolo ether (7b) followed by hydrogenation at elevated pressure and temperature over Pd/C.



In benzomorphan series, variation of the substituent on nitrogen often causes profound changes in biological response. Conversion of 7a to the (-)-norbenzomorphan (10) was effected by 2,2,2-trichloroethyl chloroformate and anhydrous K₂CO₃ in toluene¹⁹ followed by Zn/HOAc reduction. The *N*-allyl and *N*-phenylethyl derivatives (11 and 12, respectively) were prepared by direct alkylation with allyl bromide and phenylethyl bromide. In each case some O-alkylation occurred, but in the case of the phenylethyl, yields were improved by O-dealkylation with BBr₃.

Biological Results and Discussion

(-)-2,6-Methano-3-benzazocines bearing an 11 α -*n*-propyl group have been reported to exhibit twice the mouse hot-plate antinociceptive activity of the corresponding racemate,^{6,8} and a furanbenzomorphan analogue of phenazocine¹⁰ had a similar enhanced activity relative to morphine. Thus, analgesic responses of a similar order were anticipated in 11 α -propyl derivatives in the current series. 1,2,3,4,5,6-Hexahydro-6 α ,7-(methyleneoxy)-2,6-

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Table II. Responses in the Mouse Vas Deferens Assay^a

compound ^b	EC ₅₀	EC ₅₀ (vs. naltrexone) ^c	antagonism (vs. morphine) ^d
6	IA ^e (10 ⁻⁶ M) ^f		IA ^e (10 ⁻⁶ M)
7a	3.50 × 10 ⁻⁷ M ± 0.99 (n = 3) (max response 77.1 ± 8.0%)	3.32 × 10 ⁻⁶ M ± 2.02 (n = 3) (max response 43.4 ± 8.1%)	IA ^e (10 ⁻⁶ M)
8	8.52 × 10 ⁻⁸ M ± 0.23 (n = 3) (max response 80.6 ± 4.0%)	4.22 × 10 ⁻⁷ M ± 1.83 (n = 3) (max response 61.6 ± 2.8%)	IA ^e (10 ⁻⁶ M)

^aReferences 23 and 24. Response of electrically stimulated mouse vas deferens preparations to concentrations of compound ranging from 10⁻⁸ to 3 × 10⁻⁵ M. ^bTested as hydrochlorides in water. ^cResponse in the presence of naltrexone (100 nM). ^dInhibition of a maximally effective concentration of morphine (10 μM). ^eInactive at the doses level (M) indicated. ^fAt 10⁻⁵ M, 6 increased the twitch magnitude.

methano-3-benzazocines possess a benzomorphan nucleus with an intact dihydrofuran moiety, although molecular models indicate greater ring flexibility than that which occurs in 4,5-epoxymorphinans with a constraining C ring. The (-)-3-hydroxy-11α-propyl derivative **7a** afforded a morphine-like level of mouse hot-plate antinociceptive activity (ED₅₀ = 1.8 mg/kg) and correspondingly high mouse tail-flick (ED₅₀ = 0.4 mg/kg) and paraphenylquinone (ED₅₀ = 0.2 mg/kg) analgesic levels (Table I).

Masking of the phenolic hydroxyl group of **7a**, as in the corresponding methyl ether (**6**) and the acetoxy compound (**8**), gave mouse tail-flick and paraphenylquinone antinociceptive levels of about one-half those of **7a**. Removal of the oxygen function from C-8, as in **9**, once again eliminated hot-plate activity and substantially reduced the other analgesic responses.

In vitro evaluation of **6**, **7a**, and **8** on the isolated and electrically stimulated mouse vas deferens^{23,24} (Table II) confirmed the morphine-like agonist responses of **7a**, which were reversed by naltrexone, suggesting that the activity is predominantly at μ receptors. A similar observation was made for the 3-acetoxy derivative (**8**), whereas **6** was devoid of opiate agonist actions. Compounds **6**, **7a**, and **8** failed to antagonize the actions of morphine in the mouse vas deferens assay.

Rat membrane binding studies²³ supported these findings, with **7a** and **8** each exhibiting good levels of receptor binding (EC₅₀ = 39.0 and 133 nM, respectively) when measured by the displacement of [³H]etorphine. In contrast **6** displaced [³H]etorphine only at very high concentrations.

The presence of a 3-OH function is clearly important for receptor binding and antinociceptive activity in this series of 6α,7-(methyleneoxy)-2,6-methano-3-benzazocines. This observation contrasts with those for 3,6-dideoxydihydromorphine¹³ and *N*-methyl-4-methoxymorphinan-6-one,¹⁵ both of which have good receptor binding affinities. In addition, whereas codeine has about 1/7 the potency of morphine in antinociceptive tests, in these furano-benzomorphans the agonist potency after masking the 3-OH function is substantially less (1/20). Loss of the 3-oxygen function further reduced analgesic activity. Thus, as in morphine and benzomorphan series, these furano-benzomorphans require a 3-OH group for optimal analgesic activity in rodent tests. Because a free 3-OH is so important for both binding and analgesic responses in furano-benzomorphans, and this appears not to be the case for either morphinan-6-ones or 4,5-epoxymorphinans, it is possible that an intact C-ring assists in affording an improved receptor fit. Alternatively, benzomorphans may act at selective, non-μ binding sites.^{25,26}

Replacement of *N*-Me by *N*-allyl as in **11** eliminated analgesic responses and, as expected, afforded an opiate antagonist (AD₅₀ = 0.4 mg/kg) about 1/10 as active as naloxone.

The corresponding *N*-phenethyl analogue (**12**), which might have been expected to give an agonist activity at least equivalent to that of **7a**, exhibited only modest responses in the mouse tail-flick and paraphenylquinone tests but gave good mouse hot-plate activity (ED₅₀ = 1.7 mg/kg), comparable with a similar phenazocine analogue described previously.¹⁰

The 11α-ester (**4**) and 11α-alcohol (**5**) were without agonist or antagonist actions.

Experimental Section

The infrared spectra (liquids as films and solids as Nujol mulls) were recorded with a Unicam SP1025 spectrometer, and melting points (uncorrected) were taken on a Gallenkamp melting point apparatus.

Proton noise and off-resonance-decoupled ¹³C NMR spectra were recorded with a JEOL FX90Q spectrometer operating at 22.5 MHz and ¹H NMR spectra on a JEOL JNM-PMX 60SI and a JEOL PS100 spectrometer operating at 60 and 100 MHz, respectively. Samples were prepared in 5-mm-o.d. tubes as approximately 10% solutions in CDCl₃ or (CD₃)₂SO with Me₄Si as reference, and deuterium of the solvents provided the lock signal for ¹³C NMR. Mass spectra were measured on a VG 7070E mass spectrometer operating at 70 eV (EI). Optical rotations were measured on an AA-10 (Optical Activity Ltd.) polarimeter.

C, H, N values are within ±0.4% of the theory unless otherwise indicated.

Dihydrocodeinone Oxime (1). A stirred mixture of dihydrocodeinone (117.6 g, 0.39 mol), hydroxylamine hydrochloride (70 g, 1 mol), and sodium acetate (41 g, 0.5 mol) in water (2 L) was heated under reflux for 2 h, cooled, and made alkaline by addition of 10% aqueous ammonia. The precipitated oxime was collected by filtration, washed with water until washings were neutral, finally washed with ethyl acetate (400 mL), and dried in vacuo at 110 °C for 4 h to give 121.8 g (98.6%) of **1**: mp 262–264 °C (lit.¹² mp 264–265 °C); EIMS, *m/z* 314 (M⁺).

(-)-11α-(2-Cyanoethyl)-6α-formyl-7-hydroxy-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (2). Dihydrocodeinone oxime (60 g, 0.19 mol) was added in small portions to freshly distilled thionyl chloride (210 mL) maintained at between -5 and -10 °C, and the mixture was stirred at that temperature for 2 h. The thionyl chloride was then removed in vacuo at room temperature. Iced water (150 mL) was added slowly to the residue over 10 min. The mixture was stirred vigorously for 30 min to induce precipitation and was kept overnight at 2 °C. The separated solid was collected, washed with cold water (20 mL), taken up in water (100 mL), and heated strongly until SO₂ and HCl were no longer evolved. The filtrate was also heated until SO₂ and HCl were no longer evolved. The solutions were basified separately with 10% aqueous ammonia and extracted with CH₂Cl₂ (3 × 200 mL), the extracts were dried (MgSO₄), and the solvent was removed under reduced pressure to give crude **2**, 19.6 and 22.1 g, respectively. Repeated crystallizations from methanol yielded **2** (18.2 g, 30.2%): mp 194–195 °C (lit.⁸ mp 190–194 °C); [α]_D²⁰ -46° (c 1, 95% EtOH); ¹H NMR (base) δ 2.35

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(s, 3 H, NCH₃), 3.83 (s, 3 H, OCH₃), 9.64 (s, 1 H, CHO); ¹³C NMR (base) δ 198.66 (CHO). Anal. (C₁₈H₂₂O₃N₂) C, H, N.

(-)-11α-(2-Cyanoethyl)-7-hydroxy-6α-(hydroxymethyl)-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (3). To a solution of sodium borohydride (8 g) in ethanol (800 mL) was added finely powdered 2 (29.5 g, 0.094 mol) in small portions. After being stirred at room temperature for 1 h, the solution was filtered and acidified with 2 N HCl and the solvent removed in vacuo. The white solid obtained was dissolved in water (1 L), and the resultant solution was washed with ether (3 × 300 mL), saturated with Na₂CO₃, and extracted with CHCl₃ (5 × 300 mL). The combined extracts were dried (MgSO₄) and evaporated in vacuo to give 3 (26.2 g, 88%) as a white solid: mp 79–80 °C; [α]_D²⁰ -56° (c 1, 95% EtOH); ¹H NMR (base) δ 2.42 (s, 3 H, NCH₃), 3.82 (s, 3 H, OCH₃); EIMS, *m/z* 316 (M⁺). Anal. Calcd for C₁₈H₂₄N₂O₃: 316.1787. Found: 316.1786.

(-)-11α-[2-(Ethoxycarbonyl)ethyl]-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (4). To a solution of 3 (13.5 g, 0.043 mol) in dry ethanol (500 mL) was added slowly 200 mL of concentrated H₂SO₄. The solution was heated under reflux for 4 h, cooled, basified with aqueous Na₂CO₃ solution, and extracted with CHCl₃ (5 × 300 mL). The combined extracts were dried (MgSO₄), and evaporation in vacuo gave crude 4 as a viscous yellow oil (12.85 g, 87%). Conversion to the oxalate and crystallization from acetone-ethanol gave fine needles, mp 167–170 °C. Anal. (C₂₂H₂₉NO₃) C, H, N. The base gave [α]_D²⁰ -51° (c 1, 95% EtOH); Ir (CHCl₃) 1735 cm⁻¹ (C=O); ¹H NMR (CDCl₃) δ 2.4 (s, 3 H, NCH₃), 3.82 (s, 3 H, OCH₃), 4.25, 4.57 (AB q, 2 H, *J* = 8 Hz, CH₂O); ¹³C NMR (CDCl₃) δ 172.93 (C=O); EIMS, *m/z* 345 (M⁺). The hydrochloride crystallized from EtOAc-Et₂O as colorless needles, mp 102–103 °C.

(-)-11α-(Hydroxypropyl)-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (5). To a suspension of LAH (7 g) in dry THF (200 mL) was added slowly a solution of 4 (13 g, 0.038 mol) in dry THF (500 mL). After the mixture had been stirred for 1 h at room temperature, a saturated solution of Na₂CO₃ (12 mL) was added to it dropwise, followed by CHCl₃ (1 L). The mixture was dried (MgSO₄) and filtered. Evaporation of the solvent in vacuo afforded 5 (11.2 g, 98%) as a viscous yellow oil. The hydrochloride crystallized from EtOH-Et₂O as white needles, mp 190–192 °C. Anal. (C₁₈H₂₆NO₃Cl·1/2H₂O) C, H, N. The base gave [α]_D²⁰ -43° (c 1, 95% EtOH).

(-)-8-Methoxy-3-methyl-11α-propyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (6). Methyltriphenoxyphosphonium iodide (20 g, 0.044 mol) was added under dry N₂ to a solution of 5 (4.8 g, 0.016 mol) in dry THF (150 mL). After the addition of sodium cyanoborohydride (5 g), the mixture was heated at 50–60 °C for 3 h, cooled, basified with aqueous Na₂CO₃, and mixed with Et₂O (200 mL). The aqueous layer was extracted further with CHCl₃ (2 × 300 mL), the combined organic extracts were dried (MgSO₄), and the solvent was removed in vacuo. The crude residue was dissolved in 6 M HCl (300 mL), washed with Et₂O (5 × 200 mL), basified with Na₂CO₃, and extracted with Et₂O (5 × 200 mL). The ethereal extracts were dried (MgSO₄), and evaporation of the solvent gave crude 6 (3.3 g, 72%) as a yellow viscous oil. Distillation (130 °C (0.01 mmHg)) gave 1.98 g, (43%) of 6: [α]_D²⁰ -51° (c 0.96, 95% EtOH); EIMS, *m/z* 287 (M⁺). The hydrochloride crystallized from EtOAc-EtOH as colorless needles, mp 222–224 °C. Anal. (C₁₈H₂₆NO₂Cl) C, H, N.

(-)-8-Hydroxy-3-methyl-11α-propyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (7a). A solution of 6 (3.8 g, 0.013 mol) in dry CHCl₃ (150 mL) was added during 5 min to a well-stirred solution of BBr₃ (34.45 g, 0.138 mol) in dry CHCl₃ (150 mL). After being stirred at room temperature for 1 h, the mixture was poured onto a stirred mixture of ice (200 g) and concentrated NH₄OH (50 mL). The layers were separated, and the aqueous layer was extracted further with CHCl₃ (2 × 200 mL). The combined organic solutions were dried (MgSO₄), and the solvent was evaporated to give a light brown solid, 7a (3.0 g, 83%). The material crystallized from acetone as prisms (2.55 g, 70%): mp 180–181 °C; [α]_D²⁰ -59° (c 1, 95% EtOH); EIMS, *m/z* 273 (M⁺). The hydrochloride crystallized from EtOAc-EtOH, mp 172–174 °C. Anal. (C₁₇H₂₄NO₂Cl) C, H, N.

(-)-8-Acetoxy-3-methyl-11α-propyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (8). To a solution of 7a (0.8 g, 0.0029 mol) in dry THF (40 mL) was added triethylamine (4 mL) followed by the dropwise addition of acetyl chloride (4 mL). The mixture was stirred at room temperature for 30 min and filtered, and the solvent was removed in vacuo. The residue was dissolved in 1 M HCl (50 mL) and the solution washed with Et₂O (3 × 50 mL), basified with NaHCO₃, and extracted with Et₂O (3 × 50 mL). The combined ethereal extracts were dried (MgSO₄) and evaporated to yield a light yellow oil, 8 (0.6 g, 65%). The hydrochloride crystallized from EtOAc-Et₂O as needles, mp 146–148 °C. The base had [α]_D²⁰ -52° (c 1, 95% EtOH); EIMS, *m/z* 315 (M⁺); ¹H NMR (base) δ 2.22 (s, 3 H, COCH₃), 2.41 (s, 3 H, NCH₃); ¹³C NMR (base) δ 168.59 (C=O). Anal. Calcd for C₁₉H₂₆NO₃Cl·1.5H₂O: C, 60.24; H, 7.72; N, 3.69. Found: C, 59.67; H, 7.53; N, 3.82.

(-)-3-Allyl-8-hydroxy-11α-propyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (11). A mixture of 7a (1.3 g, 0.0048 mol), freshly distilled 2,2,2-trichloroethyl chloroformate (7.4 mL, 0.023 mol), anhydrous K₂CO₃ (6 g), and dry toluene (130 mL) was heated under reflux for 65 h. The cooled mixture was filtered, the solvent removed under reduced pressure, and excess 2,2,2-trichloroethyl chloroformate removed by in vacuo distillation (100 °C (0.5 mmHg)). The residue was dissolved in 90% AcOH (87 mL), Zn dust (4.3 g) was added, and the mixture was stirred at room temperature for 16 h. The mixture was filtered, basified with Na₂CO₃, and extracted with CHCl₃ to give, after solvent evaporation, 10 (1 g, 81%). Compound 10 (1 g, 0.0039 mol) was alkylated by heating with allyl bromide (3.22 g, 0.0266 mol) and anhydrous K₂CO₃ (2 g) in CHCl₃ (75 mL) at 60 °C for 3 h. The mixture was cooled and filtered and the solvent evaporated to give a yellow oil (1.1 g). This was dissolved in 2 M NaOH (100 mL) and washed with Et₂O (3 × 100 mL). The combined ether layers were extracted with 50 mL of NaOH. The combined aqueous solutions were acidified with dilute HCl, washed with Et₂O (3 × 100 mL), basified with NH₄OH, and extracted with Et₂O (5 × 100 mL). The combined ether extracts were dried (MgSO₄), and the solvent was removed to give 0.2 g of 11 (14%) as a white solid: mp 135–137 °C; [α]_D²⁰ -90° (c 1, 95% EtOH). The hydrochloride crystallized from AcMe-EtOH-Et₂O and had mp 245–246 °C. Anal. (C₁₉H₂₆NO₂Cl·1/2H₂O) C, H, N.

(-)-8-Hydroxy-3-phenethyl-11α-propyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (12). A mixture of 10 (0.6 g, 0.0023 mol), dry ethanol (15 mL), phenylethyl bromide (0.94 g, 0.0051 mol), and anhydrous K₂CO₃ (1 g) was refluxed for 8 days. The cooled mixture was filtered and the solvent evaporated to give a residue (0.95 g). This was dissolved in 6 M HCl (100 mL) and washed with Et₂O (3 × 100 mL). The aqueous layer was basified with Na₂CO₃ and extracted with ether (5 × 100 mL). The combined ether extracts were dried (MgSO₄) and evaporated to give 0.7 g of mixed N- and O-dialkylated product. This mixture was dissolved in dry CHCl₃ (100 mL) and added to a well-stirred solution of BBr₃ (12.5 g, 0.05 mol) in dry CHCl₃ (100 mL). The mixture was stirred for 5 h at room temperature and poured onto a stirred mixture of ice and concentrated NH₄OH (20 mL). The layers were separated, and the aqueous phase was further extracted with CHCl₃ (3 × 100 mL). The combined organic layers were dried (MgSO₄) and the solvent evaporated to give a light brown semisolid (0.6 g). This was purified by column chromatography on silica gel (8 g) with CHCl₃ as eluent. Compound 12 was isolated as an almost colorless solid (0.2 g, 24%): mp 87–90 °C; [α]_D²⁰ -68° (c 1, 95% EtOH). The hydrochloride crystallized from acetone as needles, mp 270–275 °C dec. Anal. (C₂₄H₃₀NO₂Cl) C, H, N.

(-)-3-Methyl-11α-propyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (9). A mixture of 7a (3.6 g, 0.0132 mol), 5-chloro-1-phenyl-1*H*-tetrazole (2.71 g, 0.015 mol), and anhydrous K₂CO₃ (3.6 g) was heated under reflux in dry acetonitrile (150 mL) for 2 days. The reaction mixture was cooled and filtered and the solvent evaporated under reduced pressure to give crude 7b as a viscous yellow oil. Without further purification, crude 7b was hydrogenated in a Parr apparatus at 200 psi and 60 °C for 3 days over 5% Pd/C (5 g) in methanol.

Removal of the catalyst by filtration and evaporation of solvent under reduced pressure gave a residue, which was partitioned

between EtOAc (200 mL) and 2 N NaOH (100 mL). The combined organic layers were extracted with 6 N HCl (3 × 100 mL). The combined acid extracts were washed with Et₂O (2 × 100 mL), basified with Na₂CO₃, and extracted with Et₂O (2 × 200 mL). The combined ethereal layers were dried (MgSO₄), and the solvent was evaporated under reduced pressure to give **9** (3 g, 88%) as a yellow solid. The **9** oxalate crystallized from EtOAc-EtOH and had mp 139-140 °C. Anal. (C₁₉H₂₅NO₅) C, H, N.

The base had a $[\alpha]_D^{20}$ value of -100° (c 0.5, 95% EtOH). The hydrochloride crystallized from EtOAc-EtOH and had mp 205-207 °C.

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Tissue Distribution Properties of Technetium-99m-Diamide-Dimercaptide Complexes and Potential Use as Renal Radiopharmaceuticals

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A series of new ligands and the corresponding technetium-99m chelates based on diamide dimercaptide donor groups were synthesized as derivatives of technetium-99m 1,2-bis(2-thioacetamido)ethane, a complex shown to be excreted by renal tubular secretion. Chelation with ^{99m}Tc resulted in single radiochemical products or the expected numbers of stereoisomers. They were purified by high-performance liquid chromatography (HPLC) and evaluated in mice as potential renal tubular function agents. The in vivo properties were sensitive to the presence of functional groups, the positional isomerism of the carboxylate group functionality, and the chelate ring stereochemistry of the ligand. The presence of methyl groups slowed renal transit and decreased renal specificity. Cyclohexyl rings fused to the ethylene bridge of the center chelate ring decreased renal excretion while aromatic rings essentially abolished renal excretion. Slow hepatobiliary clearance was observed as an alternate mode of excretion. Polar groups, such as hydroxyl, carboxylate, and carboxamide, increased renal excretion rates and specificity in a stereochemically dependent manner. ^{99m}Tc chelates of 1,3-bis(2-thioacetamido)-2-hydroxypropane, 3,4-bis(2-thioacetamido)butanoate and 1,8-dimercapto-2,7-dioxo-3,6-diazanonanoate were identified as promising new renal radiopharmaceuticals.

Technetium-99m diethylenetriaminepentaacetate (DTPA) and *o*-iodohippurate (OIH) are both currently clinically used for the evaluation of renal function.¹ Renal perfusion is evaluated by rapid serial imaging during the first circulation after bolus injection of about 15 mCi of ^{99m}Tc-DTPA. Normally, OIH cannot be used for the same purpose since the ¹³¹I limits the amount of radioactivity that can be injected, because of increased radiation dose, to about 300 μCi. Renal clearance can be conveniently evaluated with either ^{99m}Tc DTPA or OIH. However, ^{99m}Tc DTPA is excreted solely by glomerular filtration and thus has a maximum renal extraction efficiency of about 20% in humans. This low extraction efficiency results in a low kidney-to-background ratio and poor-quality images in patients with impaired renal function. In contrast, OIH is secreted by the tubular cells in addition to some filtration and thus has a higher extraction efficiency of about 75% as measured in dogs.^{2,3} The extraction efficiency of OIH increases the kidney-to-background image ratio and thus increases the sensitivity of OIH for detection and evaluation of renal disease in patients with poor kidney function. Since the excretion of OIH involves active transport by the renal tubular cells, the uptake and excretion reflect levels of cellular function.⁴

Because of the reasons outlined above, there is a need to provide radiopharmaceuticals for the evaluation of renal function that do not contain iodine-131 yet exhibit a high

specificity for renal tubular excretion equal to or greater than levels obtained with iodine-131-labeled *o*-iodohippurate. In 1979 Davison and co-workers⁵ introduced a new class of tetradentate chelating agents for technetium based on amide and mercaptide donor groups. In a later report, the authors presented structural data for the characterized compounds.⁶ The initial report described the rapid renal excretion in animals of technetium-99m 1,2-bis(2-thioacetamido)ethane (1). This was independently corroborated by animal^{7,8} and clinical studies.¹ With an interest in developing an improved ^{99m}Tc replacement for ¹³¹I OIH, we reported⁹ the synthesis of technetium-99m

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