Synthesis, Antinociceptive Activity and Opioid Receptor Profiles of 3-(Octahydro-1*H*-pyrano- and -thiopyrano[4,3-*c*]pyridin-8a-yl)phenols

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The synthesis of a series of novel *cis*- and *trans*-3-(octahydro-1*H*-pyrano[4,3-*c*]pyridin-8a-yl)-phenols (**13a**—**1**), (**15a, b**), (**20a**—**d**), (**21a**—**e**) and the *trans*-3-(octahydro-1*H*-thiopyrano[4,3-*c*]-pyridin-8a-yl)phenol (**26**) is described. Alkylation of 1-methyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (**7**) with 2-chloro-1-(chloromethoxy)ethane or 2-chloro-1-(chloromethoxy)-propane, and subsequent cyclization, generated the bicyclic enamines (**9a**) and (**9b**) respectively. Hydrogenation of (**9a, b**) under neutral conditions provided the *trans*-fused octahydropyrano[4,3-*c*]-pyridines (**10a**), (**16a**), and (**17a**), whereas hydrogenation of (**9a**) in acidic media gave the corresponding *cis*-fused system (**11a**). The *trans*-fused octahydrothiopyrano[4,3-*c*]pyridine (**23**) was synthesized *via* the analogous enamine (**22**). Selected *N*-substituents were introduced *via* a vinyl chloroformate *N*-demethylation/re-alkylation sequence and subsequent *O*-demethylation afforded the title phenols. The antinociceptive activity and opioid receptor profile of these compounds has been determined and structure activity relationships are discussed.

Of the numerous substructural analogues of the morphine (**1**) skeleton that have been described,[1] *trans*-4a-aryldecahydroisoquinolines (**2**) represent a relatively recent class to be explored, both by synthetic[2] and medicinal[3] chemists. These compounds retain the rigid *trans* C/D ring system and axial aromatic moiety of morphine, and certain derivatives [*e.g.* (**3**)[3]] have been reported to possess opioid analgesic properties. The recent disclosure that 6-oxamorphinans [*e.g.* proxorphan (**4**)[4]] display good antinociceptive activity, but with reduced narcotic side-effects, stimulated our interest in synthesizing and evaluating the analogous structural fragment: *trans*-8a-aryloctahydropyrano[4,3-*c*]pyridine system (**5**). In this paper we describe the synthesis of a series of novel *cis*- and *trans*-3-(octahydro-1*H*-pyrano[4,3-*c*]pyridin-8a-yl)phenols (**6a**) and the related thiopyrano system (**6b**). In addition to varying the nature of the nitrogen substituent, we have investigated the effect of substitution in the pyran ring at C-4. The latter modification was prompted by the interesting pharmacological profiles of some morphinans bearing substituents in the C ring.[5]

It is well established that exogenous and endogenous opioids interact with three distinct subtypes of opioid receptor, designated as μ-, κ-, and δ-receptors.[6] From the different pharmacological profiles of μ- and κ-agonists it has been suggested that opioids with a prominent κ-agonist component might be safer analgesics than traditional morphine-like or μ-agonists.[7] Thus, we tested the title compounds for antinociceptive activity and, where possible, assessed their interaction with μ- and κ-opioid receptor subtypes.

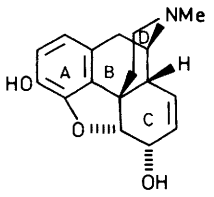
Chemistry.—The recent application by Evans *et al.* of metallated enamines in the synthesis of morphinan-based systems provided the basis for our synthetic approach to the title compounds.[2a] Thus, in the first instance (Scheme 1, R = H) alkylation of the lithiated species generated from the tetrahydropyridine (**7**) with the bifunctional alkylating agent 2-chloro-1-(chloromethoxy)ethane gave the intermediate enamine (**8a**). It was expected that the different reactivities at the termini of the alkylating agent would result in the desired regioselectivity. Without purification (**8a**) was converted directly into the bicyclic enamine (**9a**) (40% overall) by refluxing in acetonitrile in the presence of sodium iodide. Hydrogenation of (**9a**) over platinum under neutral conditions afforded the *trans*-fused pyrano[4,3-*c*]pyridine (**10a**) with *ca.* 95% stereoselectivity. The minor, *cis*-fused isomer (**11a**) was removed either by column chromatography or by crystallization of the hydrochloride salt. The ^{1}H n.m.r. spectrum of (**10a**) showed a characteristic AB pattern for 1α-(δ 3.30) and 1β-H (δ 4.22) ($J_{1\alpha,1\beta}$ 11 Hz), thereby establishing the regiochemistry of the alkylation step. The *trans* geometry of the ring fusion was assigned on the basis of n.O.e. difference experiments: irradiation of the aromatic signal at δ 7.05 (2′,6′-ArH) gave enhancements for 1β-, 4β-, 5β-, and 8β-H.†

When the hydrogenation of (**9a**) was performed in acetic acid the *cis*-fused isomer (**11a**) was now the predominant product in *ca.* 95% stereoselectivity, analogous to the observation of Evans *et al.* with aryldecahydroisoquinolines.[2a] Although the ^{1}H n.m.r. of (**11a**), recorded in CD_3OD, was broadened due to the presence of two conformations, addition of DCl–D_2O slowed the exchange and 'froze out' the two forms in a ratio of *ca.* 85:15. Analysis of the coupling pattern of the ring junction proton 4aα-H (major component) revealed a single axial–axial coupling ($J_{4a\alpha,5\beta}$ 13 Hz) and two small couplings ($J_{4a\alpha,4\beta} \sim 1$ Hz, $J_{4a\alpha,4\alpha}$ 4 Hz), consistent only with a *cis*-fused stereochemistry.

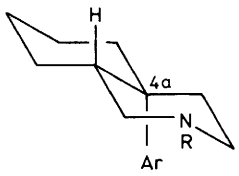
In the *trans*-fused series alternative nitrogen substituents were introduced *via* *N*-demethylation of (**10a**), using vinyl chloroformate,[8] followed by sequential hydrolysis of the carbamate group, alkylation ‡ (Table 1), and *O*-demethylation (Table 2) to provide the target phenols (**13a**—**1**). The *N*-cyclopropylmethyl and *N*-allyl analogues in the *cis*-fused series, (**15a**) and (**15b**) respectively, were obtained in a similar manner *via* (**14**), (**11b**), and (**11c**).

The above methodology was also used to prepare 4-methyl

† See Experimental section for full data.
‡ An exception is (**10j**) which was prepared *via* acylation of (**12**) and reduction of the resultant amide.



(1)



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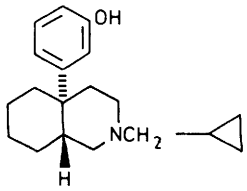

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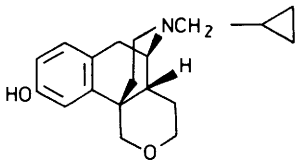

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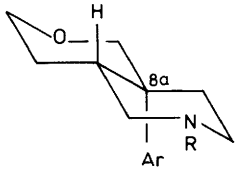

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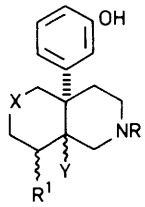
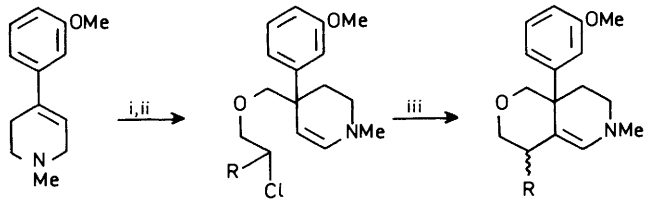


(6) **a**; X = O, Y = H (α) or H (β)

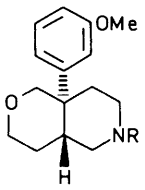
b; X = S, Y = H (β)



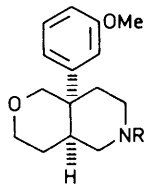
(7) (8) **a**; R = H **b**; R = Me (9) **a**; R = H **b**; R = Me

Scheme 1. *Reagents:* i, BuLi, THF, −20 °C; ii, $ClCH_2OCH_2CH_2Cl$ (R = H) or $ClCH_2OCH_2CH(Me)Cl$ (R = Me); iii, NaI, MeCN, 85 °C; (R = H), or 1-methylpyrrolidin-2-one, NaI, 130 °C; (R = Me)

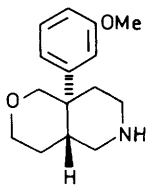
substituted pyrano[4,3-*c*]pyridines. However, in contrast to the unsubstituted series, cyclization of intermediate (**8b**) in acetonitrile at reflux did not afford any of the desired bicyclic enamines (**9b**). This difficulty was overcome by heating (**8b**) in 1-methylpyrrolidin-2-one in the presence of sodium iodide whereupon (**9b**) was obtained in 45% yield. Subsequent hydrogenation of (**9b**) over platinum in ethanol afforded a 3:2 mixture of the *trans*-fused methyl-substituted analogues (**16a**) and (**17a**). After separation of these epimers by column chromatography, the integrity of their ring-junction stereochemistry was confirmed by ^1H n.m.r. spectral data. Thus, the 4aα-H signal of (**16a**) displayed two axial–axial couplings ($J_{4a\alpha,4\beta}$ 11 Hz, $J_{4a\alpha,5\beta}$ 11 Hz), consistent only with a *trans*-fused geometry, whereas the 4aβ-H signal of (**17a**) showed only one



(10) **a**; R = Me
b; R = Pr
c; R = $CH_2CH{=}CH_2$
d; R = $CH_2C{\equiv}CH$
e; R = Bu^i
f; R = $CH_2\overline{CHCH_2CH_2}$
g; R = $CH_2C(Me){=}CH_2$
h; R = $CH_2CH_2\overline{CHCH_2CH_2}$
i; R = $CH_2CH_2CH{=}CH_2$
j; R = $CH_2\overline{CHCH_2CH_2CH_2}$
k; R = $CH_2CH{=}CMe_2$
l; R = CH_2CH_2Ph



(11) **a**; R = Me
b; R = $CH_2\overline{CHCH_2CH_2}$
c; R = $CH_2CH{=}CH_2$



(12)

Table 1. Preparation of 8a-(3-methoxyphenyl)octahydro-1*H*-pyrano- and thiopyrano-[4,3-*c*]pyridines

Compound	Conditions[a]	Yield (%)	Formula[b]	Analysis (%) Found (required) C	H	N
(**10b**)	PrI, 20 °C, 23 h	54	$C_{18}H_{27}NO_2$	75.0 (74.7)	9.75 (9.40)	5.05 (4.85)
(**10c**)	CH_2=CHCH$_2$Br, 100 °C, 19 h	80	$C_{18}H_{25}NO_2$	$M^{+\cdot}$ 287.1885 (287.1887)		
(**10d**)	HC≡CCH$_2$Br, 140 °C, 1 h	67	$C_{18}H_{23}NO_2$·HCl·0.75H_2O	64.9 (64.5)	7.3 (7.65)	4.25 (4.2)
(**10e**)	Bu^{i}Br, 150 °C, 2 h	46	$C_{19}H_{29}NO_2$	75.6 (75.2)	9.7 (9.65)	4.5 (4.6)
(**10f**)	$\overline{CH_2CH_2CH}$–CH$_2$Br, 2 h	78	$C_{19}H_{27}NO_2$	*c*		
(**10g**)	CH_2=C(Me)CH$_2$Cl, 100 °C, 2 h	74	$C_{19}H_{27}NO_2$·0.25H_2O	74.95 (74.6)	8.95 (9.05)	4.5 (4.6)
(**10h**)	$\overline{CH_2CH_2CHCH_2CH_2}OSO_2$Me, 110 °C, 2 h	77	$C_{20}H_{29}NO_2$	*c*		
(**10i**)	CH_2=CHCH$_2$CH$_2$Br, 100 °C, 2 h	87	$C_{19}H_{27}NO_2$	$M^{+\cdot}$ 302.2120 (302.2123)		
(**10j**)[d]	(a) $\overline{CH_2CH_2CH_2CH}$–COCl, Et_3N, CH_2Cl_2 (b) $LiAlH_4$	88	$C_{20}H_{29}NO_2$·0.25H_2O	*c* 75.3 (75.1)	9.55 (9.3)	4.25 (4.4)
(**10k**)	(Me)$_2$C=CHCH$_2$Br, 150 °C, 2 h	67	$C_{20}H_{29}NO_2$	75.95 (76.15)	9.25 (9.25)	4.2 (4.45)
(**10l**)	PhCH$_2$CH$_2$Br, 120 °C, 2 h	83	$C_{23}H_{29}NO_2$	78.3 (78.6)	8.55 (8.3)	4.0 (4.0)
(**11b**)	$\overline{CH_2CH_2CH}$–CH$_2$Br, 150 °C, 2 h	86	$C_{19}H_{27}NO_2$	75.4 (75.7)	8.55 (9.05)	4.75 (4.65)
(**11c**)	CH_2=CHCH$_2$Br, 150 °C, 2 h	92	$C_{18}H_{25}NO_2$	75.4 (75.2)	8.75 (8.75)	5.0 (4.85)
(**16b**)	CH_2=CHCH$_2$Br, 120 °C, 2 h	57	$C_{19}H_{27}NO_2$	75.75 (75.7)	9.35 (9.05)	4.65 (4.65)
(**16c**)	$\overline{CH_2CH_2CH}$–CH$_2$Br, 100 °C, 3.5 h	65	$C_{20}H_{29}NO_2$	76.3 (76.15)	9.45 (9.25)	4.45 (4.45)
(**17b**)	CH_2=CHCH$_2$Br, 125 °C, 6 h	67	$C_{19}H_{27}NO_2$	75.9 (75.7)	9.1 (9.05)	4.95 (4.65)
(**17c**)	$\overline{CH_2CH_2CH}$–CH$_2$Br, 125 °C, 4.5 h	58	$C_{20}H_{29}NO_2$	76.1 (76.15)	9.25 (9.25)	4.5 (4.45)
(**17d**)	CH_2=C(Me)CH$_2$Cl, 100 °C, 4 h	50	$C_{20}H_{29}NO_2$	76.35 (76.15)	9.5 (9.25)	4.35 (4.45)
(**25**)	$\overline{CH_2CH_2CH}$–CH$_2$Br, 130 °C, 3 h	54	$C_{19}H_{27}NOS$	71.55 (71.9)	8.45 (8.55)	4.3 (4.4)

[a] Unless otherwise stated, all reactions conducted in DMF in the presence of $NaHCO_3$ (2 mol equivalents). [b] All compounds isolated as viscous oils except (**10d**), m.p. 80 °C (softens at 60 °C). [c] This intermediate was used directly in the next stage without rigorous purification. ^{1}H N.m.r. spectroscopy indicated >95% purity. [d] See Experimental section.

large ($J_{4a\beta,5\alpha}$ 12 Hz) and two small (J 4 Hz) couplings. In the latter case an n.O.e. difference experiment showed an enhancement of the aromatic protons (2′,6′-ArH) upon irradiation of the 4-methyl group and of 5α-H, thereby excluding an alternative *cis*-fused structure. To obtain the requisite phenols (**20a—c**) and (**21a—c** and **e**) for biological testing, *N*-demethylation, alkylation (Table 1), and *O*-demethylation (Table 2) were carried out as described above. The *N*-isobutyl derivatives (**20d**) and (**21d**) were prepared *via* hydrogenation of (**20c**) and (**21e**) respectively.

Finally, by using analogous chemistry we have established a route to the corresponding thiopyrano[4,3-*c*]pyridine system (Scheme 2). The presence of the thioether linkage in the bicylic enamine (**22**) clearly necessitated an alternative to catalytic hydrogenation as a means of reducing the enamine double bond. Accordingly, the *trans*-iminium salt derived from enamine (**22**), under kinetic control, was reduced using sodium borohydride to give selectively the *trans*-fused thiopyran[4,3-*c*]pyridine (**23**). Standard manipulations were then used to convert (**23**) into the *N*-cyclopropylmethyl substituted phenol (**26**) (Tables 1 and 2).

Pharmacology.—The *trans*-3-(octahydro-1*H*-pyrano[4,3-*c*]pyridin-8a-yl)phenols (**13a—l**), (**20a—d**), and (**21a—d**) were assayed *in vivo* for antinociceptive activity using the mouse acetylcholine-induced abdominal constriction test[9] and for their effect on urine output in the water-loaded rat (Table 3). The latter test has proven to be a useful model for the *in vivo* characterization of different types of opioid receptor agonists: μ-agonists induce antidiuresis whereas κ-agonists cause diuresis.[10] Furthermore, high efficacy κ-agonists produce marked diuretic effects whereas partial κ-agonists produce low maximum diuresis.[11] Compounds having activity at both μ- and κ-opioid receptors produce a biphasic effect: an initial antidiuretic effect followed by a more sustained diuresis.[12]

In vitro assessment of the μ/κ selectivity of the title compounds was made using the guinea-pig ileum (GPI) preparation. Blockade at μ-receptors was produced by the irreversible opioid antagonist β-funaltrexamine (β-FNA). An effective κ-receptor blockade was produced using the non-selective irreversible antagonist β-chlornaltrexamine (β-CNA), with concomitant μ-receptor protection using the selective μ-agonist [D-Ala,^{2} MePhe,^{4} Gly(ol)^5] enkephalin (DAGO). Agonists 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.[13] The κ-agonist (or antagonist) activity of compounds was also determined using the rabbit vas

Table 2. Preparation of 3-(octahydro-1*H*-pyrano- and thiopyrano-[4,3-*c*]pyridin-8a-yl)phenols

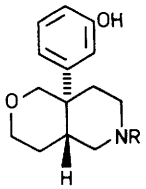
Compound	*N*-Substituent	Conditions[a]	Yield[b] (%)	Formula[c]	M.p. (°C)	Analysis (%) Found (required) C	H	N
(13a)	Me	A	47	$C_{15}H_{21}NO_2$	200—203	72.6 (72.85)	8.25 (8.55)	5.35 (5.65)
(13b)	Pr	B	64	$C_{17}H_{25}NO_2{\cdot}C_4H_4O_4$	170—171	64.55 (64.45)	7.55 (7.45)	3.35 (3.6)
(13c)	$CH_2CH{=}CH_2$	B	74	$C_{17}H_{23}NO_2{\cdot}C_4H_4O_4$	155—160	64.6 (64.75)	6.95 (7.0)	3.55 (3.60)
(13d)	$CH_2C{\equiv}CH$	C	39	$C_{17}H_{21}NO_2{\cdot}C_4H_4O_4$	162—164	65.0 (65.1)	6.6 (6.5)	3.7 (3.6)
(13e)	Bu^i	A	47	$C_{18}H_{27}NO_2{\cdot}C_4H_4O_4$	137—139	65.05 (65.15)	7.75 (7.7)	3.35 (3.45)
(13f)	$CH_2\overline{CHCH_2CH_2}$	A	52	$C_{18}H_{25}NO_2{\cdot}C_4H_4O_4$	185—187	65.45 (65.5)	7.4 (7.25)	3.4 (3.45)
(13g)	$CH_2C(Me){=}CH_2$	A	51	$C_{18}H_{25}NO_2{\cdot}C_4H_4O_4$	137—139	65.4 (65.5)	7.3 (7.25)	3.55 (3.45)
(13h)	$CH_2CH_2\overline{CHCH_2CH_2}$	A	34	$C_{19}H_{27}NO_2{\cdot}C_4H_4O_4{\cdot}0.17H_2O$	172—173	65.5 (65.7)	7.45 (7.5)	3.35 (3.3)
(13i)	$CH_2CH_2CH{=}CH_2$	A	68	$C_{18}H_{25}NO_2{\cdot}C_4H_4O_4$	174—175	65.4 (65.5)	7.45 (7.25)	3.35 (3.45)
(13j)	$CH_2\overline{CHCH_2CH_2CH_2}$	C	38	$C_{19}H_{27}NO_2$	147—149	$M^{+\cdot}$ 301.2048 (301.2043)		
(13k)	$CH_2CH{=}C(Me)_2$	A	60	$C_{19}H_{27}NO_2{\cdot}C_4H_4O_4$	156—160	66.15 (66.15)	7.7 (7.5)	3.25 (3.35)
(13l)	CH_2CH_2Ph	A	67	$C_{22}H_{27}NO_2{\cdot}C_4H_4O_4{\cdot}0.5H_2O$	185—187	67.35 (67.45)	6.8 (7.0)	2.85 (3.05)
(15a)	$CH_2\overline{CHCH_2CH_2}$	C	9[e]	$C_{18}H_{25}NO_2{\cdot}C_4H_4O_4{\cdot}0.75H_2O$	50—55	63.4 (63.4)	7.1 (7.35)	3.2 (3.35)
(15b)	$CH_2CH{=}CH_2$	C	15[e]	$C_{17}H_{23}NO_2{\cdot}C_4H_4O_4$	85—87	64.4 (64.75)	6.85 (7.0)	3.45 (3.6)
(20a)	Me	B	75	$C_{16}H_{23}NO_2{\cdot}C_4H_4O_4$	184—186	63.65 (63.65)	7.2 (7.2)	3.55 (3.7)
(20b)	$CH_2CH{=}CH_2$	B	77	$C_{18}H_{25}NO_2{\cdot}C_4H_4O_4{\cdot}0.22H_2O$	172—173	64.7 (64.85)	7.25 (7.3)	3.35 (3.45)
(20c)	$CH_2\overline{CHCH_2CH_2}$	B	76	$C_{19}H_{27}NO_2{\cdot}C_4H_4O_4$	192—194	66.2 (66.15)	7.65 (7.5)	3.3 (3.35)
(20d)	Bu^i	*d*	*d*	$C_{19}H_{29}NO_2{\cdot}C_4H_4O_4{\cdot}0.25H_2O$	187—190	64.95 (65.15)	8.1 (7.95)	3.2 (3.3)
(21a)	Me	B	81	$C_{16}H_{23}NO_2{\cdot}C_4H_4O_4$	163—165	63.45 (63.65)	7.25 (7.2)	3.6 (3.7)
(21b)	$CH_2CH{=}CH_2$	B	54[e]	$C_{18}H_{25}NO_2{\cdot}0.8C_4H_4O_4$[f]	198—200	66.65 (66.95)	7.55 (7.45)	3.75 (3.7)
(21c)	$CH_2\overline{CHCH_2CH_2}$	B	71	$C_{19}H_{27}NO_2{\cdot}C_4H_4O_4{\cdot}0.33H_2O$	80—84	64.9 (65.25)	7.15 (7.55)	3.25 (3.3)
(21d)	Bu^i	*d*	*d*	$C_{19}H_{29}NO_2{\cdot}C_4H_4O_4{\cdot}0.2CH_3OH$[f]	194—198	65.05 (65.4)	7.9 (8.0)	3.15 (3.3)
(21e)	$CH_2C(Me){=}CH_2$	B	87	$C_{19}H_{27}NO_2{\cdot}C_4H_4O_4$[f]	198—200	65.9 (66.15)	7.6 (7.5)	3.25 (3.35)
(26)	$CH_2\overline{CHCH_2CH_2}$	B	42	$C_{18}H_{25}NOS{\cdot}C_4H_4O_4{\cdot}0.75H_2O$	133—135	61.0 (61.0)	7.15 (7.1)	3.4 (3.25)

[a] A, NaSEt, DMF; B, LiSMe, DMF;[17] C, BBr_3, CH_2Cl_2. [b] Yield for salt unless otherwise indicated. [c] Maleate salt unless otherwise indicated. Fractional amounts of water were experimentally determined. [d] See Experimental section. [e] Yield for free base. [f] Fumarate salt.

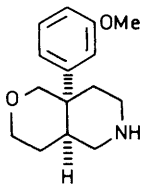
deferens (LVD) preparation, which contains only κ-opioid receptors.[14] However, this tissue only detects compounds with high efficacy and partial κ-agonists, which have insufficient efficacy to produce agonist effects, behave as antagonists.[15]

Most of the analogues (**13a**—**l**), (**15a**, **b**) displayed moderate antinociceptive activity of a similar order to that of the D-propoxyphene standard (Table 3). An exception was the highly potent (**13l**) where replacement of *N*-methyl by *N*-phenethyl resulted in a 75 fold increase in potency, parallelling the increase in antinociceptive activity that has been reported for the analogous structural modification in the benzomorphan series[16] (*i.e.* metazocine and phenazocine).

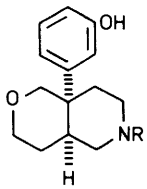
Varying the nature of the nitrogen substituent had a significant effect on the opioid receptor profile and the following discussion is confined to those derivatives where the available data is relatively clear cut. The *N*-allyl and *N*-cyclopropylmethyl analogues, (**13c**) and (**13f**) respectively, were the most selective κ-agonists of this series. *In vitro* (GPI) the β-FNA and β-CNA dose ratios for both compounds were consistent with selective κ-agonist profiles (Table 4) and this was substantiated *in vivo* by their diuretic effects (Table 3). However, both the diuresis and the LVD data indicate that (**13c**) is a lower efficacy compound than (**13f**) at the κ-opioid receptor. In contrast, the corresponding *cis*-fused analogues (**15a**) and (**15b**) and the direct homologues (**13h**) and (**13i**) showed a dramatic swing to predominantly μ-agonist profiles, as indicated by their marked



(13) **a**; R = Me
b; R = Pr
c; R = $CH_2CH=CH_2$
d; R = $CH_2C\equiv CH$
e; R = Bu^i
f; R = $CH_2\overline{CHCH_2CH_2}$
g; R = $CH_2C(Me)=CH_2$
h; R = $CH_2CH_2\overline{CHCH_2CH_2}$
i; R = $CH_2CH_2CH=CH_2$
j; R = $CH_2\overline{CHCH_2CH_2CH_2}$
k; R = $CH_2CH=CMe_2$
l; R = CH_2CH_2Ph



(14)



(15) **a**; R = $CH_2\overline{CHCH_2CH_2}$
b; R = $CH_2CH=CH_2$

antidiuretic effects and β-FNA shifts in the GPI. Similar μ-agonist profiles were shown by the *N*-cyclobutylmethyl (**13j**), *N*-3,3-dimethylallyl (**13k**), and *N*-phenethyl (**13l**) analogues.

We have also synthesized the *trans*-4a-aryldecahydroisoquinoline (**3**)[3,*] and compared its activity with that of its oxa analogue (**13f**). Although (**3**) possessed slightly greater antinociceptive activity, it is probably a less selective κ-agonist than (**13f**) since at doses of 5 mg/kg and 20 mg/kg, s.c. an *initial antidiuresis* was observed, followed by a low maximum diuresis. The thia analogue (**26**) displayed *ca.* a 5 fold greater antinociceptive activity than (**13f**).

Some intriguing changes in activity were observed upon substitution of a methyl group at C-4 of the pyran ring system. The 4-(equatorial)-methyl derivatives (**20a—d**) showed a marked fall in antinociceptive potency whereas, in contrast, several of the 4-(axial)-methyl series (**21a—d**) showed significantly increased activity over their unsubstituted counterparts. Of particular note is the *N*-cyclopropylmethyl analogue (**21c**) which was *ca.* 70 fold more potent than (**13f**). A further interesting feature is that these increases in antinociceptive activity apparently occurred without significant changes in receptor profile.

In summary, we have demonstrated that tetrahydropyridinyl anion chemistry is applicable to the synthesis of the pyrano- and thiopyrano[4,3-*c*]pyridine ring systems and substituted variants thereof. For the most part those analogues which we have examined showed moderate antinociceptive activity but some derivatives [*e.g.* (**13l**) and (**21c**)] were highly potent and comparable to the level observed for 6-oxamorphinans. The combination of new *in vivo* and *in vitro* test systems has enabled us to investigate the receptor profiles of the title compounds and in some instances clearly distinguish between μ- and κ-agonists.

Experimental

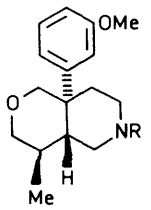
^{1}H N.m.r. spectra were measured ($SiMe_4$ internal standard) on a Bruker WM250 (250 MHz) spectrometer using 16K data points and a spectral width of 4.5 KHz. For the n.O.e. difference experiments 32 transients were collected at each irradiating frequency in turn, including the control (off-resonance) frequency. The decoupler power employed was 30L (fH_2 3.5 Hz). The addition and substraction of FIDS and spectra were accomplished using standard Bruker software. I.r. spectra were recorded on Perkin-Elmer 357 or 377 spectrometers. Mass spectral data were obtained using a VG 7070E instrument interfaced to an 11-250 data system. Spectroscopic and microanalytical data were obtained by Glaxo Chemical Analysis Department. All m.p.s are uncorrected.

Column chromatography was performed using either Merck Kieselgel 60 (Art 9385, flash chromatography) or alumina UG1 (Phase Separations Ltd.). Solvents were dried according to standard procedures.[18]

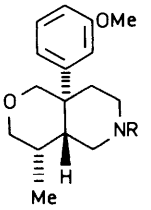
3,4,6,7,8,8a-*Hexahydro*-8a-(3-*methoxyphenyl*)-6-*methyl*-1H-*pyrano*[4,3-c]*pyridine* (**9a**).—Butyl-lithium (1.6M solution in hexane) was added dropwise to a stirred solution of the tetrahydropyridine (**7**)† (25.4 g, 125 mmol) in dry tetrahydrofuran (THF) (1 l) under nitrogen at −30 °C until a permanent red colour had formed. Further butyl-lithium (78 ml, 125 mmol) was then added slowly over 20 min with cooling at −30 °C. The resulting deep red solution was stirred for 15 min before it was cooled to −60 °C and transferred, *via* a double-ended needle, over a period of 1 h to a stirred solution of 2-chloro-1-(chloromethoxy)ethane (53.3 g, 415 mmol) in dry THF (200 ml) at −70 °C under nitrogen. The resulting solution was allowed to warm to −50 °C over a 2 h period before it was quenched with saturated brine (400 ml). The layers were separated and the aqueous layer extracted with pre-cooled diethyl ether (2 × 200 ml). The combined organic fractions were extracted with ice-cold 1M hydrochloric acid (2 × 400 ml). The acidic extracts were combined and washed with ice-cold diethyl ether (4 × 400 ml) before being adjusted to pH 14 by addition of 2M sodium hydroxide and extracted with dichloromethane (3 × 400 ml). The combined dichloromethane extracts were dried (Na_2SO_4) and evaporated to give the intermediate (**8a**) as a brown oil which was used directly in the next stage without further purification. This oil was dissolved with sodium iodide (75 g) in acetonitrile (800 ml) and the mixture was heated at reflux for 16 h. The reaction mixture was concentrated and the residue was stirred vigorously with a mixture of 2M sodium hydroxide (500

* Since the completion of our work Zimmerman *et al.*[3c] have published full details on the synthesis and analgesic properties of (**3**).

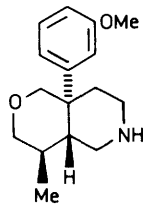
† **CAUTION** is recommended in the use of (**7**) which has been shown to possess neurotoxic properties. It is suggested that the corresponding *N*-ethyl derivative, which is considerably less neurotoxic, now be employed in place of (**7**).[19]



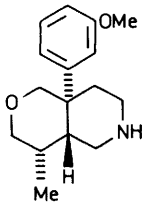
(16) a ; R = Me
b ; R = $CH_2CH=CH_2$
c ; R = $CH_2\overline{CHCH_2CH_2}$



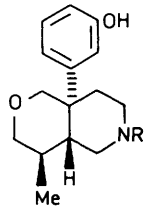
(17) a ; Me
b ; $CH_2CH=CH_2$
c ; $CH_2\overline{CHCH_2CH_2}$
d ; $CH_2C(Me)=CH_2$



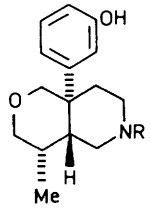
(18)



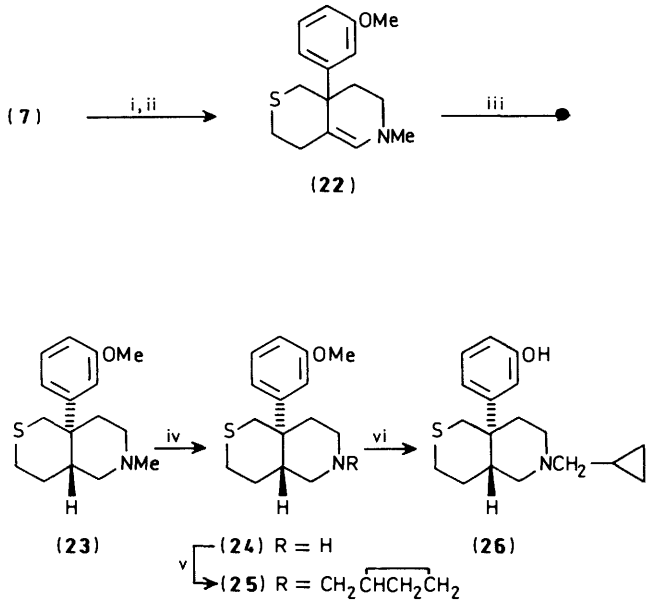
(19)



(20) a ; R = Me
b ; R = $CH_2CH=CH_2$
c ; R = $CH_2\overline{CHCH_2CH_2}$
d ; R = Bu^i



(21) a ; R = Me
b ; R = $CH_2CH=CH_2$
c ; R = $CH_2\overline{CHCH_2CH_2}$
d ; R = Bu^i
e ; R = $CH_2C(Me)=CH_2$



Scheme 2. *Reagents:* i, (a) BuLi, THF, −20 °C; (b) $ClCH_2SCH_2CH_2Cl$, −70 °C; ii, NaI, CH_3CN, heat; iii, (a) $MeSO_3H$, MeOH, −65 °C; (b) $NaBH_4$; iv, (a) $ClCO_2Ph$, Bu^i_3N, $ClCH_2CH_2Cl$, (b) KOH, EtOH; v, $\overline{CH_2CH_2CH}$–CH_2Br, $NaHCO_3$, DMF; vi, LiSMe, DMF

ml) and diethyl ether (1 l). The ether layer was separated and the aqueous/oily gum phases were washed vigorously with diethyl ether (2 × 1 l). The combined ether fractions were dried ($MgSO_4$) and concentrated to give a dark brown oil. This material was purified by pressure-assisted column chromatography on alumina, eluting with diethyl ether, to provide the *title compound* (**9a**) (12.8 g, 40%) as a pale yellow oil; $\delta_H(CDCl_3)$ 1.65—1.95 (3 H, m), 2.40—2.78 (3 H, m), 2.62 (3 H, s, NCH_3), 3.30 (1 H, d, *J* 11 Hz, 1-H), 3.38 (1 H, ddd, *J* 3, 11, 13 Hz, 3β-H), 3.82 (3 H, s, OCH_3), 3.92 (1 H, dd, *J* 5.5, 11 Hz, 3α-H), 4.64 (1 H, d, *J* 11 Hz, 1-H), 5.96 (1 H, s, 5-H), 6.73 (1 H, m, ArH), 7.04 (2 H, m, ArH), and 7.25 (1 H, m, ArH).

3,4,6,7,8,8a-*Hexahydro*-8a-(3-*methoxyphenyl*)-4,6-*dimethyl*-1H-*pyrano*[4,3-c]*pyridine* (**9b**).—Butyl-lithium (1.55M solution in hexane) was added dropwise to a stirred solution of the tetrahydropyridine (**7**) (10.2 g, 50 mmol) in dry THF (200 ml) under nitrogen at −30 °C until a permanent red anion colour had formed. Further butyl-lithium (32 ml, 50 mmol; 1.55M solution in hexane) was then added dropwise over a 15 min period, with cooling at −30 °C. After being stirred for 15 min at −30 °C the deep red solution was cooled to −60 °C and transferred, *via* a double-ended needle, over a period of 1 h to a stirred solution of 2-chloro-1-(chloromethoxy)propane (9.3 g, 65 mmol) in THF (40 ml) at −70 °C under nitrogen. The resulting solution was stirred at −60 °C for 2 h before it was quenched with saturated brine (100 ml). After shaking, the layers were separated and the aqueous phase was extracted with diethyl ether (2 × 50 ml). The combined organic fractions were extracted with 1M hydrochloric acid (3 × 100 ml). The acidic extracts were combined, washed with diethyl ether (3 × 100 ml), basified to pH 14 using 2M aqueous sodium hydroxide, and extracted with dichloromethane (3 × 100 ml). The combined dichloromethane extracts were washed with saturated brine (30 ml), dried ($MgSO_4$), and concentrated to give a light brown oil. This was dissolved in 1-methylpyrrolidin-2-one (200 ml) and sodium iodide (30 g) and sodium bromide (10 g) was added. The stirred reaction mixture was heated at 130 °C for 6.5 h before it was cooled and quenched with 1M sodium hydroxide (250 ml). The mixture was extracted with diethyl ether (4 × 150 ml) and the combined ethereal extracts were washed with water (2 × 75 ml) and saturated brine (75 ml), dried ($MgSO_4$), and concentrated to give a dark red oil (9.9 g). This material was purified by column chromatography on alumina (activity II), eluting with diethyl ether–hexane–methanol (12:37:1), to give the *title compound* (**9b**) (6.14 g, 45%) as a pale brown oil (Found: C, 74.45; H, 8.65; N, 5.3. $C_{17}H_{23}NO_2$ requires C, 74.7; H, 8.5; N, 5.1%); $\delta_H(CDCl_3)$ 0.92 major, 0.86 minor (3 H, d, *J* 7 Hz, CH_3CH), 1.46 (dt), 1.61—1.83 (2 H, m), 2.25 (m), 2.37—2.75 (3 H, m), 2.65 major, 2.68 minor (3 H, s, NCH_3), 2.95 (1 H, t, *J* 11 Hz, 3-H axial), 3.29 major, 3.22 minor (1 H, d, *J* 11 Hz, 1-H), 3.7—3.9 (1 H, m, 3-H equatorial), 3.81 (3 H, s, OCH_3), 4.65 major, 4.79 minor (1 H, d, *J* 11 Hz, 1-H), 5.88 major, 6.02 minor (1 H, s, 5-H), 6.76 (1 H, m, ArH), 6.98—7.12 (2 H, m, ArH), and 7.25 (1 H, m, ArH). Irradiation of the signal at δ 5.88 caused a 4.7% n.O.e. enhancement to the signal at δ 0.92. Irradiation at δ 6.02 caused an 11% n.O.e. enhancement of the signal at δ 2.25 (1 H, m, 4-H).

trans-*Octahydro*-8a-(3-*methoxyphenyl*)-6-*methyl*-1H-*pyrano*-[4,3-c]*pyridine* (**10a**).—A solution of the enamine (**9a**) (560 mg,

Table 3. *In vivo* activities of 3-(octahydro-1*H*-pyrano- and thiopyran-[4,3-*c*]pyridin-8a-yl)phenols

Compound[a]	*N*-Substituent	Antinociceptive[b] ED_{50}	Urine Output[c]
(**13a**)	Me	3.6 (1.8—5.0)	NT[d]
(**13b**)	Pr	0.76 (0.43—1.30)	Mixed activity
(**13c**)	$CH_2CH{=}CH_2$	1.00 (0.66—1.55)	Diuretic[e]
(**13d**)	$CH_2C{\equiv}CH$	13.0 (7.9—22.8)	NT
(**13e**)	Bu^i	1.4 (0.9—2.5)	Antidiuretic
(**13f**)	$CH_2\overline{CHCH_2CH_2}$	3.6 (1.8—6.8)	Diuretic
(**13g**)	$CH_2C(Me){=}CH_2$	44% inhibition at 10	NT
(**13h**)	$CH_2CH_2\overline{CHCH_2CH_2}$	1.6 (0.6—3.2)	Antidiuretic
(**13i**)	$CH_2CH_2CH{=}CH_2$	0.5 (0.2—0.9)	Antidiuretic
(**13j**)	$CH_2\overline{CHCH_2CH_2CH_2}$	0.41 (0.19—0.67)	NT
(**13k**)	$CH_2CH{=}C(Me)_2$	2.2 (1.1—3.9)	NT
(**13l**)	CH_2CH_2Ph	0.048 (0.026—0.088)	Antidiuretic
(**15a**)	$CH_2\overline{CHCH_2CH_2}$	2.5 (1.2—4.3)	Antidiuretic
(**15b**)	$CH_2CH{=}CH_2$	2.1 (1.1—3.6)	NT
(**20a**)	Me	57% inhibition at 10	NT
(**21a**)	Me	0.6 (0.3—1.0)	NT
(**20b**)	$CH_2CH{=}CH_2$	56% inhibition at 10	NT
(**21b**)	$CH_2CH{=}CH_2$	0.37 (0.20—0.63)	Diuretic
(**20c**)	$CH_2\overline{CHCH_2CH_2}$	3.1 (1.7—6.1)	Mixed activity
(**21c**)	$CH_2\overline{CHCH_2CH_2}$	0.05 (0.03—0.10)	Diuretic
(**20d**)	Bu^i	63% inhibition at 10	NT
(**21d**)	Bu^i	1.6 (0.4—2.4)	NT
(**26**)	$CH_2\overline{CHCH_2CH_2}$	0.73 0.39—1.29)	NT
(**3**)	$CH_2\overline{CHCH_2CH_2}$	1.1 (0.4—2.7)	Mixed activity
Proxorphan		0.02 (0.013—0.029)	Diuretic
D-Propoxyphene		1.35 (0.52—2.1)	Antidiuretic

[a] Compounds are racemic. [b] Mouse acetylcholine-induced abdominal constriction test, mg/kg, s.c. (confidence limits). [c] Water-loaded rat. [d] Not tested (NT). [e] Low maximum effect.

2.16 mmol) in ethanol (20 ml) was hydrogenated over platinum oxide (Adams catalyst, 60 mg) at 60 p.s.i. for 10 h. The catalyst was removed by filtration through Hyflo and the filtrate evaporated to dryness. The residue was purified by column chromatography on alumina, with diethyl ether as eluant, to give the *title compound* (**10a**) which was characterized as its hydrochloride salt (263 mg, 41%), m.p. 240—242 °C (Found: C, 68.85; H, 7.95; N, 4.55. $C_{16}H_{23}NO_2{\cdot}HCl{\cdot}0.25H_2O$ requires C, 63.6; H, 8.15; N, 4.65%) (Found: $M^{+\cdot}$, 261.1728. $C_{16}H_{23}NO_2$ requires *M*, 261.1728); δ_H[$CDCl_3$ (free base)] 1.43 (1 H, dt, *J* 13, 3 Hz, 4α-H), 1.67 (1 H, dt, *J* 3, 13 Hz, 8α-H), 1.88 (1 H, br d, *J* 13 Hz, 8β-H), 1.91 (1 H, dt, *J* 2, 13 Hz, 7β-H), 2.25 (1 H, m, 4aα-H), 2.26 (3 H, s, NCH_3), 2.43 (1 H, dq, *J* 5, 13 Hz, 4β-H), 2.61 (1 H, dt, *J* 11, 3.5 Hz, 7α-H), 2.71 (1 H, dd, *J* 6, 11 Hz, 5α-H), 2.75 (1 H, t, *J* 11 Hz, 5β-H), 3.30 (1 H, d, *J* 12 Hz, 1α-H), 3.56 (1 H, ddd, *J* 3, 11, 12 Hz, 3α-H), 3.80 (3 H, s, OCH_3), 4.09 (1 H, dd, *J* 5, 11 Hz, 3β-H), 4.22 (1 H, d, *J* 11 Hz, 1β-H), 6.76 (1 H, dd, *J* 2, 8 Hz, ArH), 7.03—7.08 (2 H, m, 2 × ArH), and 7.26 (1 H, t, *J* 8 Hz, ArH). Irradiation at δ 7.05 caused n.O.e. enhancements to the signals at δ 1.88, 2.43, 2.75, and 4.22 of 9, 8.5, 9, and 6.5% respectively.

trans-6-(*Cyclobutylmethyl*)*octahydro*-8a-(3-*methoxyphenyl*)-1H-*pyrano*[4,3-c]*pyridine* (**10j**).—Cyclobutanecarboxylic acid chloride (0.52 ml, *ca.* 4.4 mmol) was added dropwise to a stirred solution of (**12**) (1.0 g, 4 mmol) and triethylamine (1.2 ml) in dichloromethane (24 ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 2 h after which 2M hydrochloric acid (50 ml) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the intermediate amide as a light brown oil.

A solution of this material in dry THF (20 ml) was added over 5 min to a stirred suspension of lithium aluminium hydride (0.5g) in dry THF at room temperature under nitrogen. The resulting mixture was heated at reflux overnight. After cooling, the reaction mixture was quenched by sequential addition of saturated aqueous sodium sulphate and 2M aqueous sodium hydroxide. The resulting mixture was filtered through Hyflo and the solids were washed with ethyl acetate (100 ml). The combined filtrates were dried (Na_2SO_4) and concentrated to give the *title compound* (1.12 g, 88%) as a colourless gum.

cis-*Octahydro*-8a-(3-*methoxyphenyl*)-6-*methyl*-1H-*pyrano*-[4,3-c]*pyridine* (**11a**).—A solution of the enamine (**9a**) (450 mg, 1.74 mmol) in glacial acetic acid (20 ml) was hydrogenated at room temperature over Adams catalyst (50 mg) at 50 p.s.i. for 15 h. The catalyst was removed by filtration through Hyflo and the filtrate diluted with water (20 ml) and basified with aqueous sodium hydroxide (5M; *ca.* 65 ml). The mixture was extracted with dichloromethane (3 × 25 ml) and the combined extracts were washed with saturated brine (25 ml), dried (Na_2SO_4), and evaporated to give a pale yellow oil (540 mg). This was purified by column chromatography on alumina (13.5 g), with diethyl ether as eluant, to afford the *title compound* (**11a**) (328 mg, 72%). This was characterized as its maleate salt, m.p. 138—139 °C (Found: C, 63.6; H, 7.4; N, 3.6. $C_{16}H_{23}NO_2{\cdot}C_4H_4O_4$ requires C, 63.65; H, 7.2; N, 3.7%); δ_H(CD_3OD) 1.65—1.85 (1 H, m), 2.10—2.44 (2 H, m), 2.70—4.23 (10 H, m), 2.79 (3 H, s, NCH_3), 3.84 (3 H, s, OCH_3), 6.78 (1 H, dd, ArH), 7.00 (2 H, m, ArH), and 7.29 (1 H, t, ArH).

trans-*Octahydro*-8a-(3-*methoxyphenyl*)-1H-*pyrano*[4,3-c]-*pyridine* (**12**).—Vinyl chloroformate (6.9 ml, 75 mmol) was added dropwise, over 5 min, to a stirred mixture of *trans*-octahydro-8a-(3-methoxyphenyl)-6-methyl-1*H*-pyrano[4,3-*c*]-pyridine (**10a**) (11.24 g, 43 mmol) and anhydrous potassium carbonate (11.9 g, 86 mmol) in dry 1,2-dichloroethane (150 ml) at −30 °C and under nitrogen. The mixture was warmed to room temperature over 10 min and then heated under reflux for 1 h. After cooling to room temperature further vinyl chloroformate (2.3 ml, 25 mmol) was added and the mixture heated under reflux for a further 2 h. Insoluble material was filtered off from the cooled reaction and the filtrate evaporated to give a yellow-brown solid. This material was purified by column chromatography on neutral alumina, with ethyl acetate as eluant, to give the intermediate carbamate (11.3 g, 83%) as a

Table 4. *In vitro* activities of 3-(octahydro-1*H*-pyrano- and -thiopyrano-[4,3-*c*]pyridin-8a-yl)phenols

Compound[a]	*N*-Substituent	IC_{50} (μM) in Rabbit Vas Deferens	IC_{50} (μM) In Guinea-pig Ileum	β-FNA Dose Ratio	β-CNA Dose Ratio
(**13b**)	Pr	Antagonist, pA_2 = 6.3	0.9	14.3 (14.1[b])	NT
(**13c**)	$CH_2C{=}CH_2$	Antagonist, pA_2 = 5.2	3.2	2.1 (15.4[b])	168 (6.9[b])
(**13e**)	Bu[i]	*c*	1.5	3.0 (19.6[b])	NT
(**13f**)	$CH_2CHCH_2CH_2$	3.5 ($E_{max.}$ 75%)	0.2	1.6 (21.7[b])	96 (10.3,[b] 137[f])
(**13h**)	$CH_2CH_2CHCH_2CH_2$	*c*	0.83	4.5 (5.5[b])	NT
(**13i**)	$CH_2CH_2CH{=}CH_2$	Antagonist, pA_1 = 5.2	0.21	8.5 (7.1[b])	NT
(**13j**)	$CH_2CHCH_2CH_2CH_2$	Antagonist, pA_2 = 5.5	0.19	4.9 (10.7[b])	NT
(**13k**)	$CH_2CH{=}C(Me)_2$	*c*	0.9	34.5 (14.2[b])	NT
(**13l**)	CH_2CH_2Ph	Antagonist, pA_2 = 5.9	0.04	10.4 (12.2[b])	NT
(**15a**)	$CH_2CHCH_2CH_2$	Antagonist, pA_2 = 5.6	NT	NT	NT
(**15b**)	$CH_2CH{=}CH_2$	NT	3.8	10 (16[b])	NT
(**21b**)	$CH_2CH{=}CH_2$	Antagonist, pA_2 = 6.4	0.025	NT	79.0 (5.7,[d] 45.4[f])
(**21c**)	$CH_2CHCH_2CH_2$	0.2[e] ($E_{max.}$ 50%)	0.006	0.9 (20.3[d])	29.0 (3.0,[d] 58.0[f])
(**20c**)	$CH_2CHCH_2CH_2$	Antagonist, pA_2 = 5.6	0.34	4.4	42.0 (2.5,[d] 43.4[f])
(**21d**)	Bu[i]	Antagonist, pA_2 = 6.9	0.053	NT	18.7 (3.4,[d] 205[f])
(**26**)	$CH_2CHCH_2CH_2$	Antagonist, pA_2 = 6.4	NT	NT	NT
(**3**)	$CH_2CHCH_2CH_2$	*g*	0.15	2.9 (23.4[b])	NT
Proxorphan		*h*	0.024	1.5[i]	105[i]
Ethylketocyclazocine		0.03			
Normorphine			0.15		

[a] Compounds are racemic. [b] Data for the μ-agonist normorphine. [c] No significant agonist effect at 10^{-5}M; no antagonism of ethylketocyclazocine at 10^{-5}M. [d] Data for the μ-agonist DAGO. [e] IC_{25}. [f] Data for the κ-agonist U-50488. [g] $E_{max.}$ 24% at 1 μM. [h] $E_{max.}$ 28% at 0.1 μM. [i] See ref. 13*b*.

yellow oil. This oil (9.88 g, 31.1 mmol) was dissolved in dry methanol (150 ml) and a solution of methanolic hydrogen chloride (2M; 40 ml) added. The mixture was heated at reflux under nitrogen for 3 h. The cooled reaction mixture was evaporated to give a brown oil which was dissolved in water (150 ml) and washed with dichloromethane (3 × 50 ml). The aqueous phase was basified to *ca.* pH 12 with aqueous sodium hydroxide (5M; 15 ml) and the mixture extracted with dichloromethane (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give the *title compound* (7.63 g, 98%) as a pale yellow oil; $\delta_H(CDCl_3)$ 1.43 (**1** H, dt, *J* 13, 3 Hz, 4α-H), 1.59 (1 H, dt, *J* 3, 13 Hz, 8α-H), 1.87 (1 H, dt, *J* 13, 2 Hz, 8β-H), 2.13 (1 H, tt, *J* 3.5, 12.5 Hz, 4aα-H), 2.24 (1 H, br s, NH), 2.37 (1 H, dq, *J* 5, 13 Hz, 4β-H), 2.55 (1 H, dt, *J* 2, 13 Hz, 7β-H), 2.83—2.94 (2 H, m, 5α and 7α-H), 3.33 (1 H, d, *J* 11 Hz, 1α-H), 3.45 (1 H, t, *J* 12.5 Hz, 5β-H), 3.60 (1 H, dt, *J* 2.5, 11.5 Hz, 3α-H), 3.80 (3 H, s, OCH_3), 4.07 (1 H, dd, *J* 5, 11 Hz, 3β-H), 4.17 (1 H, d, *J* 11 Hz, 1β-H), 6.75 (1 H, m, ArH), 7.04—7.10 (2 H, m, ArH), and 7.27 (1 H, t, ArH). This material was used directly in the next stage without purification.

cis-*Octahydro*-8a-(3-*methoxyphenyl*)-1H-*pyrano*[4,3-c]-*pyridine* (**14**).—This compound (88%) was prepared from the pyrano[4,3-*c*]pyridine (**11a**) as described for the preparation of (**12**) and was obtained as a colourless oil. This material was used directly in the next stage without purification.

(4α,4aα,8aβ)-*Octahydro*-8a-(3-*methoxyphenyl*)-4,6-*dimethyl*-1H-*pyrano*[4,3-c]*pyridine* (**16a**) *and* (4α,4aβ,8aα)-*Octahydro*-8a-(3-*methoxyphenyl*)-4,6-*dimethyl*-1H-*pyrano*[4,3-c]*pyridine* (**17a**).*—The enamine (**9b**) (5.74 g, 21 mmol) was hydrogenated (70 p.s.i.) over Adams catalyst (0.50 g) in ethanol (100 ml) at room temperature for 18 h. The reaction mixture was filtered through Hyflo and the filtrate evaporated to give an orange oil. This material was dissolved in 1M hydrochloric acid (100 ml) and washed with diethyl ether (2 × 50 ml). The acidic aqueous phase was basified to pH 14 using 5M sodium hydroxide and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were washed with aqueous saturated brine (75 ml), dried (Na_2SO_4), and evaporated to give an orange oil. Trituration of this oil with diethyl ether afforded the *title compound* (**16a**) (1.40 g, 24%) as a colourless crystalline solid, m.p. 115—116 °C (Found: C, 73.75; H, 9.3; N, 5.0. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.1%); $\delta_H(CDCl_3)$ 0.84 (3 H, d, *J* 7 Hz, CH_3CH), 1.78 (1 H, dt, *J* 4, 11 Hz, 4aα-H), 1.6—1.94 (3 H, m, 8α-, 8β-, and 7β-H), 2.28 (3 H, s, NCH_3), 2.43—2.64 (3 H, m), 2.94 (1 H, dd, *J*, 11, 3 Hz, 5α-H), 3.06 (1 H, t, *J* 11 Hz, 3α-H), 3.30 (1 H, d, *J* 11 Hz, 1α-H), 3.81 (3 H, s, OCH_3), 3.92 (1 H, dd, *J* 5, 11 Hz, 3β-H), 4.22 (1 H, d, *J* 11 Hz, 1β-H), 6.72 (1 H, m, ArH), 7.08 (2 H, m, ArH), and 7.26 (1 H, m, ArH). Irradiation at δ 0.84 caused the signal at δ 2.43—2.64 to simplify and revealed (dt, *J* 5, 11 Hz, 4β-H) by decoupling difference spectroscopy. The mother liquors from the above trituration were subjected to flash chromatography on silica gel. Elution with dichloromethane–methanol–ammonia (*d* 0.880) (120:8:1) gave a second crop of (**16a**) (0.83 g, 14%) and the isomeric (**17a**) (1.37 g, 24%) as a pale orange oil (Found: C, 74.0; H, 9.4; N, 5.15. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.1%); $\delta_H(CDCl_3)$ 0.81 (3 H, d, *J* 7 Hz, CH_3CH), 1.48 (1 H, dt, *J* 13, 3 Hz, 8α-H), 1.65 (1 H, dt, *J* 4, 13 Hz, 8β-H), 1.80 (1 H, m, 4β-H), 2.38 (1 H, dt, *J* 12, 4 Hz, 4aβ-H), 2.43 (3 H, s, NCH_3), 2.44 (1 H, dt, *J* 4, 12 Hz, 7α-H), 2.62—2.72 (2 H, m, 5β-H and 7β-H), 3.04 (1 H, t, *J* 12 Hz, 5α-H), 3.19 (1 H, d, *J* 12 Hz, 1β-H), 3.70—3.82 (2 H, m, 3α- and 3β-H), 3.81 (3 H, s, OCH_3), 4.59 (1 H, d, *J* 12 Hz, 1α-H), 6.75 (1 H, dt, *J* 7.5, 2 Hz, ArH), and 7.18—7.28 (3 H, m, 3 × ArH).

(4α,4aα,8aβ)-*Octahydro*-8a-(3-*methoxyphenyl*)-4-*methyl*-1H-*pyrano*[4,3-c]*pyridine* (**18**).—Vinyl chloroformate (1.0 ml, 1.17 g, 11 mmol) was added to a stirred suspension of potassium carbonate (1.5 g) and the pyrano[4,3-*c*]pyridine (**16a**) (1.51 g, 5.5 mmol) in 1,2-dichloroethane (30 ml) at −30 °C under

* Substitutive nomenclature: The α-side of the reference plane is that side on which the preferred substituent lies at the lowest numbered stereogenic position.

nitrogen. The reaction mixture was heated at reflux for 2 h. A second portion of vinyl chloroformate (0.5 ml, 0.58 g, 5.5 mmol) was added and heating at reflux was continued for a further 2 h before filtering and concentrating to give a brown gum (2.04 g). This material was purified by flash chromatography on silica gel, using dichloromethane–methanol (19:1) as the eluant, to give the intermediate carbamate as a light orange oil. This oil was dissolved in methanol (25 ml) and methanolic HCl (65 ml) was added. The stirred solution was heated at reflux under nitrogen for 5 h and then evaporated to give an oil which was dissolved in 1M hydrochloric acid (75 ml) and washed with diethyl ether (2 × 25 ml). The aqueous phase was basified to pH 14 using 5M sodium hydroxide and extracted with dichloromethane (3 × 75 ml). The combined organic extracts were washed with aqueous saturated sodium chloride (75 ml), dried (Na_2SO_4) and concentrated to give the *title compound* (**18**) (1.14 g, 90%) as a pale brown oil (Found: $M^{+\bullet}$, 261.1728. $C_{16}H_{23}NO_2$ requires *M*, 261.1729); $\nu_{max.}$(liquid) 2 500—3 100 cm^{-1} (NH); $\delta_H(CDCl_3)$ 0.84 (3 H, d, *J* 7 Hz, CH_3CH), 1.59 (1 H, dt, *J* 4, 13 Hz, 8α-H), 1.73 (1 H, dt, *J* 4, 13 Hz, 7β-H), 1.88 (1 H, dt, 13, 2 Hz, 8β-H), 2.43—2.61 (2 H, m, 4β- and 4aα-H), 2.88 (1 H, dt, *J* 13, 3 Hz, 7α-H), 3.10 (1 H, t, *J* 11 Hz, 3α-H), 3.17 (1 H, dd, *J* 4, 12 Hz, 5α-H), 3.33 (1 H, t, *J* 12 Hz, 5β-H), 3.34 (1 H, d, *J* 11 Hz, 1α-H), 3.35 (1 H, br s, NH), 3.81 (3 H, s, OCH_3), 3.92 (1 H, dd, *J* 5, 11 Hz, 3β-H), 4.17 (1 H, d, *J* 11 Hz, 1β-H), 6.74 (1 H, m, ArH), 7.03—7.10 (2 H, m, ArH), and 7.27 (1 H, t, ArH).

(4α,4aβ,8aα)-*Octahydro*-8a-(3-*methoxyphenyl*)-4-*methyl*-1H-*pyrano*[4,3-c]*pyridine* (**19**).—This *compound* (65%) was prepared from the pyrano[4,3-*c*]pyridine (**17a**) as described for the preparation of (**18**) and was obtained, after flash chromatography on silica gel [dichloromethane–methanol–ammonia (*d* 0.880) (60:8:1) as eluant], as a pale yellow oil (Found: C, 73.45; H, 8.7; N, 5.2. $C_{16}H_{23}NO_2$ requires C, 73.55; H, 8.85; N, 5.35%); $\nu_{max.}$(liquid) 3 300 cm^{-1} (NH); $\delta_H(CDCl_3)$ 0.78 (3 H, d, *J* 7 Hz, CH_3CH), 1.39—1.55 (2 H, m, 8α- and 8β-H), 1.78 (1 H, m, 4β-H), 1.97 (1 H, br s, NH), 2.23 (1 H, dt, *J* 12, 4 Hz, 4aβ-H), 2.74 (1 H, dd, *J* 4, 12 Hz, 5β-H), 2.86 (1 H, ddd, *J* 2, 4, 13 Hz, 7β-H), 3.09 (1 H, dt, *J* 4, 12.5 Hz, 7α-H), 3.21 (1 H, d, *J* 11 Hz, 1β-H), 3.67 (1 H, t, *J* 12 Hz, 5α-H), 3.71—3.83 (2 H, m, 3α- and 3β-H), 3.81 (3 H, s, OCH_3), 4.55 (1 H, d, *J* 11 Hz, 1α-H), 6.75 (1 H, m, ArH), and 7.2—7.35 (3 H, m, ArH).

(4α,4aα,8aβ)-3-[*Octahydro*-4-*methyl*-6-(2-*methylpropyl*)-1H-*pyrano*[4,3-c]*pyridin*-8a-*yl*]*phenol* (**20d**).—A mixture of (**20c**) (maleate salt) (250 mg, 0.6 mmol) and platinum oxide (Adams catalyst, 100 mg) in acetic acid (3 ml) was hydrogenated (70 p.s.i.) at 60 °C for 3 days. The reaction mixture was filtered through Hyflo and the filtrate basified, by addition of 5M sodium hydroxide, and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed with saturated brine (50 ml), dried (Na_2SO_4), and evaporated to give a colourless gum. This material was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (*d* 0.880) (200:8:1) as the eluant, to give the *title compound* (**20d**) (70 mg, 39%) as a colourless foam. This compound was characterized as its maleate salt (see Table 2).

(4α,4aβ,8aα)-3-[*Octahydro*-4-*methyl*-6-(2-*methylpropyl*)-1H-*pyrano*[4,3-c]*pyridin*-4a-*yl*]*phenol* (**21d**).—A mixture of (**21e**) (180 mg, 0.6 mmol) and platinum oxide (Adams catalyst, 60 mg) in ethanol (5 ml) was hydrogenated (1 atm) at room temperature. The catalyst was removed by filtration through Hyflo and the filtrate evaporated to give a yellow gum. This material was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (*d* 0.880) (150:8:1) as eluant, to give the *title compound* (**21d**) (50 mg, 28%) which was characterized as its fumarate salt (see Table 2).

3,4,6,7,8,8a-*Hexahydro*-8a-(3-*methoxyphenyl*)-6-*methyl*-1H-*thiopyrano*[4,3-c]*pyridine* (**22**).—Butyl-lithium (1.55M solution in hexane) was added dropwise to a stirred solution of the tetrahydropyridine (**7**) (2.0 g, 9.84 mmol) in dry THF (60 ml) under nitrogen at −20 °C until a permanent red anion colour had formed. Further butyl-lithium (7 ml, 10.85 mmol; 1.55M solution in hexane) was then added dropwise with cooling at −20 °C. The mixture was stirred at −20 °C for 10 min before cooling to −70 °C. This solution was transferred *via* a double-ended needle to a stirred solution of 2-chloroethylchloromethyl sulphide (2.86 g, 19.7 mmol) in dry THF (20 ml) at −70 °C under nitrogen. Stirring was continued at −70 °C for 1 h, before quenching with saturated brine (40 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 ml). The combined organic extracts were extracted with 1M hydrochloric acid (2 × 50 ml). The combined acidic extracts were washed with diethyl ether (3 × 30 ml) and then basified by the addition of 2M sodium hydroxide. The resultant aqueous solution was extracted with ether (3 × 100 ml) and the combined ether extracts were dried ($MgSO_4$) and evaporated to afford a brown oil (2.7 g). A portion of this oil (2.0 g) was dissolved in dry acetonitrile (60 ml), sodium iodide (3.0 g, 20 mmol) was added, and the resulting mixture heated at reflux for 8 h. The cooled mixture was evaporated to dryness and the residue was partitioned between ether (70 ml) and 2M sodium hydroxide (50 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. This material was purified by column chromatography on alumina, with diethyl ether as eluant, to give the *title compound* (**22**) (680 mg, 25%) as a colourless oil; $\delta_H(CDCl_3)$ 1.82—2.05 (2 H, m), 2.2—2.3 (1 H, m), 2.4—2.75 (5 H, m), 2.60 (3 H, s, NCH_3), 2.82 (1 H, d, *J* 14 Hz, 1-H), 3.28 (1 H, d, *J* 14 Hz, 1-H), 3.82 (3 H, s, OCH_3), 5.92 (1 H, s, 5-H), 6.77 (1 H, m, ArH), 6.95 (2 H, m, ArH), and 7.3 (1 H, m, ArH).

trans-*Octahydro*-8a-(3-*methoxyphenyl*)-6-*methyl*-1H-*thiopyrano*[4,3-c]*pyridine* (**23**).—Methanesulphonic acid (0.512 g, 0.35 ml, 5.33 mmol) was added dropwise to a stirred solution of (**22**) (610 mg, 2.22 mmol) in methanol (50 ml) at −65 °C. The reaction mixture was stirred at −65 °C for 10 min, quickly warmed to 20 °C, and sodium borohydride (2.35 g, 62.1 mmol) was added portionwise. The mixture was stirred at room temperature for 30 min, saturated ammonium chloride (15 ml) was added, and the methanol was evaporated. The residue was treated with 2M hydrochloric acid (10 ml) and the solution was washed with ether (2 × 50 ml). The combined ethereal washings were re-extracted with 2M hydrochloric acid (50 ml). The combined aqueous layers were basified with 5M sodium hydroxide and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4), and evaporated to give a colourless gum. This material was purified by flash column chromatography on silica gel with dichloromethane–methanol–ammonia (*d* 0.880) (150:8:1) as eluant to give the *title compound* (**23**) (534 mg, 87%) as a colourless gum (Found: C, 69.6; H, 8.6; N, 5.0; S, 11.9. $C_{16}H_{23}NOS$ requires C, 69.25; H, 8.35; N, 5.05; S, 11.5%); $\delta_H(CDCl_3)$ 1.70—2.10 (5 H, m), 2.25 (3 H, s, NCH_3), 2.44 (1 H, dq, *J* 4, 13 Hz, 4β-H), 2.55—2.68 (3 H, m), 2.75 (1 H, t, *J* 12 Hz, 5β-H), 2.79—2.99 (3 H, m), 3.82 (3 H, s, OCH_3), 6.75 (1 H, m, ArH), 7.05 (2 H, m, ArH), and 7.27 (1 H, t, ArH). Irradiation at δ 7.05 caused n.O.e. enhancements to the signals at δ 2.05 (7β-H), 2.44 (4β-H), 2.75 (5β-H), and 2.95 (1β-H).

trans-*Octahydro*-8a-(3-*methoxyphenyl*)-1H-*thiopyrano*-[4,3-c]*pyridine* (**24**).—Phenyl chloroformate (0.493 g, 0.39 ml, 3.15 mmol) was added to a stirred solution of (**23**) (436 mg, 1.57 mmol) and tri-isobutylamine (0.146 g, 0.2 ml, 0.785 mmol) in 1,2-dichloroethane (7 ml) at room temperature under nitrogen. The

resulting solution was heated at reflux for 2.5 h. After cooling, the solution was diluted with diethyl ether (50 ml) and washed successively with 1M hydrochloric acid (2 × 20 ml), 1M sodium hydroxide (3 × 20 ml), and saturated brine (30 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the intermediate carbamate as a colourless oil. A solution of this intermediate in a mixture of absolute ethanol (30 ml) and 50% potassium hydroxide (10 ml) was heated at reflux under nitrogen for 20 h. The solvent was evaporated from the cooled reaction mixture and the residue was diluted with water (50 ml). The aqueous layer was extracted with dichloromethane (4 × 30 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a yellow oil (410 mg) which was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (*d* 0.880) (60:8:1) as eluant, to give the *title compound* (**24**) (339 mg, 82%) as a colourless gum (Found: C, 64.8; H, 7.85; N, 5.0. $C_{15}H_{21}NOS \cdot 1.25H_2O$ requires C, 64.5; H, 7.95; N, 4.7%); $\delta_H(CDCl_3)$ 1.67—1.81 (2 H, m), 1.85—2.08 (2 H, m), 2.41 (1 H, dq, *J* 4, 12 Hz, 4β-H), 2.48—2.75 (3 H, m), 2.75—2.95 (4 H, m), 3.45 (1 H, br, NH), 3.45 (1 H, t, *J* 12.5 Hz, 5β-H), 3.82 (3 H, s, OCH_3), 6.75 (1 H, m, ArH), 7.02 (2 H, m, ArH), and 7.28 (1 H, m, ArH).

Typical Procedures for O-*Demethylation Reactions* (*see Table* 2). *Method A.*—A 1M solution of sodium ethanethiolate in dry dimethylformamide (DMF) (10 ml, 10 mmol) was added in one portion to the (3-methoxyphenyl)pyrano[4,3-*c*]pyridine (2.5 mmol) and the resulting mixture heated at reflux under nitrogen for 3 h. After cooling, the reaction mixture was concentrated and the residue was applied directly to an alumina column. Elution with dichloromethane followed by dichloromethane–methanol (9:1) gave the free base as an oil. This material was dissolved in 1M hydrochloric acid (30 ml) and the resulting solution was washed with dichloromethane (2 × 20 ml) before basification with 5M aqueous sodium hydroxide (to pH 14) and again washing with dichloromethane (2 × 20 ml). The aqueous solution was then adjusted to pH 7.5 and extracted with dichloromethane (4 × 40 ml), adjusting the pH to 7.5 after each extraction. The latter extracts were combined, dried ($MgSO_4$), and evaporated to give pure 3-(pyrano[4,3-*c*]pyridin-8a-yl)-phenol.

Method B.—Lithium methanethiolate (10 mmol) was added to a stirred solution of the (3-methoxyphenyl)pyrano[4,3-*c*]pyridine (1.67 mmol) in DMF (10 ml) under nitrogen and the resulting solution was heated at 130 °C for 3 h. The cooled reaction mixture was quenched by addition of ammonium chloride (0.54 g, 10 mmol), and then concentrated to remove the DMF. The crude product was purified by flash silica chromatography.

Method C.—Boron tribromide (3.0 ml of a 1M solution in dichloromethane, 3 mmol) was added dropwise over 3 min to a stirred solution of the (3-methoxyphenyl)pyrano[4,3-*c*]pyridine (1 mmol) in dry dichloromethane (10 ml) at room temperature under nitrogen. The reaction mixture was stirred for 16 h before adding methanol and stirring for a further 2 h. The reaction mixture was concentrated and the residue was stirred vigorously with a mixture of 5M aqueous sodium hydroxide (5 ml) and methanol (5 ml) for 2 h followed by addition of water (30 ml). The resulting mixture was washed with dichloromethane (2 × 30 ml) and then adjusted to pH 1 by addition of 5M aqueous hydrochloric acid. After a further wash with dichloromethane (2 × 30 ml), the aqueous layer was adjusted to pH 7.5 and extracted with dichloromethane (4 × 40 ml, adjusting the pH to 7.5 after each extraction). The combined extracts were dried (Na_2SO_4) and evaporated to give the crude product which was purified by flash silica chromatography.

Pharmacological Methods.—*In vivo.* The mouse acetylcholine-induced abdominal constriction test[20] and the rat urine output experiments[12] were performed as previously described.

In vitro. Activity in the rabbit vas deferens preparation was determined as previously described[15] and pA_2 values were calculated using a single antagonist concentration. Determination of the receptor selectivity of opioid agonists in the guinea-pig ileum using β-FNA[13a] and β-CNA[13b] utilized previously described methodology.

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