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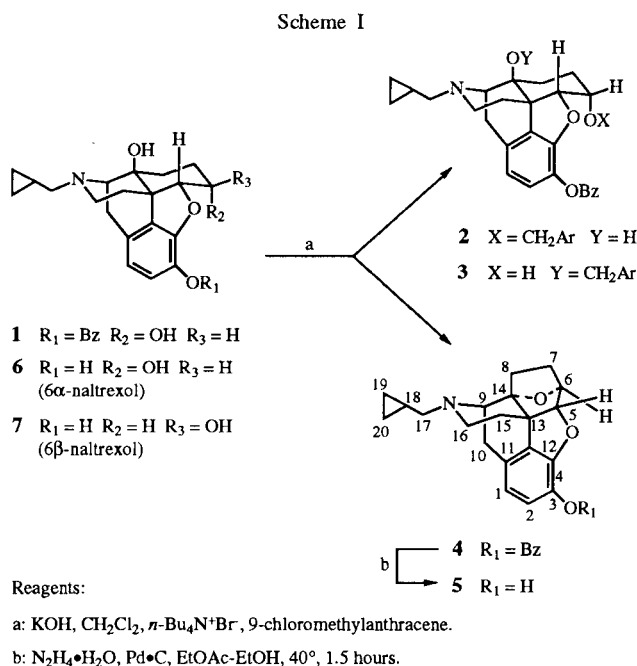
During alkylation of 3-*O*-benzyl-6 α -naltrexol (**1**) with large aralkyl halides like 2-bromomethylnaphthalene and 9-chloromethylantracene under phase transfer catalysis conditions (potassium hydroxide, tetrabutylammonium bromide, methylene chloride), formation of a new 6 α ,14-epoxide-bridged isomorphinan (**4**) was noted. Chemical and spectral evidence, including nmr and mass spectral data, are presented to prove its structure. Its formation results from 6 α -oxygen displacement of a 14-*O*-aralkyl ether intermediate under the phase transfer catalysis alkylation conditions.

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In the course of work on preparation of selective ligands for different classes of opioid receptors, we have found a novel cyclization that results in formation of a 6 α ,14-epoxy-bridged isomorphinan from a 6 α ,14-dihydroxy-substituted derivative of the more usual morphinan nucleus. The geometry of the new C-ring bridged isomorphinan is similar to that of the 6,14 β -ethano bridge in the highly potent thebaine-derived Diels-Alder adducts in the oripavine series [1] which has the new two-carbon bridge located above the C-ring of the classical opioid structure.

While preparing several 6 α -*O*-ethers of 6 α ,14-dihydroxy-4,5-epoxymorphinans via 3-*O*-benzyl-6 α -naltrexol (**1**) [2], we sought to obtain some aralkyl ethers from relatively large halides like 2-bromomethylnaphthalene and 9-chloromethylantracene by using phase-transfer catalysis [3] (Scheme 1). Besides the expected 6 α -*O*- and 14-*O*-aralkyl ethers **2** and **3**, a very nonpolar product was isolated chromatographically in 5-8% yield. This compound **4** contained neither the expected aralkyl group nor the original hydroxyl groups at C-14 and at C-6 α . In its ¹H-nmr spectrum, the signal for H₅ became a singlet at δ 4.42 and the signal for H₆ was a doublet at δ 4.52, *J* = 5.8 Hz. These data are consistent with the expected geometry of a new C-ring-derived 7-oxabicyclo[2.2.1]heptane ring, where the dihedral angles are $\theta_{H-5,H-6} \simeq 90^\circ$ and $\theta_{H-6,H-7endo} \simeq 90^\circ$. The broad band decoupled ¹³C-nmr and APT spectra were consistent with a non-olefinic structure for **4**. Removal of the benzyl ether by transfer hydrogenolysis [4] resulted in formation of the corresponding phenol **5**, having the expected *m/z* 325. Under reaction conditions where acetylation of all three hydroxyl groups in closely related structures 6 α - and 6 β -naltrexol **6** and **7** occur, a monoacetate is formed from **5** by 3-*O*-acetylation [5,6].

Formation of both **2** and **3** under the phase transfer catalysis conditions suggests that the energies of activation for the initial alkylations at the 6 α -oxygen and 14-oxygen atoms with these large halides may be similar [7]. Under the phase transfer alkylation conditions, subsequent



intramolecular displacement in **3** results in formation of the new 7-oxabicyclo[2.2.1]heptane system. This displacement process must provide some relief of steric strain upon loss of the 14-*O*-aralkyl group.

Supporting evidence for both the formation of a bicyclo[2.2.1]system in the C-ring and for the conformation required for its formation is found in closely related systems. Although the C-ring of 6 α -naltrexol (**6**) and its 6 α -*O*-methanesulfonate exist in chair conformations [5,8], formation of a twist-boat conformation of the methanesulfonate ester is required for the reported intramolecular displacement to form the 6 β ,14-epoxy-bridged morphinan system [8]. In the closely related 6 α -naltrexamine, a twist boat conformation of the C-ring has been found based on nmr and X-ray evidence [9,10].

This new bicyclic system resembles Bentley's 6,14-ethano-bridged compounds [1] more closely than the

diastereomeric 6 β ,14-epoxy-bridged morphinans which resulted from 14-oxygen displacement of the 6 α -*O*-methanesulfonate. Although **5** had less affinity than naltrexone in the radioligand displacement assay at opioid receptors [11], it provides an interesting variant on previously reported isomorphinans and the 6,14-ethano-bridged oripavine series [12]. Further work is under way to examine applications of this process of other related opioid ligands.

EXPERIMENTAL

Infrared spectra were recorded with a Perkin-Elmer 1600 series FTIR. Absorptions are expressed in unit of frequency (cm^{-1}). The nmr spectra were recorded on the Varian VXR-300 spectrometer. Chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane as the internal standard. Mass spectra were obtained on the VG-7070 and the VG-70SEQ mass spectrometers by direct-insertion probe. Elemental combustion analysis was performed by Desert Analytics, Tucson, Arizona. Analytical tlc was performed on Analtech Silica Gel HLF tlc plates (0.25 mm thickness) and the spots were detected by a uv lamp. A solvent system of hexane:ethyl acetate:triethylamine (200:150:4) was used for tlc. Merck silica gel 60 (230-400 mesh) was used for preparative flash column chromatography. All chemical reactions were performed under an argon atmosphere.

17-Cyclopropylmethyl-3-benzyloxy-4,5 α -epoxy-6 α ,14-dihydroxymorphinan (**1**).

To a solution of 6 α -naltrexol (**6**) [13] (2.00 g, 5.83 mmoles), tetrabutylammonium hydrogen sulfate (250 mg, 0.735 mmole), and benzyl bromide (1.64 ml, 15.2 mmoles) in methylene chloride (50 ml) was added aqueous 0.25 *M* sodium hydroxide (50 ml). After the reaction mixture had been stirred vigorously overnight, the phases were separated. The aqueous phase was extracted with methylene chloride (2 x 10 ml) and the combined organic phases were evaporated to dryness. The crude product was then purified by flash column chromatography using medium pore silica gel (21 g, 19 mm diameter column). The product was eluted with methylene chloride (200 ml) followed sequentially by 80:20 methylene chloride:ethyl acetate (200 ml) and ethyl acetate (200 ml). Fractions were examined by tlc and combined accordingly. Evaporation yielded 1.76 g of **6** as a white foam (70% yield); ^1H nmr (deuteriochloroform): δ 7.20-7.48 (m, 5 H, benzyl aromatic H), 6.76 (d, *J* = 7.9 Hz, 1 H, C-2 H), 6.53 (d, *J* = 8.2 Hz, 1 H, C-1 H), 5.21 and 5.10 (2d, *J* = 12.1 Hz, 2 H, PhCH_2), 4.60 (d, *J* = 4.4 Hz, 1 H, C-5 β H), 4.08-4.20 (m, 1 H, C-6 β H), 3.06 (d, *J* = 6.4 Hz, 1 H, C-9 H), 3.00 (d, *J* = 19.3 Hz, 1 H, C-10 β H), 2.50-2.70 (m, 2 H C-10 α H, C-16 H), 2.13-2.40 (m, 4 H, C-15 H, C-16 H, C-17 2 H), 1.37-1.80 (m, 4 H, C-8 2 H, C-15 H, C-7 H), 1.02-1.18 (m, 1 H, C-7 H), 0.77-0.90 (m, 1 H, C-18 H), 0.48-0.56 (m, 2 H, C-19 H, C-20 H), 0.08-0.15 (m, 2 H, C-19 H', C-20 H'); ^{13}C nmr (deuteriochloroform): δ 146.8 (C-4), 140.1 (C-22'). 137.3 (C-3), 131.6 (C-12), 127.2, 127.6, 128.2 (five benzyl aromatic C), 126.5 (C-11), 118.6 (C-1), 116.7 (C-2), 90.6 (C-5), 71.6 (C-21'), 69.6 (C-14), 66.5 (C-6), 61.9 (C-9), 59.4 (C-17), 46.8 (C-13), 43.1 (C-16),

33.3 (C-15), 28.3 (C-8), 23.6 (C-7), 22.7 (C-10), 9.3 (C-18), 3.8, 3.9 (C-19, C-20); ir (neat): (FT) 3700-3100 broad, 2933, 2872, 2816, 1633, 1605, 1501, 1452, 1380, 1172, 1122, 1047, 976, 858, 737 cm^{-1} ; hrms (FAB) Calcd. for $\text{C}_{27}\text{H}_{32}\text{NO}_4$ (M+H) $^+$: 434.2331. Found: 434.2325.

Phase Transfer Alkylation of 17-Cyclopropylmethyl-3-benzyloxy-4,5 α -epoxy-6 α ,14-dihydroxymorphinan (**1**) with 9-Chloromethylantracene.

To a solution of benzyl ether **1** (400 mg, 0.924 mmole), tetrabutylammonium bromide (100 mg, 0.310 mmole), and 9-chloromethylantracene (838 mg, 3.70 mmoles) in methylene chloride (15 ml) was added aqueous 50% potassium hydroxide (15 ml) and the mixture was stirred vigorously at room temperature. After two days, 15 ml each of water and methylene chloride were added and the phases were then separated. The remaining aqueous fraction was then extracted with ethylene chloride (2 x 15 ml). The combined organic fractions were washed with water (10 ml) and then evaporated to a viscous oil. This oil was purified by flash chromatography using medium pore silica gel (21 g, 19 mm diameter column) conditioned with methylene chloride (100 ml) and eluted sequentially with a methylene chloride:ethyl acetate gradient from 0:100 to 100:0, followed by methanol (100 ml). Fractions were examined by tlc and combined accordingly, affording 50 mg (7.9% yield) of 6 α -anthracylmethyl ether **2**. Recovery of starting benzyl ether **1** in the last fractions was greater than 50%. Fractions 11 and 12 (~25 ml fractions) were further purified on a small column of silica gel (3.0 g, 10.5 mm diameter column) conditioned with methylene chloride (25 ml) and eluted sequentially with a methylene chloride:ethyl acetate gradient from 0:100 to 100:0. Fractions were combined and evaporated to yield 20 mg (5.2% yield) of bicyclic ether **4**. Fractions 13-25 (~25 ml fractions) were further purified on a small column of silica gel (7.0 g, 10.5 mm diameter column) conditioned with methylene chloride (50 ml) and eluted sequentially with a methylene chloride:ethyl acetate gradient from 0:100 to 50:50. Like fractions were combined and evaporated to yield an additional 10 mg (2.6% yield) of bicyclic ether **4** and 30 mg (5.2% yield) of 14-*O*-anthracylmethyl ether (**3**).

Ether **2**.

This compound had ^1H nmr (deuteriochloroform): δ 8.40-8.52 (m, 2 H, An (anthracyl) C-4 H, An C-5 H), 8.40 (s, 1 H, An C-10 H), 7.84-8.03 (m, 2 H, An C-1 H, An C-8 H), 7.15-7.50 (m, 9 H, five benzyl aromatic H, An C-2, An C-3, An C-6, An C-7 H), 6.75 (d, *J* = 8.1 Hz, 1 H, C-2 H), 6.52 (d, *J* = 8.1 Hz, 1 H, C-1 H), 5.76 and 5.50 (2d, *J* = 10.4 Hz, 2 H, An- CH_2), 5.16 (s, 2 H, PhCH_2), 5.10 (d, *J* = 4.2 Hz, 1 H, C-5 β H), 4.28-4.36 (m, 1 H, C-6 β H), 3.10 (d, *J* = 5.0 Hz, C-9 H), 3.03 (d, *J* = 18.3 Hz, 1 H, C-10 β H), 2.55-2.72 (m, 2 H, C-10 α H, C-16 H), 2.20-2.40 (m, 4 H, C-15 H, C-16 H, C-17 2 H), 1.60-1.78 (m, 3 H, C-15 H, C-8 H, C-7 H), 1.45-1.60 (m, 1 H, C-8 H), 1.18-1.34 (m, 1 H, C-7 H), 0.75-0.94 (m, 1 H, C-18 H), 0.48-0.58 (m, 2 H, C-19 H, C-20 H), 0.05-0.20 (m, 2 H, C-19 H', C-20 H'); ^{13}C nmr (deuteriochloroform): δ 147.8 (C-4), 140.4 (benzyl aromatic C-1), 137.3 (C-3), 124.6, 124.7, 126.0, 126.2, 127.0, 127.2, 127.3, 127.5, 127.7, 127.9, 128.1, 128.6, 129.0, 130.9, 131.3, 131.5 (C-11, C-12, five benzyl aromatic carbons, 14 anthracyl aromatic carbons), 118.2 (C-1), 117.3 (C-2), 88.2 (C-5), 74.4 (An CH_2), 71.8 (Ph CH_2), 70.0 (C-14), 63.1 (C-6), 62.2 (C-9), 59.5 (C-17), 47.4 (C-13), 43.3 (C-16), 33.4 (C-15),

29.0 (C-8), 22.9 (C-7), 21.6 (C-10), 9.4 (C-18), 4.0, 3.9 (C-19, C-20); ir: (FT) 3600-3100 broad, 2931, 1672, 1602, 1499, 1452, 1285, 1283, 1116, 1090, 1047, 734, 700 cm^{-1} ; hrms (FAB) Calcd. for $\text{C}_{42}\text{H}_{42}\text{NO}_4$ (M+H)⁺: 624.3114. Found: 624.3120.

Ether 3.

This compound had ¹H nmr (deuteriochloroform): δ 8.47 (s, 1 H, An C-10 H), 8.37 (d, J = 8.3 Hz, 2 H, An C-4 H, An C-5 H), 8.02 (d, J = 8.3 Hz, 2 H, An C-1 H, An C-8 H), 7.20-7.62 (m, 9 H, five benzyl aromatic H, An C-2, An C-3, An C-6, An C-7 H), 6.88 (d, J = 8.4 Hz, 1 H, C-2 H), 6.80 (d, J = 8.3 Hz, 1 H, C-1 H), 5.79 and 5.58 (2 d, J = 11.2 Hz, 2 H, PhCH₂), 5.20 and 5.10 (2 d, J = 12.7 Hz, 2 H, AnCH₂), 4.91 (s, 1 H, C-9 H), 4.60 (d, J = 4.4 Hz, 1 H, C-5 β H), 4.04-4.16 (m, 1 H, C-6 β H), 3.01 (s, 1 H, C-10 β H), 2.70-2.78 (m, 1 H, C-16 H), 2.25-2.37 (m, 2 H, C-10 α H, C-17 H), 2.12-2.25 (m, 1 H, C-15 H), 1.98-2.12 (m, 1 H, C-16 H), 1.84-1.98 (m, 2 H, C-17 H), 1.48-1.62 (m, 3 H, C-7 H, C-8 H, C-15 H), 1.20-1.28 (m, 1 H, C-7 H), 0.82-1.04 (m, 2 H, C-19 H, C-20 H), 0.70-0.82 (m, 1 H, C-18 H), 0.38-0.58 (m, 2 H, C-19 H', C-20 H'); ¹³C nmr (deuteriochloroform): δ 146.2 (C-4), 141.5 (benzyl aromatic C-1), 137.1 (C-3), 123.9, 124.8, 126.3, 127.0, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 128.7, 128.8, 129.0, 130.8, 131.3 (C-11, C-12, five benzyl aromatic carbons, anthracene aromatic carbons), 119.4, (C-1), 116.9 (C-2), 90.8 (C-5), 71.4 (AnCH₂), 68.5, 68.8 (C-14, PhCH₂), 66.6 (C-6), 64.9 (C-9), 59.6 (C-17), 47.3 (C-13), 42.7 (C-16), 33.1 (C-15), 28.1 (C-8), 23.4 (C-10, C-7), 9.6 (C-18), 2.5, 3.9, 5.3 (C-19, C-20). ir (neat): (FT) 3600-3100 broad, 2929, 1672, 1602, 1499, 1449, 1283, 1050, 698 cm^{-1} ; hrms (FAB) Calcd. for $\text{C}_{42}\text{H}_{42}\text{NO}_4$ (M+H)⁺: 624.3114. Found: 624.3102.

17-Cyclopropylmethyl-6 α ,14-epoxy-4,5 α -epoxy-3-hydroxymorphinan (5).

To a solution of 17-cyclopropylmethyl-6 α ,14-epoxy-4,5 α -epoxy-3-benzylmorphinan (4) (40 mg, 0.0964 mmole) in ethyl acetate (2 ml) and ethanol (6 ml) at 40° was added 10% palladium on carbon (40 mg) and hydrazine hydrate (20 μ l). After stirring for 1.5 hours, the mixture was cooled and the catalyst removed by filtration through celite. The filtrate was evaporated and the oily residue was partitioned between water (15 ml) and methylene chloride (15 ml). The organic fraction was evaporated affording a viscous oil which was further purified by flash chromatography on medium pore silica gel (7 g, 10.5 mm diameter column). The column was conditioned with methylene chloride (50 ml) and then the product eluted sequentially with a methylene chloride:ethyl acetate gradient from 100:0 to 0:100. Evaporation of combined like fractions containing product yielded 30 mg (94% yield) of 5; ¹H nmr (deuteriochloroform): spectral assignments were supported by decoupling experiments; δ 6.61 (d, J = 8.0 Hz, 1 H, C-2 H), 6.52 (d, J = 8.2 Hz, 1 H, C-1 H), 4.52 (d, J = 5.8 Hz, 1 H, C-6 β H), 4.42 (s, 1 H, C-5 β H), 3.77 (d, J = 6.0 Hz, 1 H, C-9 H), 3.11 (d, J = 18.1 Hz, 1 H, C-10 β H), 2.62-2.75 (m, 1 H, C-16 H), 2.27-2.58 (m, 5 H, C-8 H, C-10 α H, C-16 H, C-17 2 H), 2.03-2.16 (m, 1 H, C-15 H), 1.89-1.97 (m, 1 H, C-15 H), 1.60-1.82 (m, 2 H, C-7 2 H), 1.37-1.48 (m, 1 H, C-8 H), 0.76-0.92 (m, 1 H, C-18 H), 0.45-0.58 (m, 2 H, C-19 H, C-20 H), 0.10-0.17 (m, 2 H, C-19 H', C-20 H'); ¹³C nmr (deuteriochloroform): spectral assignments were supported by APT analysis; δ 146.2 (C-4), 137.5 (C-3), 132.6 (C-12), 127.5, (C-11), 119.5 (C-1), 116.4 (C-2), 93.7 (C-5),

84.5, 84.6 (C-6, C-14), 59.5 (C-17), 57.2 (C-9), 54.3 (C-13), 43.9 (C-16), 28.6, 29.6 (C-8, C-15), 23.1, 26.5 (C-7, C-10), 9.6 (C-18), 3.1, 4.0 (C-19, C-20); ir (neat): (FT) 3600-3100 broad, 2996, 2926, 2815, 1632, 1608, 1500, 1451, 1316, 1141, 1026, 955, 888 cm^{-1} ; ms: (EI) m/z 325 (M⁺), 297, 269, 254, 230, 200, 174, 115, 98, 84, 55; hrms (EI) Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_3$ (M⁺): 325.1678. Found: 325.1661.

Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_3 \cdot \text{H}_2\text{O}$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.70; H, 7.09; N, 3.79.

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