5-(Benzyloxy)-1-hydroxy-2,2-indandipropionic Acid δ-Lactone (23). By use of conditions virtually identical with those employed in the reduction of keto acids **3–6, 22** afforded δ-lactone **23**, mp 175–176 °C ($CHCl_3$/benzene/hexane), in 90% yield: IR (KBr) 3400, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.8–7.67 (m, 8 H, aromatic), 5.4 (s, 1 H, C-1 H), 5.05 (s, 2 H, benzylic), 2.95 (s, 2 H, benzylic), 1.25–2.48 (m, 8 H, aliphatic); MS (70 eV), *m/e* 366 (M^+). Anal. ($C_{22}H_{22}O_5$) C, H.

Pharmacological Methods. Female albino CD-1 mice, weighing on average 22 ± 0.2 g and in natural estrous, were sacrified by cervical dislocation. The uterine horns were isolated and prepared for isometric contraction recordings under 200-mg tension in oxygenated tissue baths maintained at 37 °C.[6,14] The composition of the bathing solution was as follows (g/L): NaCl, 8.046; KCl, 0.2; $CaCl_2 \cdot 2H_2O$, 0.132; $MgCl_2 \cdot 6H_2O$, 0.106; $NaHCO_3$, 1.0; $NaH_2PO_4 \cdot H_2O$, 0.065; dextrose, 1.0. Following an equilibration period of 30 min, two 5-min control responses to $PGF_{2\alpha}$ (10^{-7} M) wer obtained, followed each time by a 20-min washout period. The agent to be tested was then added at a given concentration to the bath and left in contact with the tissue for 5 min prior addition of 10^{-7} M $PGF_{2\alpha}$. After recording of the 5-min response to $PGF_{2\alpha}$ in presence of the test agent, the tissue was washed for 20 min with the physiological medium. Recovery of the responsiveness of the tissue to $PGF_{2\alpha}$ was then ascertained by adding 10^{-7} M $PGF_{2\alpha}$ for 5 min. Finally, the tissue was washed for 10 min and the resting tension recorded for 3 min. Control uterine tissues were not exposed to the test compound but were otherwise treated similarly to the test tissues. In these control tissues, the response to $PGF_{2\alpha}$ did not decline with repeated exposure.

In a few experiments, KCl (54 mM) or $BaCl_2$ (2.2×10^{-4} M) was used instead of $PGF_{2\alpha}$ to stimulate the uterine strip.

The integrated contractile force generated by the agonist ($PGF_{2\alpha}$, KCl, or $BaCl_2$) in the presence of the test compound was expressed as a percentage of the mean of the two initial control responses to the agonist recorded prior to addition of the test agent. Recovery responses were expressed similarly.

The test compounds were dissolved in 100 μL of 0.25 N NaOH and diluted with 100 μL of distilled water to pH 7. The agonists and test compounds were added in 10-μL volumes to the 10-mL tissue bath to obtain the desired concentrations.

Registry No. **1**, 68935-40-0; **2**, 90606-30-7; **3**, 90606-31-8; **4**, 78326-94-0; **5**, 80106-55-4; **6**, 90606-32-9; **7**, 90606-33-0; **8**, 90606-34-1; **9**, 78326-92-8; **10**, 90606-35-2; **11**, 90606-36-3; **12**, 90606-37-4; **13**, 90606-38-5; **14**, 90606-39-6; **15**, 90606-40-9; **17**, 90606-41-0; **18**, 90606-42-1; **19**, 90606-43-2; **20**, 78326-88-2; **21**, 90606-44-3; **22**, 90606-45-4; **23**, 90606-46-5; methyl acrylate, 96-33-3.

Potential Synthetic Codeine Substitutes: (–)-3-*O*-Aryl-*N*-methylmorphinans

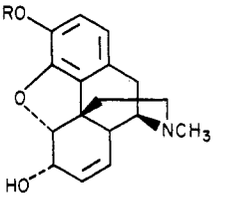
Erno Mohacsi,*† Tom Hayes,† and Jerry Sepinwall‡

Chemical Research Department and Pharmacology Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
Received December 19, 1983

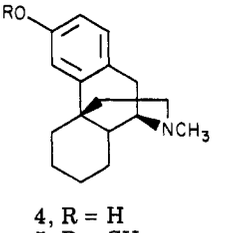
A series of novel *O*-aryl-*N*-methylmorphinans (**7–19**) were synthesized by the Ullmann reaction from levorphanol (**4**) in our search for a synthetic codeine (**2**) substitute with reduced addition liability. The compounds were evaluated for antinociceptive potency and receptor binding affinity. Among these compounds, (–)-3-phenoxy-*N*-methylmorphinan (**7**) is an orally active analgesic comparable in potency to codeine (**2**), which exhibits decreased physical dependence liability and longer duration of action.

In recent years, there has been considerable interest in attempting to provide alternative sources for or to replace with synthetic substitutes analgesics prepared from opium.[1] In connection with this latter approach directed at the search for a synthetic codeine (**2**) substitute with reduced addiction liability, we reported[2] the synthesis of 3-*O*-*tert*-butylmorphine (**3**) and (–)-3-*tert*-butoxy-*N*-methylmorphinan (**6**). Our rationale for preparing these novel codeine (**2**) and levomethorphan (**5**) analogues was based on the expectation that a tertiary butyl group on the phenolic oxygen would prevent their in vivo metabolic conversion to morphine (**1**) and levorphanol (**4**), respectively, thus eliminating the pharmacological effects of these metabolites. Metabolic studies[3] have shown that the tertiary butyl group successfully blocks the enzymatic O-dealkylation of these compounds. However, unlike codeine (**2**) and levomethorphan (**5**), the analogues **3** and **6** were only marginally active as analgesics and were unstable under acidic conditions.

We therefore shifted our synthetic efforts toward the preparation of aryl ethers of levorphanol (**4**). The lipophilic aryl group was expected to facilitate transport while retarding metabolic inactivation. An additional attractive feature of these aryl ethers (**7–19**) (Table I) was their anticipated chemical stability under conditions which cause degradation of codeine (**2**) to morphine (**1**), thus providing a safeguard against abuse.



1, R = H
2, R = CH_3
3, R = $C(CH_3)_3$



4, R = H
5, R = CH_3
6, R = $C(CH_3)_3$
7, R = C_6H_5

Chemistry. The aryl ethers (**7–16**) in Table I were prepared from **4** by the Ullmann reaction.[4] For example, treatment of **4** with bromobenzene in pyridine in the presence of potassium carbonate and copper gave **7** in 52% yield. The substituted *O*-aryl-*N*-methylmorphinans (**8–16**) were prepared by this method from **4** and the appropriate aryl halides. O-Demethylation of the methoxyphenyl-substituted analogues **9–11** with pyridine hydrochloride at elevated temperature gave the hydroxyaryl ethers **17–19** without cleavage of the aryl ether bond.

Similarly, when **7** was treated with pyridine hydrochloride at 220 °C for 25 min[5] or with other O-dealkylating

† Chemical Research Department.
‡ Pharmacology Department.

(1) Greentree, L. B. *N. Engl. J. of Med.* **1974**, *291*, 1411.
(2) Mohacsi, E.; Leimgruber, W.; Baruth, H. *J. Med. Chem.* **1982**, *25*, 1264.
(3) Kamm, J. J.; Bastone, V. B.; Mohacsi, E.; Vane, F. M. *Xenobiotica* **1971**, *1*, 273.
(4) Ullmann, F.; Sponagel, P. *Ann. Chem.* **1906**, *350*, 83.

0022-2623/84/1827-1219$01.50/0