Synthesis, Antinociceptive Activity, and Opioid Receptor Profiles of Substituted *trans*-3-(Decahydro- and Octahydro-4a-isoquinolinyl)phenols

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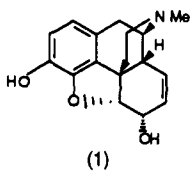
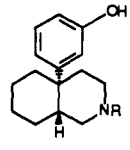
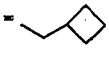
A series of *trans*-3-(6- and 7-substituted-decahydro-4a-isoquinolinyl)phenols and *trans*-3-(octahydro-4a-isoquinolinyl)phenols have been synthesized as potential opioid analgesics. Using a combination of in vitro and in vivo test systems, the receptor profiles of selected compounds have been assessed and in some instances distinguish between μ- and κ-receptor agonists. In general, introduction of a 6-exocyclic methylene group into the *trans*-3-(decahydro-4a-isoquinolinyl)phenol system enhanced both antinociceptive activity and κ-opioid receptor selectivity. For each series, analogues bearing an *N*-cyclopropylmethyl substituent exhibited greater κ-receptor selectivity while *N*-methyl derivatives showed greater μ-receptor selectivity. The 7-substituted compounds (**3b**) were significantly less potent antinociceptive agents than their 6-substituted counterparts (**3a**), the octahydroisoquinoline analogues exhibiting intermediate activity. The axial 8-methyl-6-exocyclic methylene isoquinoline (**20**) is the most potent compound in the mouse abdominal constriction assay (ED_{50} = 0.05 mg/kg sc), whereas the equatorial 8-methyl isomer (**16**) was significantly less potent (ED_{50} = 3.3 mg/kg sc).

Of the numerous substructural analogues of morphine (1) that have been described,[1] *trans*-4a-aryldecahydroisoquinolines (2) represent a relatively recently class to be investigated.[2,3] This series of compounds retain the rigid trans C/D ring system and the axial aromatic moiety of morphine, and a study of Zimmerman et al.[3c] has demonstrated that certain derivatives, e.g. **2a–d**, possess opioid analgesic activity, with this mainly residing in the 4a*R*,8a*R* isomer.

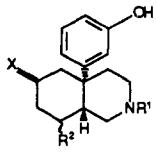


(1)

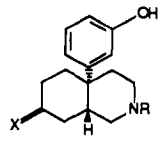


2a; R = Me
b; R = $CH_2CH{=}CH_2$
c; R = 
d; R = 

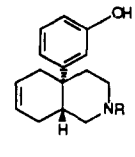
We now report the synthesis and pharmacological activity of a series of novel *trans*-3-(decahydro-4a-isoquinolinyl)phenols (**3a,b**), incorporating substitution of the isoquinoline nucleus at C-6, C-7, and C-8, and a series of *trans*-3-(octahydro-4a-isoquinolinyl)phenols (**4**). These modifications were prompted by the interesting profiles of some morphinan analogues bearing substituents in the C ring.[4] The importance of the nature of the N-substituent of morphinans/benzomorphans in determining opioid receptor subtype interactions is well established and accordingly we have also evaluated this aspect for the presently described classes of compound.



(3a)



(3b)



(4)

It is generally accepted that exogenous and endogenous opioids interact with three distinct subtypes of opioid receptor, designated as κ, μ, and δ receptors.[5] Most clinically used opioid analgesics act via activation of μ receptors and as a consequence also possess undesirable properties; notably they cause constipation, respiratory depression, and physical dependence. It has been argued that analgesics with a prominent κ-agonist component may be safer than the traditional "morphine-like" or μ agonists.[6] Thus, in addition to testing the title compounds for their antinociceptive activity, we have assessed selected compounds for their interaction with κ- and μ-opioid receptors.

Chemistry

***trans*-3-(6-Substituted-decahydro-4a-isoquinolinyl)phenols.** For the synthesis of the phenols **10** and **11a–d** we applied the metalated enamine strategy described by Evans et al.[2a] Annelation of the anion of the tetrahydropyridine **5** with 4-bromo-2-(bromomethyl)-1-

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‡ Department of Neuropharmacology.

(1) Casy, A. F.; Parfitt, R. T. *Opioid Analgesics: Chemistry and Receptors*; Plenum Press: New York, 1986.
(2) (a) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. Application of Metalated Enamines to Alkaloid Synthesis. An Expedient Approach to the Synthesis of Morphine-Based Analgesics. *J. Am. Chem. Soc.* **1980**, *102*, 5955–5956. (b) Moos, W. H.; Gless, R. D.; Rapoport, H. Codeine Analogues. Synthesis of 4a-Aryldecahydroisoquinolines Containing Nitrogen Ring Functionality and of Octahydro-1*H*-indeno[1,2,3-ef]isoquinolines. A Total Synthesis of Codeine. *J. Org. Chem.* **1983**, *48*, 227–238. (c) Handa, S.; Jones, K.; Newton, C. G.; Williams, D. J. A Short, Stereospecific Synthesis of a Morphine Fragment via an Intramolecular Diels–Alder Reaction. *J. Chem. Soc., Chem. Commun.* **1985**, 1362–1363.
(3) (a) Zimmerman, D. M.; Marshall, W. S. 2-Cycloalkylmethyl-4a-(substituted phenyl)decahydroisoquinolines. U.S. Patent 4 029 796, 1975. (b) Britetelli, D. R.; Ripka, W. C. 4a-Aryltrans-Decahydroisoquinolines. U.S. Patent 4 419 517, 1983. (c) Zimmerman, D. M.; Cantrell, B. E.; Swartzendruber, J. K.; Jones, N. D.; Mendelsohn, L. G.; Leander, J. D.; Nickander, R. C. Synthesis and Analgesic Properties of N-Substituted trans-4a-Aryldecahydroisoquinolines. *J. Med. Chem.* **1988**, *31*, 555–560. (d) Cantrell, B. E.; Paschal, J. W.; Zimmerman, D. M. An Efficient Synthesis of the 4a-Aryl-6-oxodecahydroisoquinolines. *J. Org. Chem.* **1989**, *54*, 1442–5.
(4) See ref 1, Chapter 3, p 146.
(5) For reviews, see: Martin, W. R. Pharmacology of Opioids. *Pharmacol. Rev.* **1983**, *35*, 283–323. Paterson, S. J.; Robson, L. E.; Kosterlitz, H. W. Classification of Opioid Receptors. *Br. Med. Bull.* **1983**, *39*, 31–36. Zukin, R. S.; Zukin, S. R. The Case For Multiple Opiate Receptors. *Trends Neurosci.* **1986**, *7*, 160–164.
(6) Cowan, A.; Gmerek, D. E. In-vivo Studies on Kappa Opioid Receptors. *Trends Pharmacol. Sci.* **1986**, *7*, 69–72.

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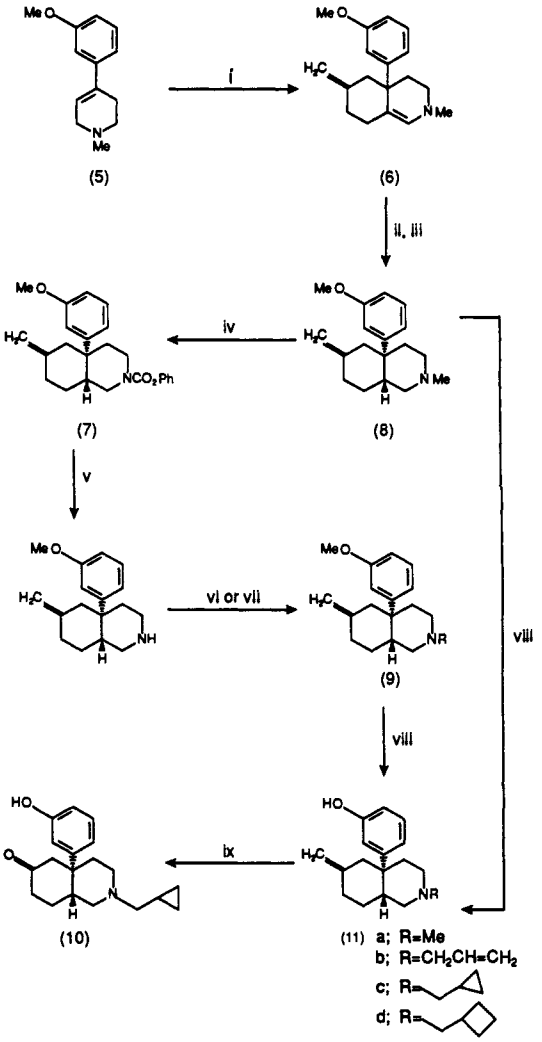
Scheme I[a]

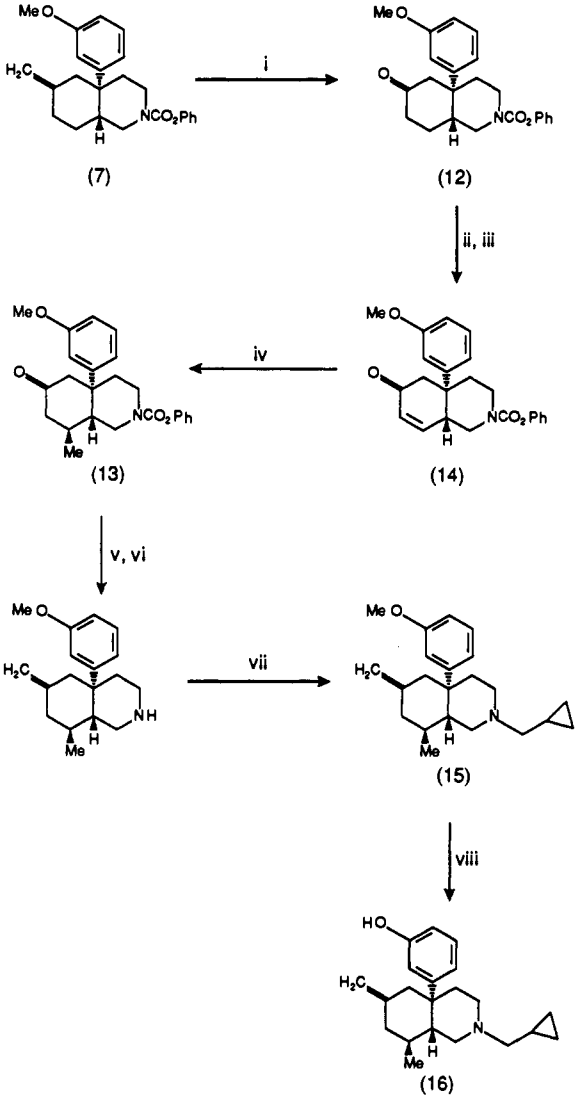


[a] (i) nBuLi, $BrCH_2CH(=CH_2)CH_2CH_2Br$, then NaI, K_2CO_3, CH_3CN, Δ; (ii) $MeSO_3H$, MeOH, −60 °C; (iii) $NaBH_4$; (iv) $ClCO_2Ph$, iPr_2NEt; (v) KOH, EtOH; (vi) alkylation; (vii) acylation, then $LiAlH_4$; (viii) LiSMe, (ix) OsO_4, $NaIO_4$.

butene[7] gave the bicyclic enamine **6**. Formation of the kinetic iminium salt with methanesulfonic acid at −50 °C, and subsequent sodium borohydride reduction gave exclusively the required *trans*-decahydroisoquinoline **8** in a 64% yield. The trans geometry of the ring fusion was assigned on the basis of NOE difference experiments: irradiation of the aromatic signal at δ 7.18 (2′-Ar-H) gave enhancements for 1α-, 4α-, and 5α-H. The trans relationship of 1α-H[8] and 8aβ-H was established by the axial–axial coupling of the 1α-H signal (δ 2.58, J = 11 Hz).

Alternative nitrogen substituents were introduced via N-demethylation of **8** using phenyl chloroformate, followed by hydrolysis of the resultant carbamate group and subsequent N-alkylation. O-Demethylation then provided the target phenols (**11a–d**). An exception was **9d**, which was prepared via acylation and reduction of the resultant amide. Subsequent oxidative cleavage of the *exo*-methylene function of **11c** using osmium tetraoxide and sodium periodate gave ketone **10** (Scheme I).

Scheme II[a]



[a] (i) OsO_4, $NaIO_4$; (ii) PhSeCl; (iii) H_2O_2; (iv) Me_2CuLi; (v) $TiCl_4$, CH_2Br_2, Zn; (vi) KOH, EtOH; (vii) $BrCH_2cC_3H_5$; (viii) LiSMe.

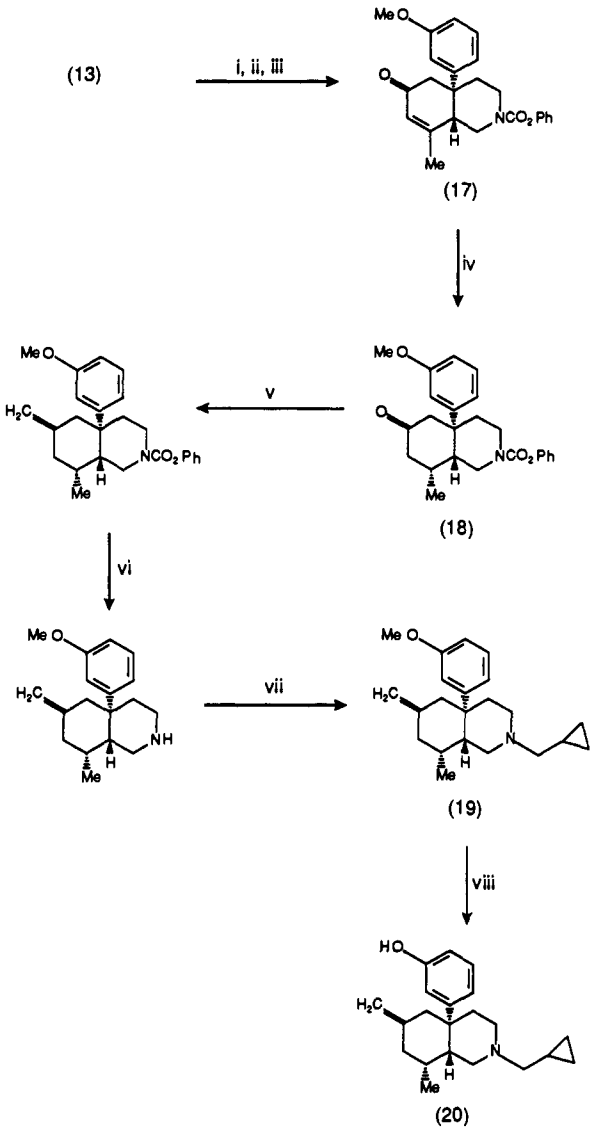
***trans*-3-(8-Methyl-6-substituted-decahydro-4a-isoquinolinyl)phenols.** An 8β-methyl group was introduced through further manipulation of carbamate **7** (Scheme II). Thus, treatment of ketone **12**, prepared via oxidative cleavage of **7**, with benzeneselenyl chloride and elimination of the subsequently generated selenoxide gave the α,β-unsaturated ketone **14**. Treatment of the latter with lithium dimethylcuprate exclusively afforded the required 8β-methyl derivative **13** in high yield. Conversion of **13** to the *N*-cyclopropylmethyl analogue **16** was achieved as described above. The orientation of the 8-methyl group was determined from the ^1H NMR spectrum of the isoquinoline **15**: decoupling the C-8 methyl signal reveals H-8 (δ 2.37) as a doublet of triplets (J = 4.6, 11.6, and 11.6 Hz), the two axial–axial couplings only being consistent with an equatorial methyl substituent.

The 8α-methyl analogue **20** was prepared from the 8β-methyl derivative **13** via selenation and then oxidative elimination to give the α,β-unsaturated ketone **17**. Hydrogenation of **17** from the less hindered β face afforded the 8α-methyl ketone **18** with good stereoselectivity (98:2). Methylenation of ketone **18** and hydrolysis of the carbamate, followed by N-cyclopropylmethylation and O-demethylation, provided the desired phenol (**20**) (Scheme III). The stereochemistry of the 8α-methyl group was

(7) Evans, D. A.; Mitch, C. H. Studies Directed Towards the Total Synthesis of Morphine Alkaloids. *Tetrahedron Lett.* **1982**, *23*, 285–288.

(8) Substitutive nomenclature: The α-side of the reference plane is that side on which the preferred substituent (by sequence rules) lies at the lowest numbered stereogenic position.

Scheme III[a]



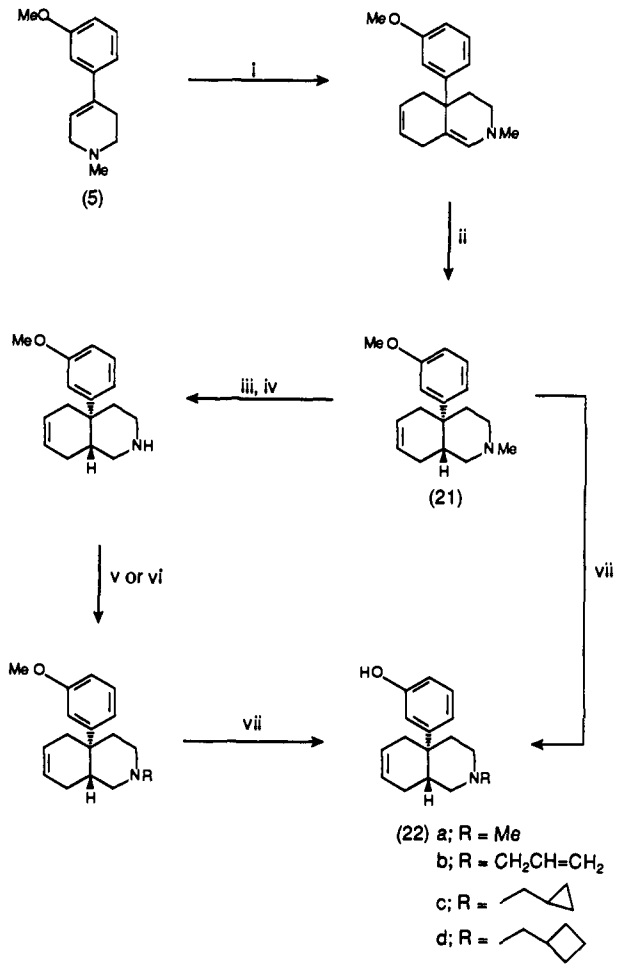
[a] (i) PhSeCl; (ii) O_3; (iii) Et_3N; (iv) H_2, Pd; (v) $TiCl_4$, CH_2Br, Zn; (vi) KOH; (vii) $BrCH_2cC_3H_5$; (viii) LiSMe.

confirmed by a double resonance difference experiment[9] on **19** for H-8 with $\sum J(J_{7\alpha 8} + J_{7\beta 8} + J_{8a\beta 8} + 3.J8\text{-Me})$ equal to 34 Hz. Allowing for J8-Me, then $\sum J$ vicinals is 11.2 Hz. This indicates that the methyl group is in the axial α position. Two axial–axial couplings of 11–13 Hz each would have been expected, and indeed are observed, for the 8β-methyl analogue (**15**), i.e. $\sum J$ vicinal > 20 Hz (see above).

3-(1,2,3,4,4a,7,8,8a-Octahydro-4a-isoquinolinyl)-phenols. Entry into the 3-(octahydro-4a-isoquinolinyl)-phenol series (**22a–d**) was achieved via annelation of the anion of the tetrahydropyridine **5** with *cis*-1,4-dichlorobutene (Scheme IV). As described above, reduction of the kinetic iminium salt, generated with methanesulfonic acid at –60 °C, by sodium borohydride gave predominantly the *trans*-4a-aryloctahydroisoquinoline (**21**; 15:1 trans:cis). The trans geometry of the ring fusion of the major component was confirmed on the basis of NOE difference experiments: irradiation of the aromatic signals at δ 7.0–7.1 (2′,6′-Ar-H)

(9) Feeney, J.; Partington, P. Pseudo INDOR Nuclear Magnetic Resonance Spectra Using Double Resonance Difference Spectroscopy and the Fourier Transform Technique. *J. Chem. Soc., Chem. Commun.* **1973**, 611–614.

Scheme IV[a]



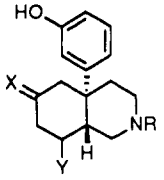
[a] (i) BuLi, $ClCH_2CH{=}CHCH_2Cl$, NaBr, Δ; (ii) $MeSO_3H$, MeOH, –60 °C, $NaBH_4$; (iii) $ClCO_2CH{=}CH_2$, K_2CO_3; (iv) MeOH, HCl; (v) alkylation; (vi) acylation, $LiAlH_4$; (vii) MeSLi.

gave enhancements for 1α-, 3α-, 4α-, and 8α-H. The 1α-H signal (δ 2.54, J = 11 and 11 Hz) shows axial–axial coupling to 8aβ-H, confirming that the aromatic group and 8aβ-H are trans.

To obtain the requisite phenols (**22a–d**) for biological testing, N-demethylation, alkylation (or acylation and then reduction in the case of the *N*-cyclobutylmethyl derivative (**22d**)), and O-demethylation were carried out in a manner analogous to that described above (Scheme I).

***trans*-3-(7-Substituted-decahydro-4a-isoquinolinyl)phenols.** The observation that the hydroxyselenation of the octahydroisoquinoline **23a** gave the 4a-aryl-6-(phenylselenyl)-7-hydroxy derivative (**24a**) allowed convenient entry into the 7-substituted isoquinolinyl series (Scheme V). The stereochemistry was assigned on the basis of ^{1}H NMR spectral data of **24a**. Thus, the signals for H-6 (δ 3.45, J vicinals < 3 Hz) and H-7 (δ 4.12, J vicinals < 3 Hz) reveals the lack of axial–axial coupling, indicating the phenylselenyl and hydroxyl groups are diaxial. The phenylselenyl group was assigned to the 6-position on the basis of spectral data of the allylic alcohol **25** which was obtained after oxidative elimination on **24a**. The lack of vicinal coupling to H-5 (δ 5.92) indicates the double bond is in the 5,6-position. The β configuration of hydroxyl is indicated by a small vicinal coupling of the H-7 (δ 4.03, J < 3 Hz). Subsequent O-demethylation of **25** gave the phenol **26**, whereas deselenation of **24a** with Raney nickel afforded alcohol **27a**. For the cyclobutylmethyl analogue, alcohol **27b** was prepared in a similar

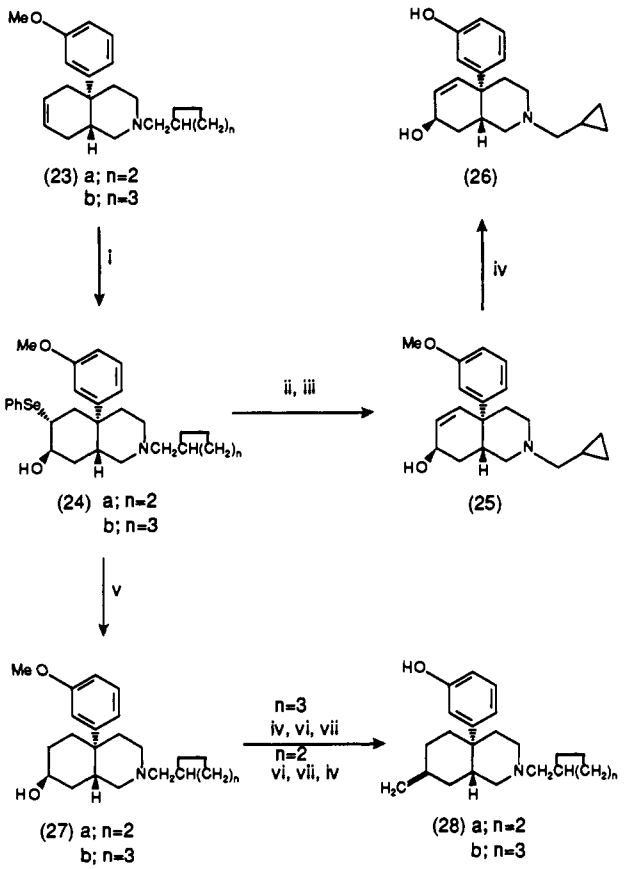
Table I. Antinociceptive Activity and in Vitro Activity of 6-Substituted *trans*-4a-Aryldecahydroisoquinolines



no.	R	X	Y	mouse abdominal contriction: ED_{50}, mg/kg sc	rabbit vas deferens: pK_B,[d] ν EKC	guinea pig ileum: IC_{50}, M	guinea pig ileum: β-FNA[e]	guinea pig ileum: β-CNA[f]
2c	CH_2-c-C_3H_5	H_2	H	1.09 (0.44–2.74)	24% inhibition 10^{-6} M[a]	1.5×10^{-7} (0.6–2.5)	2.8, 3.0	16.9 (10–23)
11a	CH_3	CH_2=	H	0.18 (0.09–2.36)	5.9, 6.1	6×10^{-8} (2–10)	22 (11–30)	2.7 (1.5–6.9)
11b	$CH_2CH{=}CH_2$	CH_2=	H	0.55 (0.32–0.82)	5.5, 6.1	1.4×10^{-7} (0.5–2.3)	3.3[b] (1.9–7.2)	29 (19–39)
11c	CH_2-c-C_3H_5	CH_2=	H	0.17 (0.1–0.29)	6.3, 7.1	1.5×10^{-8} (0.8–2.2)	1.7 (1.0–2.4)	>100
11d	CH_2-c-C_4H_7	CH_2=	H	0.23 (0.16–0.33)	5.3, 5.7	NT	NT	NT
10	CH_2-c-C_3H_5	O=	H	1.6 (1.0–2.6)	6.1, 6.7	1.2×10^{-7} (0.6–1.8)	1.4 (0.9–2.1)	15[c] (10–20)
16	CH_2-c-C_3H_5	CH_2=	━ Me	3.3 (2.1–5.4)	4.8[h]	NT	NT	NT
20	CH_2-c-C_3H_5	CH_2=	···· Me	0.05 (0.03–0.08)	$IC_{50} = 2.8 \times 10^{-5}$ M (0.9–48)[a]	NT	NT	NT
	EKC			0.08 (0.04–0.15)	$IC_{50} = 5.9 \times 10^{-8}$ M (3–9)[a]	5×10^{-10} (1–9)	3.1 (2.5–3.7)	28.5 (21–36)
	DAMGO			NT	NT	1.4×10^{-8} (0.6–2.2)	30 (21–39)	2.5 (2–3)
	morphine			0.47 (0.34–0.6)	NT	2.8×10^{-8} (2–3.6)	45 (35–55)	7.5 (5–10)

[a] Agonist activity. [b] 16-methylcyprenorphine 10^{-7} M, 30-min pretreatment. [c] Nonparallel shift 24% (17–30) depression of maximum of dose–response curve. [d] pK_B is antagonist affinity constant = log (dose ratio − 1) − log [antagonist]. [e] Dose ratio IC_{50} after β-FNA 10^{-6} M, 30-min pretreatment ÷ IC_{50} before β-FNA treatment. [f] Dose ratio IC_{50} after β-CNA 10^{-7} M, 15-min pretreatment in presence of DAMGO + IC_{50} before β-CNA/DAMGO treatment 10^{-5} M. NT = not tested. [g] Values in parentheses are 95% confidence limits; alternatively if only two determinations were made, then both values are given. [h] Only one determination. All compounds are racemic.

Scheme V[a]



[a] (i) PhthalSeCl, H_2O, CH_3CN; (ii) $NaIO_4$; (iii) Et_3N, $CHCl_3$; (iv) LiSMe; (v) RaNi; (vi) DMSO, ClCOCOCl, Et_3N; (vii) $Ph_3P^+MeBr^-$, tBuOK.

manner, and O-demethylation of **27b** followed by oxidation and methylenation gave the exocyclic olefin **28b**. Finally the cyclopropylmethyl analogue **28a** was prepared via an alternative order from **27a** by oxidation, subsequent methylenation, and O-demethylation.

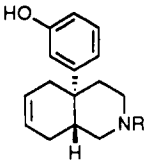
Pharmacology

The phenols **2c**, **10**, **11a–d**, **22a–d**, **26**, **28a,b**, **29a,b**, and **30a,b** were tested in vivo for antinociceptive activity using the mouse acetylcholine-induced abdominal constriction test.[10] Only compounds with significant antinociceptive activity were evaluated in the rabbit vas deferens (LVD) preparation, which contains only κ opioid receptors.[11] However, this tissue only detects agonists of high efficacy, whereas κ partial agonists, which have insufficient efficacy to produce agonist effects, behave as antagonists.[12]

In vitro assessment of the μ/κ opioid selectivity in the guinea pig ileum (GPI) preparation was made by comparing the dose ratios of the title compounds after either μ- or κ-receptor blockade. Blockade at μ receptors was produced by the irreversible opioid antagonist β-funaltrexamine (β-FNA).[13] An effective κ-receptor blockade was produced using the nonselective irreversible antagonist β-chlornaltrexamine (β-CNA),[14] with concomitant μ-receptor protection using the selective μ agonist [D-Ala^2,MePhe^4,Gly(ol)^5] enkephalin (DAMGO).[15] Agonists

(10) Collier, H. O. J.; Dinneen, L. C.; Johnson, C. A.; Schneider, C. The Abdominal Constriction Response and its Suppression by Analgesic Drugs in the Mouse. *Br. J. Pharmacol. Chemother.* **1968**, *32*, 295–310.
(11) Oka, T.; Negishi, K.; Suda, M.; Matsumiya, T.; Inazu, T.; Ueki, M. Rabbit Vas Deferens: A Specific Bioassay for Opioid κ-Receptor Agonists. *Eur. J. Pharmacol.* **1980**, *73*, 235–236.
(12) Hayes, A. G.; Kelly, A. Profile of Activity of κ-Receptor Agonists in the Rabbit Vas Deferens. *Eur. J. Pharmacol.* **1985**, *110*, 317–322.
(13) Portoghese, P. S.; Larson, D. L.; Sayre, L. M.; Fries, D. S. A Novel Opioid Receptor Site Directed Alkylating Agent with Irreversible Narcotic Antagonistic and Reversible Agonistic Activity. *J. Med. Chem.* **1980**, *23*, 233–234.
(14) Portoghese, P. S.; Larson, D. L.; Jiang, J. B.; Takemori, A. E.; Caruso, T. P. 6β-[*N*,*N*-Bis(2-chloroethyl)amino]-17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan (Chlornaltrexamine), a Potent Opioid Receptor Alkylating Agent with Ultralong Narcotic Antagonist Activity. *J. Med. Chem.* **1978**, *21*, 598–600.
(15) Kosterlitz, H. W.; Paterson, S. J.; Robson, L. E. Characterization of the κ-Subtype of the Opiate Receptor in the Guinea-Pig Brain. *Br. J. Pharmacol.* **1981**, *73*, 939–949.

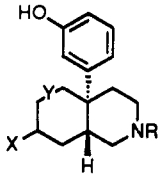
Table II. Antinociceptive Activity and in Vitro Activity of *trans*-4a-Aryloctahydroisoquinolines



no.	R	mouse abdominal constriction: ED_{50}, mg/kg sc	rabbit vas deferens: pK_B,[b] ν EKC	guinea pig ileum: IC_{50}, M	guinea pig ileum: β-FNA[c]	guinea pig ileum: β-CNA[d]
22a	CH_3	0.5 (0.3–0.8)	5.4, 5.4	1.3×10^{-7} (0.1–1.9)	>30	NT
22b	$CH_2CH{=}CH_2$	1.91 (0.8–4.6)	5.6, 6.2	NT	NT	NT
22c	CH_2-c-C_3H_5	0.53 (0.26–0.98)	$IC_{50} = 4.9 \times 10^{-7}$ M (3–6.8)[a]	9×10^{-8} (5–13)	2.3 (2–2.6)	>100
22d	CH_2-c-C_4H_7	0.39 (0.05–0.78)	5.7, 6.1	6×10^{-8} (3–9)	14.7 (10–18)	NT

[a] Agonist activity E_{max} 63% (53, 73%). [b] See footnote *d*, Table I. [c] See footnote *e*, Table I. [d] See footnote *f*, Table I. See also footnote *g*, Table I. NT = not tested. All compounds are racemic.

Table III. Antinociceptive Activity and in Vitro Activity of 7-Substituted *trans*-4a-Aryloctahydro and -decahydroisoquinolines



no.	R	X	Y	mouse abdominal constriction: ED_{50}, mg/kg sc	rabbit vas deferens: pK_B,[a] ν EKC
26	CH_2-c-C_3H_5	HO—	double bond	>10	5.6, 6.0
28a	CH_2-c-C_3H_5	CH_2=	single bond	1.3 (0.8–2.0)	5.8, 6.0
28b	CH_2-c-C_4H_7	CH_2=	single bond	1.06 (0.37–2.3)	5.3, 5.9
29a	CH_2-c-C_3H_5	O=	single bond	>10	NT
29b	CH_2-c-C_4H_7	O=	single bond	>10	NT
30a	CH_2-c-C_3H_5	HO—	single bond	>10	NT
30b	CH_2-c-C_4H_7	HO—	single bond	>10	NT

[a] See footnote *d*, Table I; see also footnote *g*, Table I. [b] NT = not tested. All compounds are racemic.

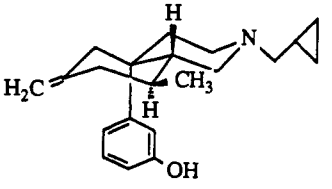
which are μ-selective show large β-FNA dose ratios and small β-CNA dose ratios; those which are κ-selective display the opposite profile.[16]

Results and Discussion

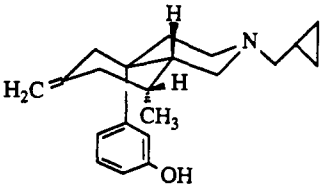
The title compounds displayed a range of antinociceptive activity with the 6-substituted series (**10**, **11a–d**) possessing greater antinociceptive activity than the corresponding 7-substituted analogues (**26**, **28a,b**, **29a,b**, **30a,b**) and (octahydroisoquinolinyl)phenols (**22a–d**). Introduction of a 6-exocyclic methylene group (**11c**) enhanced antinociceptive activity by 6-fold over the corresponding unsubstituted compound (**2c**).

Varying the nature of the nitrogen substituent had a significant effect on the in vitro opioid receptor profile. In the 6-exocyclic methylene decahydro series the *N*-cyclopropylmethyl analogue **11c** was the most selective κ agonist, as evidenced by the large β-CNA and small β-FNA ratios in the GPI preparation (Table I). In contrast, the *N*-methyl derivative **11a** showed a large shift of the dose–response curve in the GPI assay in the presence of β-FNA, indicating predominant μ-receptor activity. The corresponding *N*-allyl analogue **11b** was nonselective. A similar in vitro profile is observed in the octahydroisoquinolinyl series (Table II) with the *N*-cyclopropylmethyl derivative **22c** being the most κ-selective analogue of that series. The generally low level of antinociceptive activity of the 7-substituted series (Table III) did not warrant a detailed in vitro characterization.

Scheme VI



(16)



(20)

Examination of the in vivo and in vitro activities of the 6-substituted series (Table I) indicates that the 6-exocyclic methylene derivative (**11c**) is more active as an antinociceptive agent and is a more selective κ agonist than either the corresponding ketone **10** or the unsubstituted decahydroisoquinoline **2c**. Further analysis of the in vivo activity of **11c** revealed there were few of the typical μ-opioid-related effects associated with this compound. Thus, there was no significant effect in the mouse on respiratory depression, sedation, and body temperature at doses up to 30 mg/kg sc. In the rat, **11c** caused diuresis in the dose range 2–32 mg/kg sc, further indicating the prominant κ-agonist profile of this compound.[17]

(16) (a) Hayes, A. G.; Sheehan, M. J.; Tyers, M. B. Determination of the Receptor Selectivity of Opioid Agonist in the Guinea-Pig Ileum and Mouse Vas Deferens by use of β-Funaltrexamine. *Br. J. Pharmacol.* **1985**, *86*, 899–904. (b) Sheehan, M. J.; Hayes, A. G.; Tyers, M. B. Irreversible Selective Blockade of κ-Opioid Receptors in the Guinea-Pig Ileum. *Eur. J. Pharmacol.* **1986**, *129*, 19–24.

(17) Leander, J. D. A Kappa-Opioid Effect: Increased Urination in the Rat. *J. Pharmacol. Exp. Ther.* **1983**, *244*, 89–94. *Ibid.* Further Study of Kappa-Opioids on Increased Urination **1983**, *227*, 35–41.

Some intriguing changes in activity were observed upon introduction of a methyl group at C-8 of the isoquinoline system. The equatorial 8-methyl derivative **16** showed a marked fall in antinociceptive potency, whereas the axial 8-methyl derivative **20** showed a significant increase in activity over its unsubstituted counterpart (**11c**) (Scheme VI). A similar effect on activity has been observed previously[18] in methyl-substituted (pyrano[3,4-*c*]pyridin-4-yl)phenols. The increased antinociceptive activity of **20** may be due to steric repulsion between the axial methyl and phenol moiety placing the latter in a more favorable conformation for binding at the receptor.

Conclusion

The antinociceptive activities and opioid receptor profiles of the title compounds are sensitive both to substitution in the carbocyclic ring and to the nature of the nitrogen substituent. For example, in comparing **2c** and **11c** introduction of a 6-exocyclic methylene group into the *trans*-3-(decahydro-4a-isoquinolinyl)phenol system enhances antinociceptive potency and κ-receptor selectivity. 7-Substituted compounds are significantly less potent analgesics than their 6-substituted counterparts, the octahydroisoquinoline analogues exhibiting intermediate activity. Where examined, analogues bearing an *N*-cyclopropylmethyl substituent demonstrate greater κ-receptor selectivity, whereas *N*-methyl derivatives show greater μ-receptor selectivity.

Experimental Section

^{1}H NMR spectra were measured ($SiMe_4$ internal standard) on a Bruker WM250 (250 MHz) spectrometer. Mass spectra data were obtained using a VG 7070E instrument interfaced to an 11-250 data system. Only the critical assignments and coupling constants are given.

Spectroscopic and microanalytical data were obtained by Glaxo Chemical Analysis Department. All melting points are uncorrected.

Column chromatography was performed using either Merck Kieselgel 60 (Art. 9385) or alumina VG1 (Phase Separations Ltd.).

2,3,4,4a,5,6,7,8-Octahydro-4a-(3-methoxyphenyl)-2-methyl-6-methyleneisoquinoline (6). *n*-BuLi (1.6 M solution in hexane; 15.7 mL, 25 mmol) was added dropwise to a stirred solution of 4-(3-methoxyphenyl)-1-methyl-1,2,5,6-tetrahydropyridine (**5**) (5.1 g, 25 mmol) in dry THF (200 mL) at −20 °C under nitrogen. The resulting dark red reaction mixture was stirred for 10 min at −20 °C before cooling to −70 °C and transferring, over 20 min via a double-ended needle, to a stirred solution of 4-bromo-2-(bromomethyl)-1-butene (12.0 g, 53 mmol, ca. 70% pure) in dry THF (50 mL) at −70 °C under nitrogen. The resulting solution was allowed to warm to −40 °C over 45 min before quenching with brine (100 mL).

The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL). The combined organic fractions were extracted with 1 M HCl (2 × 100 mL), and the acidic extracts were washed with Et_2O (2 × 200 mL) before being basified to pH 14 with 2 M aqueous NaOH (ca. 130 mL). The resulting basic solution was extracted with Et_2O (3 × 150 mL), and these extracts were dried ($MgSO_4$) and concentrated in vacuo. CH_3CN (200 mL) was added to the residue, and the resulting solution was concentrated in vacuo.

A mixture of the residue, NaI (15 g), and K_2CO_3 (15 g) in dry CH_3CN (200 mL) was heated at reflux in the dark under nitrogen for 4 h, cooled, and concentrated in vacuo. The residue was partitioned between 1 M aqueous NaOH (100 mL) and Et_2O (100 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to give a brown oil (4.5 g). This crude product was purified by chromatography on alumina, eluted with Et_2O to give the title compound (1.95 g, 29.5%) as a white solid: mp 48–52 °C; ^{1}H NMR ($CDCl_3$) δ 1.8–2.0 (7 H, m's, 4α,4β,5β,7α,7β,8α,8β), 2.49 (1 H, dt, 3α), 2.59 (3 H, s, *N*-Me), 2.66 (1 H, dt, 3β), 3.08 (1 H, d, 5α), 3.79 (3 H, s, *O*-Me), 4.53 and 4.56 (2 H, 2 × s, C=CH_2), 5.93 (1 H, s, C*H*), 6.70–7.23 (4 H, m, aromatic). Anal. ($C_{18}H_{23}NO$) C, H, N.

Caution is recommended in the use of **5**, which has been shown to possess neurotoxic properties. It is suggested that the *N*-ethyl derivative, which is less neurotoxic, now be employed in place of **5**.[3c]

Similarly prepared from **5** and *cis*-1,4-dichlorobutane was **2,3,4,4a,5,8-hexahydro-4a-(3-methoxyphenyl)-2-methylisoquinoline**, isolated as an oil in a 24% yield. Anal. ($C_{17}H_{21}NO$) C, H, N.

***trans*-Decahydro-4a-(3-methoxyphenyl)-2-methyl-6-methyleneisoquinoline (8).** A solution of 2,3,4,4a,5,6,7,8-octahydro-4a-(3-methoxyphenyl)-2-methyl-6-methyleneisoquinoline (**6**) (281 mg, 1.04 mmol) in MeOH (10 mL) was cooled to −60 °C with stirring under nitrogen. To the resulting suspension was added a solution of $MeSO_3H$ (120 mg, 1.3 mmol) in MeOH (2 mL) over 1 min. The resulting solution was warmed to 25 °C over 5 min before addition of $NaBH_4$ (450 mg, 12 mmol) in four portions over 1 min. After stirring for 30 min at room temperature, NH_3 (0.88; 10 mL) was added and the MeOH was removed in vacuo. The residue was partitioned between 2 M HCl and Et_2O (50 mL). The aqueous layer was basified to pH 14 with 10 M aqueous NaOH and then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil (280 mg). This crude product was purified by column chromatography on silica using CH_2Cl_2/MeOH/NH_3 95:4:1 as eluant to give the title compound (240 mg, 83%) as a colorless oil: ^{1}H NMR (C_6D_6) δ 1.38 (1 H, m, 8β), 1.78 (1 H, m, 4β), 1.88 and 1.93 (2 H, m's, 3α and 4α), 1.98 (1 H, br d, J = 12.8 Hz, 5β), 2.0–2.15 (3 H, m, 7β, 8α, 8aβ), 2.12 (3 H, s, *N*-Me), 2.23 (1 H, m, 7α), 2.45 (1 H, m, 3β), 2.52 (1 H, dd, J = 3, 11.6 Hz, 1β), 2.58 (1 H, t, J = 11.6, 11.6 Hz, 1α), 2.65 (1 H, dd, J = 1.5, 12.8 Hz, 5α), 4.38 and 4.52 (2 H, =CH_2) and 6.5–7.2 (4 H, m, aromatics).

Similarly prepared from the corresponding enamine was ***trans*-1,2,3,4,4a,5,8,8a-octahydro-4a-(3-methoxyphenyl)-2-methylisoquinoline (21)** (61%): mp 72–3 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (1 H, ddd, 4β), 2.00 (1 H, ddd, 3α), 2.1–2.25 (1 H, m, 4α), 2.3–2.55 (4 H, m's, 5β, 8α, 8β, 8aβ), 2.28 (3 H, s, *N*-Me), 2.48 (1 H, dd, 5α), 2.54 (1 H, t, J = 11, 11 Hz, 1α), 2.64 (1 H, m, 3β), 2.76 (1 H, m, 1β), 5.5–5.6 (1 H, m, 7-H), 5.63–5.72 (1 H, m, 6-H), 6.7–7.2 (4 H, m, aromatics). Anal. ($C_{17}H_{23}NO$) C, H, N.

***trans*-Phenyl Octahydro-4a-(3-methoxyphenyl)-6-methylene-2(1*H*)-isoquinolinecarboxylate (7).** A mixture of phenyl chloroformate (3.4 mL, 27.1 mmol) (**8**) (2.93 g, 10.8 mmol) and diisopropylethylamine (0.92 mL, 10.8 mmol) in $ClCH_2CH_2Cl$ (43 mL) was heated at reflux for 1.5 h. The cooled mixture was diluted with Et_2O (300 mL) and washed sequentially with HCl (1 M, 70 mL), NaOH (0.5 M; 140 mL), and water (70 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was filtered through alumina to give the title compound as a colorless oil (3.56 g, 88%). Anal. ($C_{24}H_{27}NO_3 \cdot 0.5H_2O$) C, H, N.

Similarly prepared from the corresponding amine (**21**), K_2CO_3, and vinyl chloroformate was ***trans*-ethenyl 3,4,4a,5,8,8a-hexahydro-4a-(3-methoxyphenyl)-2(1*H*)-isoquinolinecarboxylate** in a 95% yield isolated as an amber gum. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

***trans*-Decahydro-4a-(3-methoxyphenyl)-6-methyleneisoquinoline.** A mixture of 7 (2.98 g, 7.89 mmol), KOH (50% w/v aq; 50 mL), and EtOH (200 mL) was heated under reflux for 17 h. The solvent was evaporated in vacuo, and the residue was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 150

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(20) 16-Methylcyprenorphine (RX8008M) was used in place of β-FNA; see: Smith, C. F. C. 16-Me Cyprenorphine (RX8008M): A potent opioid Antagonist with some δ selectivity. *Life Sci.* **1987**, *40*, 267–274.

mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in HCl (1 M; 20 mL) and washed with Et_2O (3 × 10 mL). The aqueous solution was basified with NaOH (5 M; 5 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the title compound as a yellow oil (1.51 g; 74%). Anal. ($C_{17}H_{23}NO$) C, H, N.

Similarly prepared from the corresponding carbamate was **(4aα,8α,8aβ)-decahydro-4a-(3-methoxyphenyl)-8-methyl-6-methyleneisoquinoline** in an 85% yield and isolated as a colorless gum [anal. ($C_{18}H_{25}NO·0.5H_2O$) C, H, N] and **(4aα,8β,8aβ)-decahydro-4a-(3-methoxyphenyl)-8-methyl-6-methyleneisoquinoline** in a 95% yield and isolated as a brown oil [anal. ($C_{18}H_{25}NO$) C, H, N].

***trans*-1,2,3,4,4a,5,8,8a-Octahydro-4a-(3-methoxyphenyl)-isoquinoline.** A mixture of *trans*-ethenyl 3,4,4a,5,8,8a-hexahydro-4a-(3-methoxyphenyl)-2(1*H*)-isoquinolinecarboxylate (10.5 g, 0.0335 mol) and HCl in MeOH (0.35 M; 300 mL) was heated at reflux for 6 h. The solvent was removed in vacuo, and the residue was dissolved in HCl (0.2 M; 250 mL) and washed with Et_2O (2 × 150 mL). The aqueous solution was basified with NaOH (2 M; 50 mL), and the product was extracted with CH_2Cl_2 (400 mL). The organic extract was dried and evaporated to afford an oil (7.42 g; 91%), which was characterized as the HCl salt isolated from Et_2O: mp 213–4 °C. Anal. ($C_{16}H_{21}NO·HCl$) C, H, N.

***trans*-2-(Cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-6-methyleneisoquinoline (9c).** A mixture of cyclopropylmethyl bromide (0.578 g, 4.0 mmol), *trans*-decahydro-4a-(3-methoxyphenyl)-6-methyleneisoquinoline (1 g, 3.89 mmol), and $NaHCO_3$ (0.82 g, 9.73 mmol) in dry DMF (7 mL) was heated at 150 °C for 4 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography using EtOAc/C_6H_{14} 1:1 as eluant to give the title compound as a yellow oil (0.66 g; 54%). Anal. ($C_{21}H_{29}NO$) C, H, N.

Similarly prepared was **(4aα,8β,8aβ)-2-(cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-8-methyl-6-methyleneisoquinoline (15)** from the corresponding amine and isolated as a maleate salt: mp 142–3 °C; 70% yield; ^1H NMR (C_6D_6) (freebase) δ 0.88 (3 H, d, J = 6.4 Hz, C-8-CH_3), 1.72 (1 H, br t, J = 11.6, 13.1 Hz, 7β), 1.87 (1 H, dt, J = 4.0, 11.6, 11.6 Hz, 8aβ), 1.85–2.0 (3 H, m, 3α, 4α, and 4β), 2.07 (1 H, br d, 12.8 Hz, 5β), 2.23 (1 H, ddd, J = 1.8, 4.6, 13.1 Hz, 7α), 2.37 (1 H, m, J = 4.6, 11.6, 11.6, 3 × 6.4 Hz, 8α), 2.64 (1 H, t, J = 11.6, 11.6 Hz, 1α), 2.69 (1 H, dd, J = 1.8, 12.8 Hz, 5α), 2.8 (1 H, m, H 3β), 3.18 (1 H, ddd, J = 1.0, 4.0, 11.4 Hz, 1β). Anal. ($C_{22}H_{31}NO·C_4H_4O_4$) C, H, N.

(4aα,8α,8aβ)-2-(Cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-8-methyl-6-methyleneisoquinoline (19) was also prepared from the corresponding amine and (bromomethyl)cyclopropane and isolated in a 45% yield as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 7.6 Hz, C-8-CH_3), 1.72 (1 H, dt, J = 2.9, 2.9, 13.2 Hz, 4α), 1.85 (1 H, dt, J = 3.9, 12.2, 13.2 Hz, 4β), 2.00 (1 H, dt, J = 1.7, 1.7, 13.2 Hz, 7α), 2.07 (1 H, br d, J = 13.2 Hz, 5β), ca. 2.14 (1 H, m, hidden, 8β), 2.18 (1 H, dt, J = 2.7, 12.2, 12.2 Hz, 3α), 2.4–2.6 (2 H, m, 7β + 8aβ), 2.82 (1 H, dt, J = 2.9, 3.9, 12.2 Hz, 3β), 2.93 (1 H, br d, J = 4.2, 12.2 Hz, 1β), 3.04 (1 H, t, J = 12.2, 12.2 Hz, 1α), 3.11 (1 H, dd, J = 1.5, 13.2 Hz, 5α). Anal. ($C_{22}H_{31}NO$) C, H, N.

Similarly prepared from the corresponding amine and the corresponding alkyl halide were ***trans*-2-(cyclopropylmethyl)-1,2,3,4,4a,5,8,8a-octahydro-4a-(3-methoxyphenyl)-isoquinoline** isolated in an 85% yield as the HCl salt [mp 184 °C; anal. ($C_{20}H_{27}NO·HCl$) C, H, N]; ***trans*-decahydro-4a-(3-methoxyphenyl)-6-methylene-2-(2-propenyl)isoquinoline (9b)**, isolated as a brown oil in a 59% yield, and used directly in the next reaction; and ***trans*-1,2,3,4,4a,5,8,8a-octahydro-4a-(3-methoxyphenyl)-2-(2-propenyl)isoquinoline**, isolated as the HCl salt in a 99% yield from Et_2O [mp 139–40 °C; anal. ($C_{19}H_{25}NO·HCl$) C, H, N].

***trans*-2-(Cyclobutylmethyl)-1,2,3,4,4a,5,8,8a-octahydro-4a-(3-methoxyphenyl)isoquinoline.** A solution of *trans*-1,2,3,4,4a,5,8,8a-octahydro-4a-(3-methoxyphenyl)isoquinoline (2.0 g, 8.23 mmol) and Et_3N (2.7 mL, 19.4 mmol) in dry CH_2Cl_2 (25 mL) was treated with a solution of cyclobutanecarboxylic acid chloride (1.3 g, 10.9 mmol) in dry CH_2Cl_2 (5 mL) over a 5-min period. The mixture was stirred at ambient temperature for 3 h and then diluted with CH_2Cl_2 (150 mL). The organic solution was washed with aqueous Na_2CO_3 (1 M; 100 mL) and HCl (1 M; 100 mL), dried, and evaporated in vacuo. The residue was purified by flash chromatography using $Et_2O/CH_2Cl_2/C_6H_{14}$ 1:1:1 as eluant to give the intermediate *trans*-2-(cyclobutylcarbonyl)-1,2,3,4,4a,5,8,8a-octahydro-4a-(3-methoxyphenyl)isoquinoline as a colorless oil (2.35 g; 88%). Anal. ($C_{21}H_{27}NO_2$) C, H, N. A solution of the above amide (0.85 g, 2.6 mmol) in dry THF (10 mL) was added to $LiAlH_4$ (0.2 g, 5.2 mmol) in dry THF (5 mL). The reaction mixture was stirred at ambient temperature for 2 h. Water (0.2 mL) was cautiously added followed by aqueous NaOH (0.4 mL; 2 M) and water (0.2 mL). The mixture was filtered, and the filtrate was evaporated in vacuo to give the title compound as a colorless oil (0.84 g; 100%). Anal. ($C_{21}H_{29}NO$) C, H, N. Similarly prepared from the corresponding amine was ***trans*-2-(cyclobutylmethyl)decahydro-4a-(3-methoxyphenyl)-6-methyleneisoquinoline (9d)** in a 62% yield and isolated as a maleate salt: mp 144–7 °C. Anal. ($C_{22}H_{31}NO·C_4H_4O_4$) C, H, N.

***trans*-Phenyl Octahydro-4a-(3-methoxyphenyl)-6-oxo-2-(1*H*)-isoquinolinecarboxylate (12).** A mixture of OsO_4 (50 mg), **7** (10.6 g, 28 mmol), and sodium periodate (30 g, 140 mmol) in THF and H_2O (120 mL; 3:1) was stirred at ambient temperature for 1 h. Additional OsO_4 (150 mg) was added, and the mixture was stirred for 3 h. The reaction mixture was poured into aqueous NaOH (1 M; 300 mL) and extracted with Et_2O (500 mL). The Et_2O extract was washed with aqueous NaOH (2 × 150 mL) and H_2O (200 mL), dried ($MgSO_4$), and evaporated to give the title compound as a colorless oil (9.9 g; 94%). Anal. ($C_{23}H_{25}NO_4·0.5H_2O$) C, H, N.

Similarly prepared from the olefin **11c** was ***trans*-2-(cyclopropylmethyl)decahydro-4a-(3-hydroxyphenyl)-6-isoquinolinone (10)** isolated as a maleate salt (24%): mp 137–140 °C; ^1H NMR (DMSO-d_6) δ 0.35 and 0.65 (4 H, 2 br d, cyclopropyl), 1.1 (1 H, m, cyclopropyl), 2.0–2.3 (5 H, m, 4α, 4β, 5β, 8α, and 8β), 2.5–2.8 (4 H, m + DMSO), 3.05 (2 H, br s, $NCH_2cC_3H_5$), 3.3–3.7 (4 H, m + H_2O), 6.63–7.20 (4 H, m, aromatics). Anal. ($C_{19}H_{25}NO_2·C_4H_4O_4·0.11H_2O$) C, H, N.

***trans*-Phenyl 3,4,4a,5,6,8a-Hexahydro-4a-(3-methoxyphenyl)-6-oxo-2(1*H*)-isoquinolinecarboxylate (14).** A mixture of concentrated HCl (0.5 mL), **12** (10.55 g, 27.8 mmol), and PhSeCl (5.86 g, 30.6 mmol) in EtOAc (160 mL) was stirred at ambient temperature for 30 min. EtOAc (150 mL) was added, and the solution was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in a mixture of CH_2Cl_2 (250 mL) and pyridine (15 mL), H_2O_2 (5.8 mL; 30% w/v) was added over 2 min, and the mixture was stirred for 45 min at ambient temperature. CH_2Cl_2 (250 mL) was added and the solution was washed with HCl (1 M; 200 mL) and water (200 mL), dried ($MgSO_4$), and evaporated. The residue was purified by chromatography eluting with Et_2O/C_6H_{14} 1:1 to give the title compound as a pale yellow foam (7.1 g; 68%): MS ($C_{23}H_{23}NO_4$) 377.1625 (M^+); ^1H NMR ($CDCl_3$) δ 1.95 (1 H, tt, 4α), 2.38 (1 H, dt, 4β), 2.63 (1 H, d, 5β), 2.73 (1 H, br t, 8a), 2.95 (1 H, d, 5α), 3.15 (1 H, br d, 3α), 3.59 (1 H, br t, 3β), 3.79 (3 H, s, OMe), 4.13 (1 H, br t, 1β), 4.47 (1 H, br m, 1α), 6.05 (1 H, br d, 7 H), 6.7–7.4 (10 H, m, 8 H + aromatics).

Similarly prepared from the corresponding ketone **13** using O_3 followed by Et_3N and 1-hexene was ***trans*-phenyl 3,4,4a,5,6,8a-hexahydro-4a-(3-methoxyphenyl)-8-methyl-6-oxo-2(1*H*)-isoquinolinecarboxylate (17)** isolated as a white foam in a 47% yield: ^1H NMR ($CDCl_3$) δ 1.92 (1 H, br t, 4α), 2.2 (3 H, br s, Me), 2.38 (1 H, dt, 4β), 2.58 (1 H, d, 5β), 2.73 (br t, 8a), 2.89 (1 H, d, 5α), 3.05 (1 H, br d, 3α), 3.53 (1 H, br t, 3β), 3.78 (3 H, s, OMe), 4.15 (1 H, br m, 1β), 4.63 (1 H, br m, 1α), 5.9 (1 H, br s, 7 H), 6.63–6.67 (3 H, m, 3 aromatics), 7.02–7.42 (6 H, m, aromatics). Anal. ($C_{24}H_{25}NO_3$) C, H, N.

(4aα,8α,8aβ)-Phenyl Octahydro-4a-(3-methoxyphenyl)-8-methyl-6-oxo-2(1*H*)-isoquinolinecarboxylate (18). A mixture of **17** (0.29 g, 0.75 mmol) and 10% Pd/C (60 mg) in EtOH (15 mL) was hydrogenated at room temperature and pressure for 19 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography using Et_2O/C_6H_{14} 1:1 as eluant to give the title compound as a colorless gum (0.16 g; 75%). Anal. ($C_{24}H_{27}NO_4$) C, H, N.

(4aα,6α,7β,8aβ)-2-(Cyclopropylmethyl)decahydro-4a-(3-

Table IV. Physical Properties and Yields of Target Compounds

compd[e]	anal.	mp, °C	yield, %
11a	CHN[a]	185	60
11b	CHN	217–9	61[b]
11c	CHN	165–8	33[c]
11d	CHN	168–9	51[c]
16	CHN	186–7	87[c]
20	CHN	210–2	94[c]
22a	CHN	200–2	46
22b	CHN	169–71	32
22c	CHN	168–70	53
22d	CHN	157–8	30
26	CHN	173–4	46
28a	MS	186–7	34
30a	MS	110–3	78
30b	CHN[d]	128–32	92

[a] Contains 0.02% H_2O. [b] Fumarate salt. [c] Maleate salt. [d] 0.2% CH_2Cl_2. [e] All compounds are racemic.

methoxyphenyl)-6-(phenylselenyl)-7-isoquinolinol (24a). A mixture of **23a** (1.5 g, 5.0 mmol), pTSA (1 g, 5.25 mmol), and H_2O (0.27 mL, 15 mmol) was treated with *N*-(phenylselenyl)phthalimide (1.67 g, 5.53 mmol) at ambient temperature. The mixture was vigorously stirred for 24 h, and then Na_2CO_3 (1 M; 50 mL) and NaOH (2 M; 5 mL) were added. The product was extracted with CH_2Cl_2 (2 × 100 ml), and the extracts were dried and evaporated. The residue was purified by chromatography using CH_2Cl_2/MeOH/NH_3 150:10:2 as eluant to give the title compound as a white foam (93%): mp 89–91 °C. Anal. ($C_{26}H_{33}NO_2Se \cdot H_2O$) C, H, N.

Similarly prepared from the corresponding olefin **23b** and PhSeCl was **(4aα,6α,7β,8aβ)-2-(cyclobutylmethyl)decahydro-4a-(3-methoxyphenyl)-6-(phenylseleno)-7-isoquinolinol (24b)** isolated as an off-white solid in 75% yield: mp 189–190 °C. Anal. ($C_{27}H_{35}NO_2Se$) C, H, N.

(4aα,7β,8aβ)-2-(Cyclopropylmethyl)-1,2,3,4,4a,7,8,8a-octahydro-4a-(3-methoxyphenyl)-7-isoquinolinol (25). A solution of **24a** (2.2 g, 4.67 mmol) in CH_2Cl_2 (50 mL) was treated with H_2O (0.5 mL) and sodium periodate (1.1 g, 5.14 mmol). The mixture was vigorously stirred for 2 h. Water (50 mL) was added followed by NaOH (2 M; 5 mL). The product was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in a mixture of $CHCl_3$ (30 mL) and Et_2NH (1 mL, 9.67 mmol) and heated at reflux for 2 h. The cooled mixture was washed with NaOH (0.2 M; 50 mL), dried, and evaporated and the residue purified by chromatography using CH_2Cl_2/MeOH/NH_3 150:10:2 as eluant to give the title compound as a foam (1.02 g; 70%). Anal. ($C_{20}H_{27}NO_2 \cdot 0.5H_2O$) C, H, N.

(4aα,8β,8aβ)-Phenyl Octahydro-4a-(3-methoxyphenyl)-8-methyl-6-oxo-2(1*H*)-isoquinolinecarboxylate (13). A solution of MeLi in Et_2O (1.4 M; 53.4 mL, 75 mmol) was added to a stirred suspension of CuI (7.08 g) in dry Et_2O (250 mL) at 0 °C followed by a solution of **14** (6.95 g, 18.4 mmol) in dry CH_2Cl_2 (100 mL) over 5 min. The suspension was warmed to 10 °C over 20 min and then quenched with saturated NH_4Cl (100 mL). H_2O (160 mL) and NH_3 (0.88; 40 mL) were added, and the product was extracted with CH_2Cl_2 (600 mL). This extract was dried ($MgSO_4$) and evaporated to give the title compound as a colorless foam (7.17 g; 99%): MS M^+ 393.1945 ($C_{24}H_{27}NO_4$).

(4aα,8β,8aβ)-Phenyl Octahydro-4-(3-methoxyphenyl)-8-methyl-6-methylene-2(1*H*)-isoquinolinecarboxylate. $TiCl_4$ (10.5 mL, 0.096 mol) was added dropwise over 10 min to a stirred suspension of zinc powder (24.9 g, 0.38 mol) and CH_2Br_2 (13.8 mL, 0.195 mol) in dry THF at −50 °C. The mixture was stirred at 4 °C for 3 days and then (60 mL) was added to a stirred solution of **13** (3.0 g, 0.007 62 mol) in dry CH_2Cl_2 (60 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and then poured into a mixture of aqueous $NaHCO_3$ (400 mL; 8% w/v) and Et_2O (500 mL). The mixture was shaken vigorously and the aqueous phase was further extracted with Et_2O (2 × 500 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the title compound as a colorless oil (2.98 g; 100%). Anal. ($C_{25}H_{29}NO_3 \cdot 0.5H_2O$) C, H, N.

Similarly prepared from the ketone **18** was **(4aα,8α,8aβ)-phenyl octahydro-4a-(3-methoxyphenyl)-8-methyl-6-methylene-2-(1*H*)-isoquinolinecarboxylate** as a colorless gum in a 75% yield. Anal. ($C_{25}H_{29}NO_3$) C, H, N.

(4aα,7β,8aβ)-2-(Cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-7-isoquinolinol (27a). A mixture of **24a** (1.28 g, 2.72 mol) and prereduced RaNi (12.8 g) in EtOH (250 mL) was heated at reflux for 2 h. The cooled mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography using CH_2Cl_2/MeOH/NH_3 75:8:2 as eluant to give the title compound as a white foam (0.75 g; 76%) which was used without further purification.

Similarly prepared from the phenyl selenide **24b** was **(4aα,7β,8aβ)-2-(cyclobutylmethyl)decahydro-4a-(3-methoxyphenyl)-7-isoquinolinol (27b)** as a white foam in a 78% yield and was used without further purification.

***trans*-2-(Cyclobutylmethyl)decahydro-4a-(3-hydroxyphenyl)-7-isoquinolinone (29b).** A solution of oxalyl chloride (0.8 mL, 9.16 mmol) in dry CH_2Cl_2 (6 mL) at −60 °C was treated with a solution of dry DMSO (1.6 mL, 10.6 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred at −60 °C for 10 min, and a solution of **30b** (2.05 g, 6.5 mmol) in a mixture of dry CH_2Cl_2 (12 mL) and dry DMSO (0.5 mL) was added dropwise over a 5-min period. The reaction mixture was stirred for a further 30 min at −60 °C and then treated with Et_3N (4 mL, 28.6 mmol). H_2O (0.5 mL) was added at −20 °C. The reaction mixture was poured into phosphate buffer (pH 7.5; 20 mL). The product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated, leaving an oily residue. This was purified by chromatography using CH_2Cl_2/MeOH/NH_3 100:10:2 as eluant to give the title compound as a white solid: mp 94–6 °C (1.9 g; 93%). Anal. ($C_{21}H_{27}NO_2 \cdot 0.2C_6H_{14}$) C, H, N.

Similarly prepared from the corresponding alcohols were ***trans*-2-(cyclopropylmethyl)decahydro-4a-(3-hydroxyphenyl)-7-isoquinolinone (29a)** as a white foam in 20% yield. Anal. ($C_{19}H_{25}NO_2 \cdot 0.2H_2O$) C, H, N.

***trans*-2-(Cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-7-isoquinolinone** as a colorless oil in a 46% yield and was used without further purification.

***trans*-1-(Cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-7-methyleneisoquinoline.** A mixture of methyltriphenylphosphonium bromide (0.60 g, 1.68 mmol) and ^{t}BuOK (0.188 g, 1.67 mmol) in dry THF (30 mL) was stirred at ambient temperature for 1 h. A solution of *trans*-2-(cyclopropylmethyl)decahydro-4a-(3-methoxyphenyl)-7-isoquinolinone (0.44 g, 1.40 mmol) in dry THF (10 mL) was added and stirring was continued for 2 h. The reaction mixture was poured into H_2O (20 mL) and the product was extracted with CH_2Cl_2 (20 mL). The organic extract was dried and evaporated in vacuo. The residue was purified by chromatography using CH_2Cl_2/MeOH/NH_3 150:8:1 as eluant to give the title compound as a colorless oil (0.22 g; 50%), which was used directly in the next reaction.

Similarly prepared from the corresponding ketone **29b** was ***trans*-3-[2-(cyclobutylmethyl)decahydro-7-methylene-4a-isoquinolinyl]phenol (28b)** and crystallized from MeOAc/C_6H_4 in a 40% yield: mp 166–7 °C. Anal. ($C_{21}H_{29}NO$) C, H, N.

General Procedure for the Synthesis of the Phenol Analogues. A mixture of the methyl ether (0.7 mmol) and LiSMe (3.7 mmol) in DMF (7 mL) was heated at 125 °C for 7 h. NH_4Cl (8.0 mmol) was added to the cooled mixture, the solvent was evaporated in vacuo, and the residue was purified by chromatography using CH_2Cl_2/MeOH/NH_3 100:10:2 and the product was crystallized as the free base or a salt (see Table IV).

Pharmacology Methods. In Vivo. The mouse acetylcholine-induced abdominal constriction test was performed as previously[19] described. Compounds were administered in a saline vehicle.

In Vitro. Activity in the rabbit vas deferens preparation was determined[12] as previously described. Determination of the receptor selectivity of opioid agonists in the guinea pig ileum using β-FNA[16a] (10^{-6} M, 30-min pretreatment) and β-CNA[16b] (10^{-7} M, 15 min pretreatment in the presence of DAMGO 10^{-5} M) utilized previously described methodology.

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Registry No. (±)-**2c**, 63843-35-6; **5**, 73224-22-3; (±)-**6**, 137517-45-4; (±)-**7**, 137517-46-5; (±)-**8**·HCl, 137517-47-6; (±)-**9b**,

137517-48-7; (±)-**9c**, 137539-89-0; (±)-**9d**·maleate, 137517-50-1; (±)-**9** (R = H), 137517-51-2; (±)-**10**, 137517-52-3; (±)-**11a**, 137517-53-4; (±)-**11b**, 137517-54-5; (±)-**11c**, 137517-55-6; (±)-**11d**, 137517-56-7; (±)-**12**, 137540-34-2; (±)-**13**, 137517-57-8; (±)-**13** (6-methylene derivative), 137540-35-3; (±)-**14**, 137517-58-9; (±)-**15**, 137517-59-0; (±)-**15**·maleate, 137517-60-3; (±)-**15** (des-cyclopropylmethyl derivative), 137517-61-4; (±)-**16**, 137517-62-5; (±)-**17**, 137517-63-6; (±)-**18**, 137517-64-7; (±)-**18** (6-methylene derivative), 137517-65-8; (±)-**19**, 137517-66-9; (±)-**19** (des-cyclopropylmethyl derivative), 137517-67-0; (±)-**20**, 137517-68-1; (±)-**21**, 137517-69-2; (±)-**21** (*N*-desmethyl derivative), 137517-70-5; (±)-**22a**, 137517-71-6; (±)-**22b**, 137517-72-7; (±)-**22b** methyl ether·HCl, 137517-73-8; (±)-**22c**, 137517-74-9; (±)-**22d**, 137517-75-0; (±)-**23a**, 137517-76-1; (±)-**23a**·HCl, 137517-77-2; (±)-**23b**, 137517-78-3; (±)-**24a**, 137517-79-4; (±)-**24b**, 137517-80-7; (±)-**25**, 137517-81-8; (±)-**26**, 137517-82-9; (±)-**27a**, 137517-83-0; (±)-**27a** ketone, 137517-84-1; (±)-**27b**, 137517-85-2; (±)-**28a**, 137517-86-3; (±)-**28a** methyl ether, 137517-87-4; (±)-**28b**, 137517-88-5; (±)-**29a**, 137517-89-6; (±)-**29b**, 137517-90-9; (±)-**30a**, 137517-91-0; (±)-**30b**, 137517-92-1; $BrCH_2C(=CH_2)CH_2CH_2Br$, 82359-61-3; (*Z*)-$ClCH_2CH=CHCH_2Cl$, 1476-11-5; $BrCH_2$-c-C_3H_5, 7051-34-5; ClCO-c-C_4H_7, 5006-22-4; (±)-2,3,4,4a,5,8-hexahydro-4a-(3-methoxyphenyl)-2-methylisoquinoline, 137517-93-2; ethenyl (±)-*trans*-3,4,4a,5,8,8a-hexahydro-4a-(3-methoxyphenyl)-2(1*H*)-isoquinolinecarboxylate, 137517-94-3.

Supplementary Material Available: NMR data of selected target compounds (2 pages). Ordering information is given on any current masthead page.

Di- and Triester Prodrugs of the Varicella-Zoster Antiviral Agent 6-Methoxypurine Arabinoside

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6-Methoxypurine arabinoside (9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine, 1) has potent and selective activity against varicella-zoster virus in vitro. An unfavorable metabolic profile observed with oral dosing in the rat led to the preparation of a variety of 2′,3′,5′-triesters (**2a–n**) and several 2′,3′-, 2′,5′-, and 3′,5′-diesters of this arabinoside (**3a–n**, **4a–f**, and **5a–j**, respectively). The compounds were evaluated as prodrugs by measuring the urinary levels of 1 in rat urine after oral dosing. With the exception of triacetate **2a**, the triesters failed to significantly enhance bioavailability. Administration of compound **2a** resulted in a 3-fold increase in systemic availability of 1, possibly because of its increased water solubility (1.6 times more soluble than 1) and only slightly increased relative log *P* value (1.93 vs 0.50 for 1). The longer chain aliphatic triesters and aromatic triesters had lower water solubilities and increased lipophilic partitioning. These factors might account for the lower systemic bioavailability of these compounds. In contrast, the diesters, especially the aliphatic diesters, showed significantly improved systemic availability. This might be a consequence of the higher aqueous solubilities and enhanced partition coefficients seen with these compounds. 2′,3′-Diacetate **3a** showed the best combination of high systemic availability and water solubility of all the prodrugs of 1.

The potent activity of 6-methoxypurine arabinoside (9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine, 1) as an anti-varicella-zoster agent in vitro and the molecular basis for its selectivity have been described.[1] However, in vivo and enzyme studies indicated that adenosine deaminase is responsible for catabolism of the compound to hypoxanthine arabinoside[2] and accounts for the pharmacokinetic limitations of the compound following oral dosing.[3] A similar limitation for adenine arabinoside (*ara*-A) has been observed, leading to the preparation of a wide variety of prodrugs designed to increase resistance to adenosine deaminase, increase water solubility, and modify lipophilicity.[4-9] These studies indicated that modification of the 2′- or 5′-hydroxyls of adenine arabinoside, but not the 3′-hydroxyl, increases resistance of adenine arabinoside to enzymatic deamination.[4-6] A limited series of 2′,3′- and 3′,5′-di-*O*-acyl derivatives of *ara*-A were examined, with the 2′,3′-diacetate showing enhanced water solubility. Good in vitro and in vivo antiviral activity toward herpes simplex type 2 was also noted.[5] Haskell examined the antiviral activity of a series of triesters of *ara*-A, concluding that in vitro activity was consistent with the ease of aqueous or enzymatic hydrolysis to the parent nucleoside.[7] The tri-*O*-formyl derivative possessed the best antiviral activity, although limited aqueous solubility was found. With the goal of achieving improvements in the bioavailability and solubility of 1, we prepared and evaluated a series of di- and triester prodrugs of 6-methoxypurine arabinoside.

Chemistry

The triesters of 6-methoxypurine arabinoside (1) were synthesized by adding the appropriate acid anhydride to a solution of 1 in acetonitrile and pyridine (Scheme I). As the aliphatic chain became more hindered, or in the case of the aromatic esters, it sometimes became necessary to heat the solution to reflux to drive the reaction to completion.

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