transferred to two 2000-μm silica gel chromatography plates and developed once with 35% EtOAc/hexane. The R_f 0.6 band was isolated (0.003 g): NMR ($CDCl_3/Me_4Si$) 7.45–7.0 (m, 4 H aromatic H), 5.02 (s, 2 H, methylene), 3.8 (s, 3 H methoxy H); IR (CH_2Cl_2) 1780 cm^{-1} (C=O); MS, 179.0578 (parent).

Antimicrobial Activity: Minimum Inhibitory Concentration. Minimum inhibitory concentration (MIC) for various bacteria was determined by a microplate broth dilution technique. Serial twofold dilutions of the antibiotics were prepared in 50 μL of modified brain heart infusion broth medium (reference) in the wells of a microplate. Each well was then inoculated with 50 μL of standardized cell suspension to yield a final concentration of $\sim 10^5$ viable cells per milliliter of drug-supplemented medium. The microplates were incubated at 37 °C for 20 h, and the MIC was read as the lowest concentration of drug that inhibited the visible growth of the organism.

Acknowledgment. We express our appreciation to S. L. Kuentzel for the L1210 assay data, T. F. DeKoning and J. P. McGovren for the P388 in vivo evaluation, and C. W. Ford and K. Stern for the in vivo *P. aeruginosa* and *K. pneumoniae* data.

Registry No. 1, 39830-70-1; 2, 88057-16-3; 3, 31499-90-8; 6, 33047-12-0; 7, 23091-67-0; 8, 90720-08-4; 9, 90720-09-5; 10, 90720-10-8; 11, 90720-11-9; 12, 90720-12-0; 13, 90720-13-1; 14, 90720-14-2; 15, 90720-15-3; 16, 90720-16-4; 17, 90720-17-5; 18, 90720-18-6; 19, 90720-19-7.

Synthesis and Pharmacological Evaluation of Indanpropionic Acids as Uterine Relaxants[1]

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The $PGF_{2\alpha}$ antagonist 5,6-bis(benzyloxy)-1-oxo-2-propyl-2-indanpropionic acid (1) had previously been shown to provide significant protection against the abortifacient actions of $PGF_{2\alpha}$ in mice. To explore further structural concepts in drug design employed for the development of 1, several mono(benzyloxy) ketones (3–10) and alcohols (11–15) as well as a diacid (22) were prepared. None of these structural modifications resulted in compounds of greater superiority to 1 as uterine relaxants and 22 was void of any antagonistic properties, suggesting that the original rationale requiring one carboxyl group and two benzyloxy functions appropriately placed for maximum $PGF_{2\alpha}$ antagonism in this series was a good assumption. A carbonyl rather than hydroxyl group at position C-1 of the indan is most beneficial for reversible antagonism. Reduction of the ketone to the alcohol is of synthetic interest and discussed in some detail.

Previous reports[2,3] from these laboratories describe our rationale for the design of keto-DIPA [5,6-bis(benzyloxy)-1-oxo-2-propyl-2-indanpropionic acid; 1] as a $PGF_{2\alpha}$ receptor antagonist. Noteworthy, the 15α-hydroxyl group of $PGF_{2\alpha}$, which is important for its agonist activity,[4] is replaced in 1 by a keto function having a juxtaposition to the carboxyl group similar to the juxtaposition of the 15α-hydroxyl function to the carboxyl group of $PGF_{2\alpha}$ but about one staggered ethylene moiety short of the distance between these groups in the proposed "active" hairpin conformation[5] of the prostaglandin. Studies in vitro[6] confirmed the ability of 1 to block $PGF_{2\alpha}$-induced contractions of the isolated uterus with an IC_{50} of 3.8×10^{-5} M. Investigations in vivo demonstrated the significant protective effects of 1 against the abortifacient actions of $PGF_{2\alpha}$ in mice,[3] as well as the absence of teratogenic activity.[7]

To explore further structural requirements for antagonistic activity in vitro, we prepared bis(benzyloxy) alcohol 2, a series of mono(benzyloxy) ketones (3–10) and alcohols (11–15), and diacid 22. Selected compounds were assessed for their pharmacological activity on the isolated rat uterus.

Chemistry. Keto acids 3, 4, and 6 were synthesized by using methods similar to those employed in the synthesis of keto acid 5.[2,6] Reduction of intermediate ester 9 with $NaBH_4$ in MeOH, however, did not afford the desired epimeric indanols 11 but rather two tricyclic compounds 17 (30%) and 18 (50%), which were separated by chromatography on silica gel using $CHCl_3$/*i*-PrOH (96:4) as eluting solvent. The indan C-1 proton resonance signals for 17 (δ 5.38) and 18 (δ 4.54) were particularly diagnostic. For lactones, the indan C-1 H resonance signal was consistently found to be downfield at approximately δ 5.4. Also, for 18, the additional two-proton resonance signal multiplets (X) bonded to the C α to oxygen appeared at δ 3.5–3.7. The [^{13}C]carbonyl resonance signal for 17 appeared at 172.4 ppm and the equivalent ^{13}C signal for 18 appeared at 63.5 ppm. Such a difference in chemical shift can be attributed to removal of electronegative oxygen. On the other hand, the C-1 indan ^{13}C resonance signals for 17 and 18 were identical (70.36 ppm). No OH stretching absorption was observed for 18 in the IR. Interestingly, when 17 was subjected to $NaBH_4$/MeOH reduction under conditions similar to those employed in the reduction of 9, a compound of identical R_f (0.34) [silica gel plates (5% hexane in $CHCl_3$)] with that of 18 was obtained as well as starting 17 (R_f 0.16). Further work would be necessary to elucidate the pathway of formation of 18 from 17. Thus, 17 may undergo solvolysis to ester 9 serving as intermediate to a diol precursor to 18. Reduction of other esters under similar conditions have previously been reported.[10]

(1) Supported by USPHS Grant HD-14853 from the National Institute of Child Health and Human Development.
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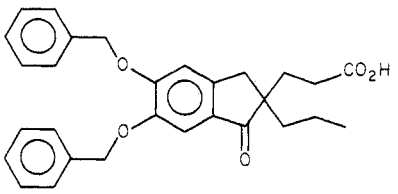
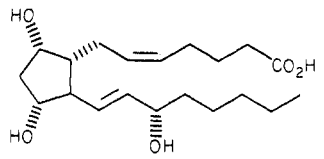
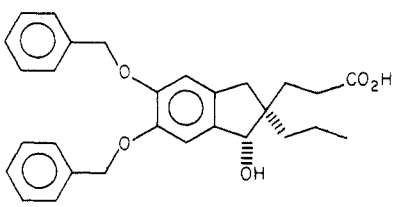


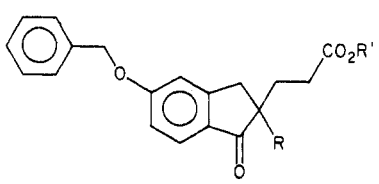
keto-DIPA (1)



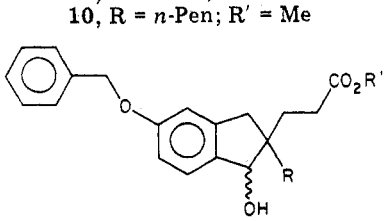
$PGF_{2\alpha}$



2



3, R = Et; R′ = H
4, R = *n*-Pr; R′ = H
5, R = *n*-Bu; R′ = H
6, R = *n*-Pen; R′ = H
7, R = Et; R′ = Me
8, R = *n*-Pr; R′ = Me
9, R = *n*-Bu; R′ = Me
10, R = *n*-Pen; R′ = Me

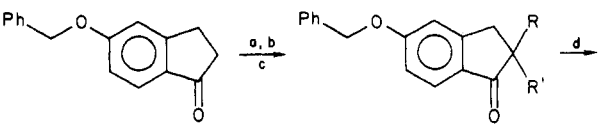


11, R = *n*-Bu; R′ = Me
12, R = Et; R′ = H
13, R = *n*-Pr; R′ = H
14, R = *n*-Bu; R′ = H
15, R = *n*-Pen; R′ = H

Alternatively, reduction of the corresponding keto acid anions[8-10] (Na salts of **3–6**) using $NaBH_4/H_2O$ for 4–6 days at room temperature afforded predominantly the respective trans hydroxy acids (**12–15**) in 80–95% yield. Since cis hydroxy acids always underwent lactonization we tentatively assigned the trans configuration to compounds **12–15**. For **3**, lactone **19** likely arising from cyclization of cis hydroxy acid also was isolated in 15% yield. The indan C-1 proton resonance signal for the trans hydroxy acids (**12–15**) appeared at δ 4.72–4.75, whereas the equivalent signal in lactone **19** again appeared downfield (δ 5.39). Comparison of the ^{13}C C-1 resonance signal for ketone **5** (208.42 ppm) and alcohol **14** (78.97 ppm) confirmed structural assignments. Similar methodology was employed for the preparation of **2** from **1** tentatively assigned the trans configuration.

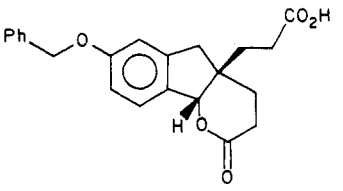
Comparative stereoselective reduction of keto ester **9** with $NaBH_4$/MeOH affording cis lactones and ethers (**17** and **18**) with reduction of keto acids (**3–6**) using

Scheme I[a]



20

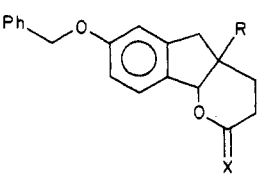
21, R = R′ = $CH_2CH_2CO_2Me$
22, R = R′ = $CH_2CH_2CO_2H$



23

[a] a = *t*-BuOK, *t*-BuOH, room temperature; b = CH_2CHCO_2Me, room temperature; c = NaOH, H_2O, MeOH; d = $NaBH_4$, NaOH, H_2O, room temperature, 4 days.

$NaBH_4/NaOH/H_2O$ affording trans hydroxy acids (**12–15**) deserves comment. For ester **9**, $NaBH_4$ reduction is sensitive to steric approach control[11,12] in MeOH. Solvation



17, X = O; R = *n*-Bu
18, X = H_2; R = *n*-Bu
19, X = O; R = Et

of the carbomethoxy group of **9** by MeOH provides for increased steric bulk over the *n*-Bu group directing hydride attack on the carbonyl carbon from the *n*-Bu side. Rationales involving electrostatic shielding[10,13] in the case of borohydride reduction of anions are excluded since such rationales should predict stereoselective attack from the side opposite the anion. House et al.[8,10] assumed that the geometry of the transition state and final product are similar and adequate to predict the major stereochemical course of borohydride reductions, providing that the molecule is not conformationally constrained such that attack is prevented from one side of the carbonyl. However, the high degree of stereoselectivity observed for reduction of **3–6** and the opposite stereochemical outcome when compared to **9** suggests to us that assisted hydride transfer via intramolecular solvation of the borohydride ion[10] is important. Since the magnitude of the nonbonded interaction between the formed hydroxyl moiety and *cis*-alkyl or *cis*-propionate groups is expected to be similar, invoking concepts of product development control[9,11] seems not to be appropriate.

5-(Benzyloxy)-1-indanone (**20**) served as starting material for preparation of dicarboxylic acid **22** via ester **21**. Anion formation followed by Michael addition to methyl acrylate and alkaline hydrolysis afforded **22** in 60% overall yield (Scheme I). Reduction of **22** using 1 molar equiv of $NaBH_4$ and NaOH afforded δ-lactone **23** in 90% yield. Lactonization of cis functions under these reaction con-

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Table I. Effects of Various Analogues of 1 on Contractions Induced by $PGF_{2\alpha}$, KCl, and $BaCl_2$ in the Isolated Mouse Uterus Preparation

compd	concn, M	% inhib of $PGF_{2\alpha}$ response	% rec of $PGF_{2\alpha}$ response	% inhib of KCL response	% rec of KCl response	% inhib of $BaCl_2$ response in Ca^{2+}-contg buffer	% rec of $BaCl_2$ response in Ca^{2+}-contg buffer	% inhib of $BaCl_2$ response in Ca^{2+}-free buffer	% rec of $BaCl_2$ response in Ca^{2+}-free buffer
2	10^{-4}	67.1 ± 3.1[a] (n = 20)	82.8 ± 3.8 (n = 20)	53.2 ± 3.7 (n = 11)	85.8 ± 4.2 (n = 11)	48.1 ± 7.1 (n = 7)	105.4 ± 8.8 (n = 7)	88.2 ± 4.6 (n = 3)	39.4 ± 18.0 (n = 3)
	3×10^{-5}	36.4 ± 3.6 (n = 8)	79.7 ± 6.0 (n = 8)						
	10^{-5}	17.2 ± 2.4 (n = 14)	81.8 ± 3.7 (n = 14)	9.4 ± 2.3 (n = 9)	84.2 ± 4.7 (n = 9)				
	10^{-6}	0.0 ± 0.0 (n = 7)	88.7 ± 6.4 (n = 7)	1.2 ± 1.0 (n = 3)	86.1 ± 2.4 (n = 3)				
3	10^{-5}	27.3 (n = 1)	69.3 (n = 1)						
	10^{-4}	44.4 ± 11.5 (n = 6)	70.4 ± 5.3 (n = 6)						
4	10^{-5}	6.4 ± 3.2 (n = 8)	85.5 ± 6.9 (n = 8)						
	10^{-4}	42.0 ± 7.0 (n = 10)	85.3 ± 5.0 (n = 10)						
14	10^{-5}	0.5 ± 0.5 (n = 7)	91.7 ± 7.5 (n = 7)						
	10^{-4}	20.4 ± 1.4 (n = 8)	103.7 ± 2.3 (n = 8)						
22	10^{-5}	10.5 ± 7.7 (n = 5)	79.9 ± 9.6 (n = 5)	8.3 ± 3.6[b] (n = 6)	105.7 ± 5.5 (n = 6)				
	10^{-4}	6.5 ± 6.8 (n = 5)	91.1 ± 8.0 (n = 5)	1.9 ± 3.2 (n = 6)	104.9 ± 5.0 (n = 6)				

[a] Values presented are the mean ±SEM. [b] Agonist activity.

ditions supports the trans configuration for **2** and **12–15**. Furthermore, when **1** was treated with $NaBH_4/NaOH/H_2O$ at reflux temperatures, a corresponding lactone was obtained identical with an authentic sample.[2] The indan C-1 proton resonance signal at δ 5.40 for **23** was consistent with the signal observed for C-1 H in **17** and **19**.

Pharmacological Results and Discussion

Table I provides a summary of the inhibitory effects of the test compounds against the oxytocic effects of the various agonists. The values are expressed as percent inhibition (±SEM) of the control agonist response. None of the selected compounds had any effect at a concentration of 10^{-6} M and exhibited little inhibitory activity at a concentration of 10^{-5} M against $PGF_{2\alpha}$-induced uterine contractions.

Analogues **3**, **4**, and **14** had approximate IC_{50} values $>10^{-4}$ M against $PGF_{2\alpha}$-induced contractions of the uterus and are therefore much weaker antagonists than **1** ($IC_{50} = 3.8 \times 10^{-5}$ M).[6] At concentrations of 10^{-6} and 10^{-5} M, compound **14** potentiated the contractile effect of oxytocin (10^{-3} μM, tissue bath concentration), but at 10^{-4} M the test compound caused a 41.5 ± 5.3% inhibition of the action of oxytocin (data not shown in Table I). In all experiments recovery of tissues from the inhibitory effects of compounds **4** and **14** was essentially complete, while recovery from compound **3** was slightly diminished.

Diacid **22** exhibited no antagonistic activity against either $PGF_{2\alpha}$-induced or KCl-induced uterine contractions and exhibited some intrinsic agonist activity. This is evident from the large standard errors. Indeed, at a concentration of 10^{-5} M, this compound consistently potentiated the KCl response (albeit to a minor extent). No tissue damage was produced by this compound as evidenced by adequate to complete recoveries of the $PGF_{2\alpha}$ and KCl control responses after washout of the test compound.

Racemic *trans*-OH-DIPA (**2**) produced a concentration-dependent and reversible inhibition of $PGF_{2\alpha}$-induced contractions of the uterus, with an IC_{50} value graphically estimated to be 4.8×10^{-5} M. Thus, *dl*-**2** is somewhat less potent than *dl*-**1**, and this is further evidenced from the fact that the 10^{-4} M concentration of **2** produced a 67% inhibition of the $PGF_{2\alpha}$ response while the same concentration of **1** produced an 80% inhibition.[6] The potency of **2** against KCl-induced uterine contractions, as well as against contractions induced by $BaCl_2$ in calcium-containing medium, was slightly less than its potency against $PGF_{2\alpha}$-induced contractions and was reversible. The hydroxy analogue **2** produced an almost complete inhibition of $BaCl_2$-induced contractions in calcium-free medium, but the effect was not reversible upon washout of the test compound. Since $BaCl_2$ induces smooth muscle contractions in calcium-free medium by mobilizing intracellular calcium stores and making the calcium available to the contractile fibers,[14] it is possible that **2** may be acting through interference with intracellular calcium mobilization or action. More likely, however, **2** may be producing nonspecific cellular toxicity in the absence of extracellular calcium since its effect in this artificial environment was not reversible.

In conclusion, none of the structural manipulations attempted resulted in compounds of greater superiority to **1** as uterine relaxants. The rationale[2,3] requiring two benzyloxy functions seems valid since removal of one[6] or both[2] of these functions provides for a marked decrease in potency. The ketone functionality at C-1 of the indan is superior to a hydroxyl group since **1** provides reversible antagonistic properties.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained with Bruker 90- and 80-MHz instruments, respectively. Infrared spectra were recorded with a Beckman IR-4230 spectrometer. Mass spectra were determined with a DuPont 491 mass spectrometer. Elemental analyses were obtained from

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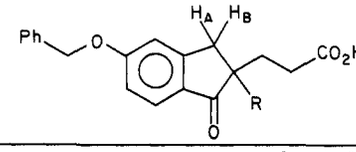
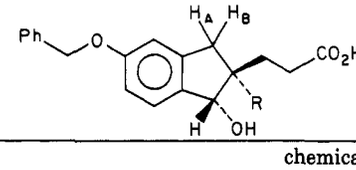
Table II. Physical and Spectral Data for Keto Acids[a] 3, 4, 6, and 22



				chemical shift, δ, relative to Me_4Si in $CDCl_3$					
compd[b]	R	mp, °C	% yield[c]	Ar	$PhCH_2O$	H_A	H_B	aliphatic	J_{AB}[d]
3	Et	155–157[e]	65	6.92–7.71	5.12	3.05	2.83	0.77–2.16	17.52
4	*n*-Pr	122–124[e]	70	6.94–7.73	5.14	3.06	2.85	0.85–2.30	17.46
6	*n*-Pen	69–71[f]	65	6.91–7.71	5.12	3.03	2.82	0.81–2.32	17.80
22	$CH_2CH_2CO_2H$	144–145[g]	60	6.93–7.79	5.14			1.96–2.30	*h*

[a] Intermediates for 3, 4, and 6, respectively, are for 2-alkyl-(5-benzyloxy)-2-carbomethoxy-1-indanone, mp (°C) (benzene/hexane) 66–68, 72–74, and 48–50; for 2-alkyl-5-(benzyloxy)-1-indanone, mp (°C) ($MeOH/H_2O$) 62–64, 55–57, and 69–71. Elemental analyses (C, H) for these synthetic intermediates were within 0.3% of calculated values. [b] Elemental analyses (C, H) were within 0.2% of calculated values. MS (70 eV) exhibited the expected molecular ions for 3, 4, and 6. [c] Overall yield of 3, 4, and 6 from 2-alkyl-5-(benzyloxy)-1-indanones and of 22 from 20. [d] Hertz. [e] Recrystallized from benzene/hexane. [f] Recrystallized from $CHCl_3$/benzene/hexane. [g] Recrystallized from MeOH/benzene/hexane. [h] Singlet for $H_A + H_B$ at δ 2.94.

Table III. Physical and Spectral Data for Hydroxy Acids 12–15



					chemical shift, δ, relative to Me_4Si in $CDCl_3$						
compd[a]	R	mp, °C	rctn time, days	% yield	Ar	$PhCH_2O$	C-1 H	H_A	H_B	aliphatic	J_{AB}[b]
12	Et	124–126[c]	5	80	6.78–7.72	5.13	4.75	2.95	2.44	0.70–2.17	15.26
13	*n*-Pr	125–127[d]	4	95	6.80–7.41	5.05	4.75	2.99	2.44	0.93–2.47	16.2
14	*n*-Bu	145–147[e]	4	85	6.77–7.45	5.03	4.72	2.95	2.43	0.83–2.44	15.89
15	*n*-Pen	143–145[d]	6	85	6.78–7.72	5.04	4.72	2.96	2.44	0.82–2.45	16.21

[a] Elemental analyses (C, H) were within 0.4% of calculated values. [b] Hertz. [c] Recrystallized from $CHCl_3$/benzene/hexane. [d] Recrystallized from MeOH/benzene/hexane. [e] Recrystallized from EtOAc/benzene/hexane.

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5,6-Bis(benzyloxy)-1-hydroxy-2-propyl-2-indanpropionic Acid (2). $NaBH_4$ (0.1 g, 0.0026 mol) was added to a solution of 1[2] (1.0 g, 0.0022 mol) in H_2O (15 mL) containing NaOH (0.1 g, 0.0025 mol). After stirring at room temperature for 20 days (reaction progress followed by TLC), the mixture was acidified with 6 N HCl solution and extracted three times with 30 mL of Et_2O. Following drying (Na_2SO_4) and concentration under reduced pressure, the white solid was recrystallized from benzene/hexane, affording 0.67 g (67%) of white flakes: mp 115–117 °C; ^1H NMR ($CDCl_3$) δ 7.24–7.47 (m, 12 h, Ar), 5.23 (s, 2 H, $PhCH_2O$), 5.15 (s, 2 H, $PhCH_2O$), 5.11 (s, 1 H, C-1 H), 2.93 (d, 1 H, H_A of indan methylene H, J = 17.1 Hz), 2.80 (d, 1 H, H_B of indan methylene H, J = 17.1 Hz), 0.83–2.5 (m, 11 H, aliphatic); 300-MHz ^{13}C NMR ($CDCl_3$) δ 208 (C=O in ketone 1) vs. 82 (COH in 2). Anal. Calcd for ($C_{29}H_{32}O_5$) C, H.

2-Alkyl-5-(benzyloxy)-1-oxo-2-indanpropionic Acids 3, 4, and 6. Keto acids 3, 4, and 6 were synthesized by using methods similar to those employed in the synthesis of keto acid 5[2,6] (Table II).

Sodium Borohydride Reduction of Methyl 5-(Benzyloxy)-2-*n*-butyl-1-oxo-2-indanpropionate (9). To a solution of methyl 5-(benzyloxy)-2-*n*-butyl-1-oxo-2-indanpropionate (9; 1.9 g, 0.005 mol) in MeOH (20 mL) was added with stirring $NaBH_4$ (0.189 g, 0.005 mol) in H_2O (10 mL). The mixture was stirred for 20 h at room temperature, and 10 mL of 1 N NaOH solution was added. The MeOH was removed under reduced pressure, and to the resulting semisolid was added concentrated HCl/H_2O (1:1). The aqueous mixture was extracted with Et_2O, and the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, affording an oil (1.53 g), which was chromatographed on silica gel [$CHCl_3$/*i*-PrOH (96:4)]. Fractions were monitored by TLC [$CHCl_3$/*i*-PrOH (96:4)].

(A) 5-(Benzyloxy)-2-*n*-butyl-1-hydroxy-2-indanpropionic Acid δ-Lactone (17). Compound 17 [0.52 g (30%)] was obtained as colorless crystals, mp 111–113 °C, following solvent removal under reduced pressure and recrystallization from $CHCl_3$/C_6H_6/hexane: IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78–7.44 (m, 8 H, aromatic), 5.38 (s, 1 H, C-1 H), 5.05 (s, 2 H, benzylic), 0.8–2.49 (m, 13 H, aliphatic), calcd for the AB part (indan methylene) (Bruker 300-MHz instrument) δ_A = 2.97, δ_B = 2.88 with J_{AB} = 16.68 Hz; MS (70 eV), *m/e* 350; ^{13}C NMR ($CDCl_3$) δ 172.41 (C=O), 70.36 (indan C-1). Anal. Calcd for ($C_{23}H_{26}O_3$) C, H.

(B) 7-(Benzyloxy)-4a-*n*-butyl-2,3,4,4a,5,9b-hexahydroindeno[1,2-*b*]pyran (18). Compound 18 [0.85 g (50%)] was obtained as colorless crystals, mp 94–95 °C, folowing solvent removal under reduced pressure and recrystallization from C_6H_6/CH_3OH. ^1H NMR (Bruker 300-MHz instrument) ($CDCl_3$) δ 6.8–7.44 (m, 8 H, aromatic), 5.04 (s, 2 H, benzylic), 4.54 (s, 1 H, C-1 H), 3.49–3.69 (m, 2 H, OCH_2), 0.87–1.68 (m, 13 H, aliphatic), calcd for the AB part (indan methylene) δ_A = 2.74 δ_B = 2.56 with J_{AB} = 15.56 Hz; MS (70 eV), *m/e* 336; ^{13}C NMR ($CDCl_3$) δ 70.36 (indan C-1), 63.52 (OCH_2). Anal. ($C_{23}H_{28}O_2$) C, H.

2-Alkyl-5-(benzyloxy)-1-hydroxy-2-indanpropionic Acids (12–15). Keto acids 3–6 (0.003 mol) in H_2O (15 mL) containing NaOH (0.12 g, 0.003 mol) were added to a solution of $NaBH_4$ (0.114 g, 0.003 mol) in aqueous 0.2 N NaOH (1.0 mL). After stirring at room temperature for 4–6 days, the mixture was slowly acidified with dilute HCl solution and extracted with Et_2O. The organic layer was extracted with aqueous 10% $NaHCO_3$ solution and the aqueous layer was acidified and extracted with Et_2O. Following drying (Na_2SO_4) and concentration under reduced pressure hydroxy acids 12–15 were obtained (Table III).

5-(Benzyloxy)-1-oxo-2,2-indandipropionic Acid (22). 5-Benzyloxy-1-indanone (20; 2.38 g; 0.01 mol) was treated with t-BuOK (0.56 g; 0.005 mol) in t-BuOH (20 mL) under N_2 with stirring. Methyl acrylate (1.72 g; 0.02 mol) was added and stirring continued overnight. The mixture was acidified with glacial HOAc, concentrated to a semi-solid under reduced pressure and diluted with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure affording a viscous oil (2.3 g) of dimethyl 5-benzyloxy-1-oxo-2,2-indandipropionate (21) which was not further purified, but hydrolysed to diacid 22 using a 10% NaOH solution [CH_3OH:H_2O (8:2)] (Table II).

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

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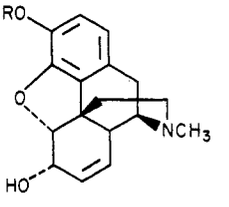
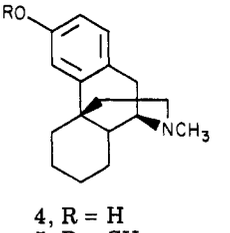
A series of novel *O*-aryl-*N*-methylmorphinans (**7–19**) were synthesized by the Ullmann reaction from levorphanol (**4**) in our search for a synthetic codeine (**2**) substitute with reduced addition liability. The compounds were evaluated for antinociceptive potency and receptor binding affinity. 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

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