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 (−)-11α-Substituted 1,2,3,4,5,6-Hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocines[1]

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*Received August 27, 1985*

Dihydrocodeinone oxime (**1**) under Beckmann rearrangement conditions gave a product (**2**) that facilitated the preparation of (−)-11α-substituted 1,2,3,4,5,6-hexahydro-6α,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 demonstration[8] that (−)-3,6-dimethyl-8-hydroxy-11α-propyl-2,6-methano-3-benzazocine and the corresponding 11β-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-6α,7-(methyleneoxy)-3-methyl-11α-propyl-2,6-methano-3-benzazocine (**7**) and a series of related compounds that we report here. Previously Sargent and Ager[10] had converted codeine via *N*-phenethyl-7,8-dihydroxydihydrodesoxycodeine into a 6α,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 thebaine[11] afforded a low yield of furanobenzomorphan, but no biological data were presented. More recently[12] an oxide-bridged 5-(*m*-hydroxyphenyl)-morphan was reported to lack in vivo opiate activity.

The main structural difference between 1,2,3,4,5,6-hexahydro-6α,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 phenazocine[10] 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 ether[15]).

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.

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(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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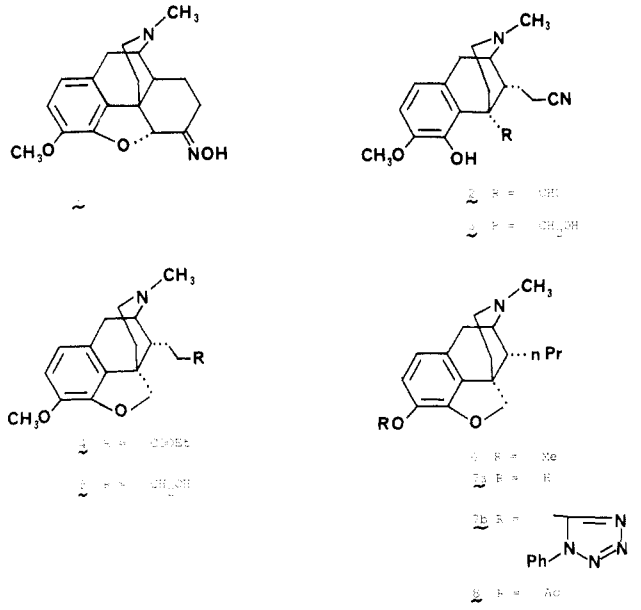
Table I. Analgesic Activities of (−)-11α-Substituted 1,2,3,4,5,6-Hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocines

| 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) |

[a] Tested as hydrochlorides (sc) in water. [b] Mouse hot-plate test[20] employing Cesarian-derived general-purpose mice at N.I.H., Bethesda. [c] Mouse tail-flick antinociceptive assay.[21,22] [d] Phenylquinone antinociceptive assay.[21,22] [e] Mouse tail-flick analgesic antagonist assay vs. morphine.[21,22] [f] Inactive at the dose level (milligram/kilogram) indicated. [g] Low level of activity exhibited, which did not follow a dose–response relationship.

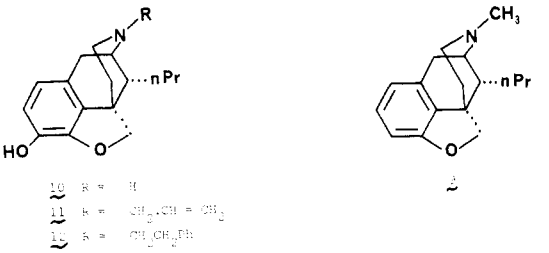
**Chemistry.** Schöpf,[16] during work on the structure of morphine, subjected dihydrocodeinone oxime (**1**) to Beckmann rearrangment conditions and isolated (−)-11α-(2-cyanoethyl)-6α-formyl-1,2,3,4,5,6-hexahydro-7-hydroxy-8-methoxy-3-methyl-2,6-methano-3-benzazocine (**2**) as the major product. Such 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 $NaBH_4$ proceeded in high yield (88%) to the 6-hydroxymethyl derivative, **3**. Alcoholysis of the nitrile function of **3** with absolute EtOH and concentrated $H_2SO_4$ 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 (−)-6α,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**. $BBr_3$ in chloroform[18] O-demethylated **7** to (−)-1,2,3,4,5,6-hexahydro-8-hydroxy-6α,7-(methyleneoxy)-3-methyl-11α-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-6α,7-(methyleneoxy)-3-methyl-11α-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 $K_2CO_3$ in toluene[19] 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 phenethylation, yields were improved by O-dealkylation with $BBr_3$.

## Biological Results and Discussion

(−)-2,6-Methano-3-benzazocines bearing an 11α-*n*-propyl group have been reported to exhibit twice the mouse hot-plate antinociceptive activity of the corresponding racemate,[6,8] and a furanobenzomorphan analogue of phenazocine[10] had a similar enhanced activity relative to morphine. Thus, analgesic responses of a similar order were anticipated in 11α-propyl derivatives in the current series. 1,2,3,4,5,6-Hexahydro-6α,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] ($10^{-5}$ M)[f] | | IA[e] ($10^{-6}$ M) |
| 7a | $3.50 \times 10^{-7}$ M ± 0.99 ($n$ = 3) (max response 77.1 ± 8.0%) | $3.32 \times 10^{-6}$ M ± 2.02 ($n$ = 3) (max response 43.4 ± 8.1%) | IA[e] ($10^{-6}$ M) |
| 8 | $8.52 \times 10^{-8}$ M ± 0.23 ($n$ = 3) (max response 80.6 ± 4.0%) | $4.22 \times 10^{-7}$ M ± 1.83 ($n$ = 3) (max response 61.6 ± 2.8%) | IA[e] ($10^{-6}$ M) |

[a] References 23 and 24. Response of electrically stimulated mouse vas deferens preparations to concentrations of compound ranging from $10^{-8}$ to $3 \times 10^{-5}$ M. [b] Tested as hydrochlorides in water. [c] Response in the presence of naltrexone (100 nM). [d] Inhibition of a maximally effective concentration of morphine (10 μM). [e] Inactive at the does level (M) indicated. [f] At $10^{-5}$ 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 ($ED_{50}$ = 1.8 mg/kg) and correspondingly high mouse tail-flick ($ED_{50}$ = 0.4 mg/kg) and paraphenylquinone ($ED_{50}$ = 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 studies[23] supported these findings, with **7a** and **8** each exhibiting good levels of receptor binding ($EC_{50}$ = 39.0 and 133 nM, respectively) when measured by the displacement of [$^3$H]etorphine. In contrast **6** displaced [$^3$H]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-dideoxydihydromorphine[13] 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 furanobenzomorphans 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 furanobenzomorphans 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 furanobenzomorphans, 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 ($AD_{50}$ = 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 ($ED_{50}$ = 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 $^{13}$C NMR spectra were recorded with a JEOL FX90Q spectrometer operating at 22.5 MHz and $^1$H 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 $CDCl_3$ or $(CD_3)_2SO$ with $Me_4Si$ as reference, and deuterium of the solvents provided the lock signal for $^{13}$C 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 $SO_2$ and HCl were no longer evolved. The filtrate was also heated until $SO_2$ and HCl were no longer evolved. The solutions were basified separately with 10% aqueous ammonia and extracted with $CH_2Cl_2$ (3 × 200 mL), the extracts were dried ($MgSO_4$), 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); $[\alpha]^{20}_D$ −46° (*c* 1, 95% EtOH); $^1$H NMR (base) δ 2.35

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(s, 3 H, $NCH_3$), 3.83 (s, 3 H, $OCH_3$), 9.64 (s, 1 H, CHO); $^{13}C$ NMR (base) $\delta$ 198.66 (CHO). Anal. ($C_{18}H_{22}O_3N_2$) 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 $Na_2CO_3$, and extracted with $CHCl_3$ (5 × 300 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give **3** (26.2 g, 88%) as a white solid: mp 79–80 °C; $[\alpha]^{20}_D$ −56° (*c* 1, 95% EtOH); $^1H$ NMR (base) $\delta$ 2.42 (s, 3 H, $NCH_3$), 3.82 (s, 3 H, $OCH_3$); EIMS, *m/z* 316 ($M^+$). Anal. Calcd for $C_{18}H_{24}N_2O_3$: 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 $H_2SO_4$. The solution was heated under reflux for 4 h, cooled, basified with aqueous $Na_2CO_3$ solution, and extracted with $CHCl_3$ (5 × 300 mL). The combined extracts were dried ($MgSO_4$), 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. ($C_{22}H_{29}NO_8$) C, H, N. The base gave $[\alpha]^{20}_D$ −51° (*c* 1, 95% EtOH); Ir ($CHCl_3$) 1735 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) $\delta$ 2.4 (s, 3 H, $NCH_3$), 3.82 (s, 3 H, $OCH_3$), 4.25, 4.57 (AB q, 2 H, $J$ = 8 Hz, $CH_2O$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 172.93 (C=O); EIMS, *m/z* 345 ($M^+$). The hydrochloride crystallized from EtOAc–$Et_2O$ 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 $Na_2CO_3$ (12 mL) was added to it dropwise, followed by $CHCl_3$ (1 L). The mixture was dried ($MgSO_4$) and filtered. Evaporation of the solvent in vacuo afforded **5** (11.2 g, 98%) as a viscous yellow oil. The hydrochloride crystallized from EtOH–$Et_2O$ as white needles, mp 190–192 °C. Anal. ($C_{18}H_{26}NO_3Cl\cdot{}^1/_2H_2O$) C, H, N. The base gave $[\alpha]^{20}_D$ −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 $N_2$ 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 $Na_2CO_3$, and mixed with $Et_2O$ (200 mL). The aqueous layer was extracted further with $CHCl_3$ (2 × 300 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude residue was dissolved in 6 M HCl (300 mL), washed with $Et_2O$ (5 × 200 Ml), basified with $Na_2CO_3$, and extracted with $Et_2O$ (5 × 200 mL). The ethereal extracts were dried ($MgSO_4$), 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**: $[\alpha]^{20}_D$ −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. ($C_{18}H_{26}NO_2Cl$) 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 $CHCl_3$ (150 mL) was added during 5 min to a well-stirred solution of $BBr_3$ (34.45 g, 0.138 mol) in dry $CHCl_3$ (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 $NH_4OH$ (50 mL). The layers were separated, and the aqueous layer was extracted further with $CHCl_3$ (2 × 200 mL). The combined organic solutions were dried ($MgSO_4$), 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; $[\alpha]^{20}_D$ −59° (*c* 1, 95% EtOH); EIMS, *m/z* 273 ($M^+$). The hydrochloride crystallized from EtOAc–EtOH, mp 172–174 °C. Anal. ($C_{17}H_{24}NO_2Cl$) 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 $Et_2O$ (3 × 50 mL), basified with $NaHCO_3$, and extracted with $Et_2O$ (3 × 50 mL). The combined ethereal extracts were dried ($mGSO_4$) and evaporated to yield a light yellow oil, **8** (0.6 g, 65%). The hydrochloride crystallized from EtOAc–$Et_2O$ as needles, mp 146–148 °C. The base had $[\alpha]^{20}_D$ −52° (*c* 1, 95% EtOH); EIMS, *m/z* 315 ($M^+$); $^1H$ NMR (base) $\delta$ 2.22 (s, 3 H, $COCH_3$), 2.41 (s, 3 H, $NCH_3$); $^{13}C$ NMR (base) $\delta$ 168.59 (C=O). Anal. Calcd for $C_{19}H_{26}NO_3Cl\cdot1.5H_2O$: 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 $K_2CO_3$ (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 $Na_2CO_3$, and extracted with $CHCl_3$ 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 $K_2CO_3$ (2 g) in $CHCl_3$ (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 $Et_2O$ (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 $Et_2O$ (3 × 100 mL), basified with $NH_4OH$, and extracted with $Et_2O$ (5 × 100 mL). The combined ether extracts were dried ($MgSO_4$), and the solvent was removed to give 0.2 g of **11** (14%) as a white solid: mp 135–137 °C; $[\alpha]^{20}_D$ −90° (*c* 1, 95% EtOH). The hydrochloride crystallized from AcMe–EtOH–$Et_2O$ and had mp 245–246 °C. Anal. ($C_{19}H_{26}NO_2Cl\cdot{}^1/_2H_2O$) 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 anhyrous $K_2CO_3$ (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 $Et_2O$ (3 × 100 mL). The aqueous layer was basified with $Na_2CO_3$ and extracted with ether (5 × 100 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated to give 0.7 g of mixed N- and O-dialkylated product. This mixture was dissolved in dry $CHCl_3$ (100 mL) and added to a well-stirred solution of $BBr_3$ (12.5 g, 0.05 mol) in dry $CHCl_3$ (100 mL). The mixture was stirred for 5 h at room temperature and poured onto a stirred mixture of ice and concentrated $NH_4OH$ (20 mL). The layers were separated, and the aqueous phase was further extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) 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 $CHCl_3$ as eluent. Compound **12** was isolated as an almost colorless solid (0.2 g, 24%): mp 87–90 °C; $[\alpha]^{20}_D$ −68° (*c* 1, 95% EtOH). The hydrochloride crystallized from acetone as needles, mp 270–275 °C dec. Anal. ($C_{24}H_{30}NO_2Cl$) 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 $K_2CO_3$ (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 $Et_2O$ (2 × 100 mL), basified with $Na_2CO_3$, and extracted with $Et_2O$ (2 × 200 mL). The combined ethereal layers were dried ($MgSO_4$), 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. ($C_{19}H_{25}NO_5$) C, H, N.

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

**Acknowledgment.** We thank the Association of Commonwealth Universities for the award of an Academic Staff Fellowship to V. K. Kapoor. Thanks also to Dr. A. E. Jacobson, of the National Institutes of health, Bethesda, MD, for analgesic evaluations and to Dr. J. H. Woods, The University of Michigan, for the rat brain membrane binding and mouse vas deferens assays.

**Registry No.** **1**, 5965-16-2; **2**, 101155-88-8; **3**, 102977-05-9; **4**, 102977-06-0; **4**·oxalate, 103064-28-4; **4**·HCl, 103064-35-3; **5**, 102977-07-1; **5**·HCl, 103064-29-5; **6**, 102977-08-2; **6**·HCl, 103064-30-8; **7a**, 102977-09-3; **7a**·HCl, 103064-31-9; **7b**, 102977-14-0; **8**, 102977-10-6; **8**·HCl, 103064-32-0; **9**, 102977-11-7; **9**·oxalate, 103064-34-2; **9**·HCl, 103064-36-4; **10**, 102977-12-8; **11**, 102977-13-9; **11**·HCl, 103064-33-1; **12**, 103066-55-3; **12**·HCl, 102977-15-1; **12** (phenyl ethyl ether), 103002-53-5; (−)-dihydrocodeinone, 125-29-1; allyl bromide, 106-95-6; phenylethyl bromide, 103-63-9; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

# 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 $^{131}$I 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-workers[5] 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 $^{131}$I OIH, we reported[9] the synthesis of technetium-99m

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