Synthesis, Antinociceptive Activity and Opioid Receptor Profiles of *trans*-3-(Octahydro-2*H*-pyrano[2,3-*c*]pyridin-4a-yl)phenols and *trans*-3-(Octahydro-1*H*-pyrano[3,4-*c*]pyridin-4a-yl)phenols

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The synthesis of a series of novel *trans*-3-(octahydro-2*H*-pyrano[2,3-*c*]pyridin-4a-yl)phenols (**12a—g**), (**20a—c**), (**21**), (**22**) and *trans*-3-(octahydro-1*H*-pyrano[3,4-*c*]pyridin-4a-yl) phenols (**28a, b**), (**34**) is described. Construction of the pyrano[2,3-*c*]pyridines is achieved *via* annulation of the pyran ring onto the arylpiperidin-3-ones (**6**) and (**14**) (R = CO_2Ph). The pyrano[3,4-*c*]pyridines are synthesized by application of metallated enamine chemistry to 1-methyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (**4**) and proceeds *via* the novel 2-oxa-8-azabicyclo[3.3.1]nonane (**23**) and the bicyclic enamines (**24**) and (**29**). Manipulation of this general methodology has afforded a number of structural variants bearing strategic substitutions in the pyran ring as well as alternative *N*-groups. The antinociceptive activity and opioid receptor profile of these compounds has been determined and structure-activity relationships are discussed.

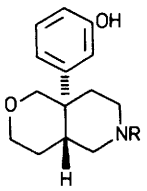
In the previous paper[1] we described the synthesis and biological activity of a series of *trans*-3-(octahydro-1*H*-pyrano-[4,3-*c*]pyridin-8a-yl)phenols (**1**). In particular we reported on their antinociceptive activity and discussed structure activity relationships in terms of their action at opioid receptor subtypes. We now report on an extension of these studies to the related bicyclic systems *trans*-3-(octahydro-2*H*-pyrano[2,3-*c*]-pyridin-4a-yl)phenols (**2a**) and *trans*-3-(octahydro-1*H*-pyrano[3,4-*c*]pyridin-4a-yl)phenols (**3a**). Mindful of our earlier observations that substitution in the pyran ring of (**1**) resulted in interesting changes in pharmacological profile,[1] we have devised syntheses of (**2a**) and (**3a**) which allow further structural modification of these systems. Thus, by analogy to known changes to the C-ring of morphinans,[2] we have incorporated substituents at C-3 and C-8a in the pyrano[2,3-*c*]pyridine series (**2b** and **c**) and a methyl group at C-1 in the pyrano[3,4-*c*]-pyridine system (**3b**).

The central intermediate in our synthesis of the pyrano[2,3-*c*]-pyridine ring system was the novel α-allyl ketone (**7**) which was obtained in three steps from the readily synthesized tetrahydropyridine (**4**) (Scheme 1). Hydroboration of (**4**), using *in situ* generation of diborane,[3] followed by oxidation of the intermediate alkylborane gave the piperidinol (**5**) in excellent yield. Swern oxidation of (**5**) afforded the piperidin-3-one (**6**) which, although unstable to silica gel or alumina chromatography, could be obtained pure by rapid crystallization of the crude reaction product from hexane. Allylation of the enolate anion generated from (**6**) provided (**7**) in 55% overall yield from (**4**). Hydroboration of the allyl side-chain of (**7**) and reduction of the ketone function were accomplished in a single stage, by using an excess of borane with oxidative work-up, giving the diol (**8a**). Only one isomer was isolated from this reaction and its relative stereochemistry (as shown) was inferred by subsequent conversion to the *trans*-fused pyrano[2,3-*c*]pyridine (**9a**) (see below). Mesylation of (**8a**) followed by treatment of the crude product with sodium hydride in dimethylformamide (DMF) afforded smooth conversion to the target bicyclic system (**9a**). Assignment of the *trans* ring fusion of (**9a**) was based upon the following ^1H n.m.r. spectral data. Thus, irradiation of 6′-ArH (proton *para* to methoxy substituent) causes an n.O.e. enhancement of the 4α-, 5α-, and 8α-H signals. Furthermore, the signal for 8aβ-H shows couplings of 11 Hz and 4 Hz to 8α- and 8β-H, respectively, indicative of a *trans*-diaxial relationship of 8aβ- and 8α-H.

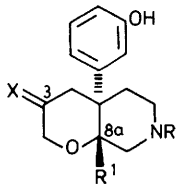
N-Demethylation of (**9a**) *via* the vinyl carbamate (**10a**) gave the secondary amine (**11a**) which was alkylated to give (**9b** and **c**). The *N*-cyclobutylmethyl derivative (**9d**) was prepared *via* acylation of (**11a**) and reduction of the resultant amide. *O*-Demethylation of (**9a—d**) (Table 1) provided the requisite phenols (**12a—d**) for biological evaluation.

Compounds in the 8a-methyl series (**9e—g**) were synthesized using an analogous approach. Thus, addition of methyl-lithium to the key intermediate α-allyl ketone (**7**) proceeded with high stereoselectivity to give a single tertiary alcohol (**13**). Subsequent hydroboration of (**13**) and cyclization of the intermediate diol (**8b**) afforded the 8a-methyl derivative (**9e**) in 40% overall yield from (**7**). The *trans* ring fusion of (**9e**) was established by n.O.e. difference experiments: irradiation of the 8a-methyl group caused enhancement of only 8β-H whereas irradiation of 6′-Ar*H* gave an enhancement of 8α-H. *N*-Demethylation of (**9e**) *via* the phenyl carbamate (**10b**) gave the secondary amine (**11b**) which was converted into (**9f**) and (**9g**) in the usual way. *O*-Demethylation of (**9e—g**) (Table 1) gave the phenols (**12e—g**) for biological testing.

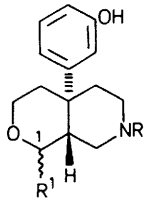
Our strategy for introducing substitution at C-3 of the pyrano[2,3-*c*]pyridine system centred on incorporating an exocyclic methylene group which could then serve as a precursor for 3-oxo- and 3-hydroxy derivatives (Scheme 2). Initial attempts to alkylate the enolate of ketone (**6**) with 3-chloro-2-chloromethylprop-1-ene resulted in low yields of polar material, presumably arising from quaternization of intermediates, *e.g.* (**15**; R = Me). We therefore elected to use the corresponding phenyl carbamate (**14**; R = CO_2Ph) in place of (**6**). Conversion of the piperidinol (**5**) into the carbamate (**17b**) in a single step, using phenyl chloroformate in 1,2-dichloroethane in the presence of potassium carbonate at reflux, gave low yields. However, a two-stage procedure in which the intermediate carbonate (**17a**) was formed at room temperature, isolated and then converted into (**17b**) under the usual conditions gave excellent yields.



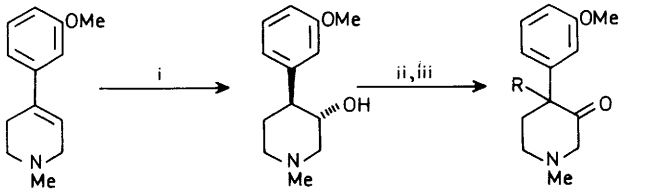
(1)



(2) a; R^1 = H, X = H_2
b; R^1 = Me, X = H_2
c; R^1 = H, X = O, CH_2



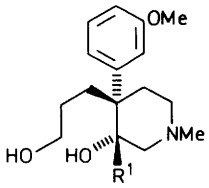
(3) a; R^1 = H
b; R^1 = Me



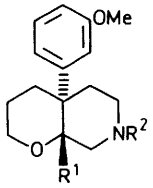
(4) (5) (6) R = H
(7) R = $CH_2CH=CH_2$

Scheme 1. *Reagents:* i, (a) $NaBH_4$, BF_3·Et_2O, diglyme; (b) H_2O_2, NaOH; ii, $(COCl)_2$, DMSO, Et_3N; iii, NaH, CH_2=$CHCH_2Br$, DMF

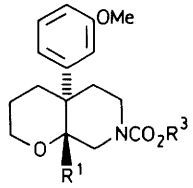
Selective hydrolysis of the carbonate group in (**17b**) is critically dependent upon the reaction conditions employed, the optimum conditions being potassium carbonate in aqueous methanol at 58 °C for 40 min to give (**17c**) in 80% yield. More vigorous conditions caused extensive formation of the corresponding methyl carbamate (**17d**). Swern oxidation of (**17c**) gave the requisite piperidinone (**14**; R = CO_2Ph) in excellent yield. The crucial alkylation of (**14**; R = CO_2Ph) with 3-chloro-2-chloromethylprop-1-ene, using sodium hydride in DMF at −50 °C to generate the enolate, now occurred in the required manner and, upon warming the reaction mixture, cyclization to the bicyclic enamide (**16a**) was also achieved. Although the yield for this step was only *ca.* 40%, it did provide



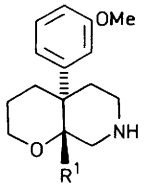
(8) a; R^1 = H
b; R^1 = Me



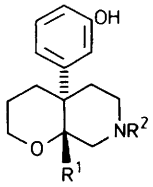
(9) a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = $CH_2\overline{CHCH_2CH_2}$
c; R^1 = H, R^2 = $CH_2CH=CH_2$
d; R^1 = H, R^2 = $CH_2\overline{CHCH_2CH_2CH_2}$
e; R^1 = R^2 = Me
f; R^1 = Me, R^2 = $CH_2\overline{CHCH_2CH_2}$
g; R^1 = Me, R^2 = $CH_2\overline{CHCH_2CH_2CH_2}$



(10) a; R^1 = H, R^3 = $CH=CH_2$
b; R^1 = Me, R^3 = Ph



(11) a; R^1 = H
b; R^1 = Me



(12) a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = $CH_2\overline{CHCH_2CH_2}$
c; R^1 = H, R^2 = $CH_2CH=CH_2$
d; R^1 = H, R^2 = $CH_2\overline{CHCH_2CH_2CH_2}$
e; R^1 = R^2 = Me
f; R^1 = Me, R^2 = $CH_2\overline{CHCH_2CH_2}$
g; R^1 = Me, R^2 = $CH_2\overline{CHCH_2CH_2CH_2}$

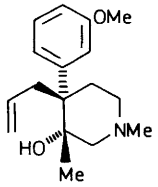


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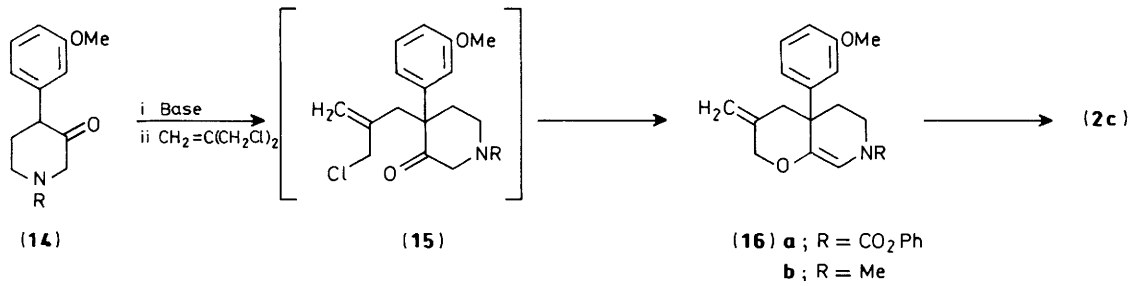
Table 1. Preparation of *trans*-3-(octahydro-2*H*-pyrano[2,3-*c*]pyridin-4a-yl)phenols and *trans*-3-(octahydro-1*H*-pyrano[3,4-*c*]pyridin-4a-yl)phenols

Compound	Conditions	Yield (%)	Formula	M.p. (°C)	Analysis (%) Found (required) C	H	N
(12a)	A	28[a]	$C_{15}H_{21}NO_2 \cdot C_4H_4O_4$[b]	106—109	62.5 (62.8)	7.05 (6.95)	3.75 (3.85)
(12b)	B	38	$C_{18}H_{25}NO_2$	202—204	75.65 (75.20)	9.0 (8.75)	4.75 (4.85)
(12c)	B	44	$C_{17}H_{23}NO_2 \cdot 0.1H_2O$[c]	180—183	74.25 (74.2)	8.9 (8.5)	5.0 (5.1)
(12d)	B	65	$C_{19}H_{27}NO_2 \cdot HCl \cdot 0.4H_2O$[c]	125—127	66.25 (66.1)	8.45 (8.4)	3.9 (4.05)
(12e)	B	62	$C_{16}H_{23}NO_2$	226—228	73.65 (73.5)	9.0 (8.85)	5.15 (5.35)
(12f)	B	70[d]	$C_{19}H_{27}NO_2 \cdot HCl \cdot 0.5H_2O$	131—133	65.4 (65.8)	8.2 (8.45)	4.15 (4.05)
(12g)	B	79	$C_{20}H_{29}NO_2 \cdot C_4H_4O_4$	187—189	66.8 (66.8)	7.5 (7.7)	3.2 (3.25)
(20a)	B	94	$C_{16}H_{21}NO_2 \cdot C_4H_4O_4 \cdot 0.5C_4H_{10}O$[e]	167—169	63.55 (64.05)	7.15 (7.35)	3.4 (3.4)
(20b)	B	86	$C_{19}H_{25}NO_2$	201—203	76.0 (76.2)	8.5 (8.4)	4.4 (4.7)
(20c)	B	28	$C_{20}H_{27}NO_2 \cdot 1.25C_4H_4O_4$	171—173	65.4 (65.5)	7.15 (7.05)	2.9 (3.05)
(28a)	B	68[a]	$C_{18}H_{25}NO_2 \cdot C_4H_4O_4$	195—198	65.55 (65.5)	7.45 (7.25)	3.4 (3.45)
(28b)	B	70[a]	$C_{19}H_{27}NO_2 \cdot C_4H_4O_4$	193—194	65.95 (66.15)	7.5 (7.5)	3.25 (3.35)
(34)		64[f]	$C_{19}H_{27}NO_2 \cdot C_4H_4O_4$	94—97	66.0 (66.15)	7.4 (7.5)	3.45 (3.35)

Conditions: A NaSEt, DMF, 150 °C, 3 h; B LiSMe,[8] DMF, 130—150 °C, 3—5 h.

[a] Yield of maleate salt. [b] $C_4H_4O_4$ represents maleic acid salt throughout. [c] Confirmed by water assay. [d] Yield of hydrochloride salt. [e] 0.5 mol of diethyl ether, confirmed by ^{1}H n.m.r. [f] Yield for two stages (see Experimental section).



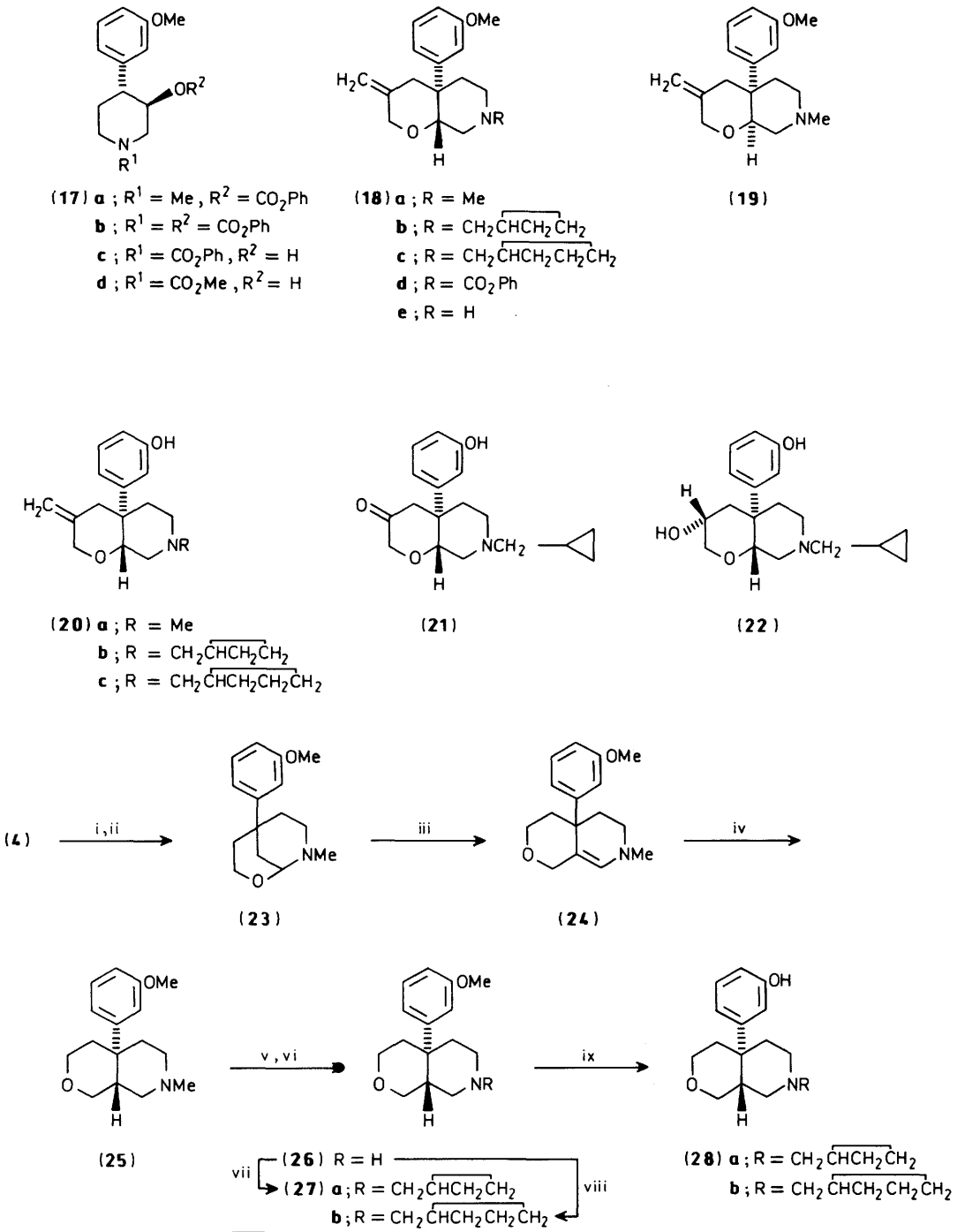
Scheme 2.

the requisite ring system in a single operation. Subsequent reduction of (**16a**) with lithium aluminium hydride gave the *N*-methyl derivative (**16b**) in excellent yield. Since the exocyclic methylene group precluded catalytic hydrogenation as a means of reducing the enamine (**16b**) to a *trans*-fused bicycle, we resorted to hydride reduction of the iminium species derivable from (**16b**). In the event, reduction of (**16b**) with sodium cyanoborohydride at pH 6.5—8 gave *ca.* 3:1 ratio of the *trans* and *cis* isomers (**18a**) and (**19**), respectively, which could be separated by column chromatography.

The ring-junction stereochemistry of both (**18a**) and (**19**) was assigned on the basis of ^{1}H n.m.r. data. The 8a-H signal of (**19**) showed only small couplings (*J* 3, 2 Hz) to adjacent protons, consistent only with a *cis*-fused geometry. Irradiation of 8aβ-H of (**18a**) caused an enhancement of the 5β- and 2β-H signals, as would be expected for a *trans* ring-junction.

Alternative *N*-substituents were introduced as described above, *via* (**18d**) and (**18e**), and *O*-demethylation furnished the phenols (**20a**—**c**). The *N*-cyclopropylmethyl derivative (**20b**) was oxidatively cleaved using osmium tetroxide/sodium periodate to give the 3-oxo compound (**21**). Sodium borohydride reduction of (**21**) gave a *ca.* 6:1 mixture of alcohols which were separated by chromatography and the major component shown to be the 3α-hydroxy isomer (**22**).

For the synthesis of the pyrano[3,4-*c*]pyridine system (**3**) we reverted to using the metallated enamine chemistry described previously.[1,4] Thus, generation of the anion from the tetrahydropyridine (**4**) followed by its reaction with ethylene oxide afforded in high yield the 2-oxa-8-azabicyclo-[3.3.1]nonane (**23**) (Scheme 3). Heating a mixture of (**23**), aqueous formaldehyde and triethylamine, adjusted to pH 3—3.5 by the addition of concentrated sulphuric acid,[5] at 70 °C gave a 53% yield of the bicyclic enamine (**24**). Hydrogenation of (**24**) over platinum, in ethanol, afforded the *trans*-fused octahydropyrano[3,4-*c*]pyridine (**25**), the ring-junction stereochemistry of which was unambiguously assigned from its ^{1}H n.m.r. spectrum which exhibited two axial–axial couplings for 8aβ-H with 1α- and 8α-H ($J_{8a\beta,1\alpha} = J_{8a\beta,8\alpha}$ 12 Hz). A small

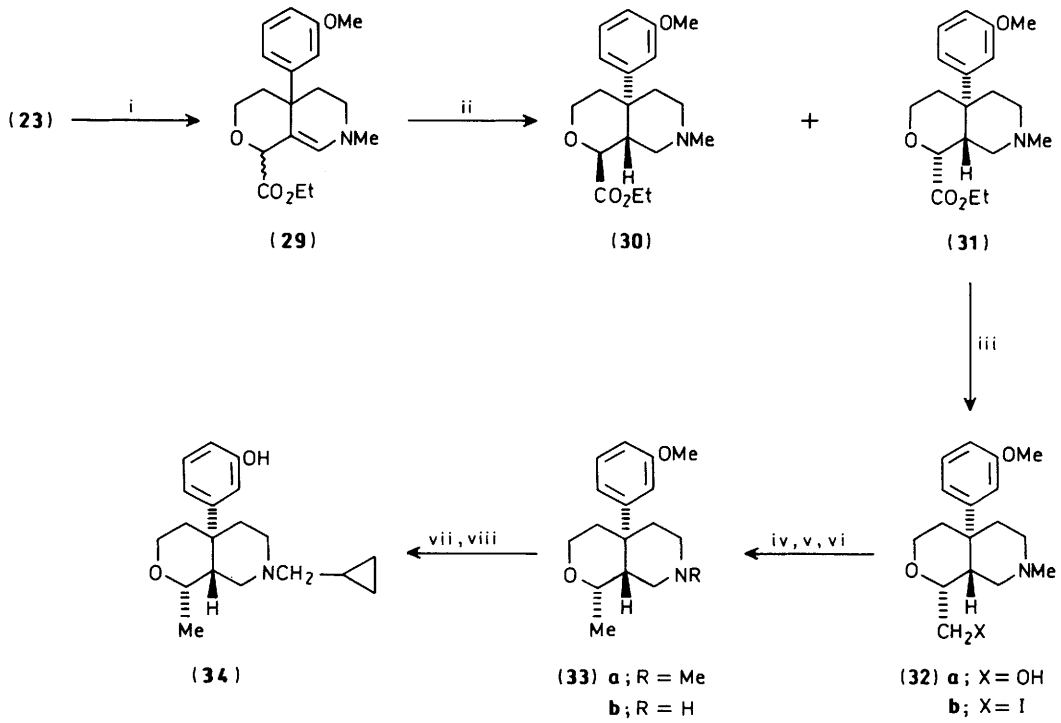


Scheme 3. *Reagents:* i, BuLi, THF; ii CH_2OCH_2; iii, Et_3N, HCHO, H^+; iv, H_2, Pt, EtOH; v, $ClCO_2CH{=}CH_2$, $ClCH_2CH_2Cl$; vi, MeOH–HCl; vii, $BrCH_2CHCH_2CH_2$, $NaHCO_3$, DMF; viii, a, $CH_2CH_2CH_2CHCOCl$, Et_3N; b, $LiAlH_4$, THF; ix, MeSLi, DMF

amount of the *cis*-isomer (*ca.* 5%) was also formed in this reaction.

Conversion of (**25**) into the *N*-cyclopropylmethyl and *N*-cyclobutylmethyl derivatives, (**28a**) and (**28b**) respectively, followed a standard sequence outlined in Scheme 3.

Since the 4α-methyl derivatives in the pyrano[4,3-*c*]pyridine series had shown good antinociceptive activity, we were keen to effect an analogous modification in the present series. However, our attempts to introduce a methyl substituent directly at C-1 of the pyrano[3,4-*c*]pyridine system, using acetaldehyde in place of formaldehyde in the above procedure, were unsuccessful, presumably because of competing aldol condensations. We therefore resorted to the multistep sequence outlined in Scheme 4. This utilized methyl glyoxalate and although it required a re-esterification step it did furnish an epimeric mixture of the esters (**29**) in 52% overall yield from (**23**). Hydrogenation of (**29**) afforded the epimers (**30**) and (**31**) (*ca.* 1:1) which were separated by column chromatography. The *trans*-fused stereochemistry of (**30**) was assigned from the presence of *trans*-diaxial couplings for $J_{1\beta,8a\alpha}$ and $J_{8a\alpha,8\beta}$ (both 12 Hz). This was corroborated by n.O.e. experiments in which irradiation of 1β-H caused enhancement of the 3β-H and the aromatic 2′-Ar*H* and 6′-Ar*H* signals. At this stage the stereochemistry of (**31**) was tentatively assigned on chemical grounds, *i.e.* hydrogenation



Scheme 4. *Reagents:* i, (a) Et_3N, $OHC–CO_2Me$, H^+, (b) EtOH, H^+; ii, H_2, PtO_2, EtOH; iii, $LiAlH_4$, THF; iv, (a) HMPT, CCl_4, −45 °C, (b) $LiEt_3BH$, THF; v, $ClCO_2Ph$, Bu^i_3N, $ClCH_2CH_2Cl$; vi, KOH, EtOH–H_2O; vii, $CH_2CH_2CHCH_2Br$, $NaHCO_3$, DMF; viii, LiSMe, DMF

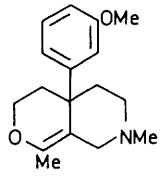


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Table 2. *In vivo* activities of *trans*-3-(octahydro-2*H*-pyrano[2,3-*c*]pyridin-4a-yl)phenols

Compound[a]	R^1	R^2	Antinociceptive[b] ED_{50}	Urine output[c]
(**12a**)	H	Me	0.28 (0.21—0.41)	Antidiuretic
(**12b**)	H	$CH_2CHCH_2CH_2$	1.8 (0.7—3.9)	Mixed activity
(**12c**)	H	$CH_2CH{=}CH_2$	6.1 (1.3—18.1)	NT[d]
(**12d**)	H	$CH_2CHCH_2CH_2CH_2$	0.6 (0.3—1.1)	NT
(**12e**)	Me	Me	0.017 (0.07—0.032)	NT
(**12f**)	Me	$CH_2CHCH_2CH_2$	0.6 (0.3—1.2)	NT
(**12g**)	Me	$CH_2CHCH_2CH_2CH_2$	0.18 (0.10—0.32)	Mixed activity
D-Propoxyphene			1.35 (0.52—2.1)	Antidiuretic

[a] Compounds are racemic. [b] Acetylcholine mouse abdominal constriction test, mg/kg, s.c. (confidence limits). [c] Water-loaded rat. [d] Not tested.

under neutral conditions occurs with delivery of hydrogen to the least hindered face of the enamines (**29**). This was later confirmed by n.O.e. studies on (**34**) (see below).

Lithium aluminium hydride reduction of (**31**) gave (**32a**) in excellent yield. However, conversion of the primary alcohol into a methyl group presented some unexpected difficulties. The primary tosylate derived from (**32a**) was prepared in the usual way but treatment with lithium triethylborohydride gave only a 10% yield of (**33a**) together with 44% recovered (**32a**). Attempts to displace the tosylate with iodide (sodium iodide, 1-methylpyrrolidin-2-one, 130 °C), with a view to subsequent catalytic hydrogenolysis, afforded a 31% yield of the enol ether (**35**) but none of the desired iodomethyl derivative (**32b**). Ultimately (**33a**) was obtained in 74% yield upon treatment of (**32a**) with hexamethylphosphorous triamide (HMPT) in carbon tetrachloride[6] followed by reduction with lithium triethylborohydride. Conversion of (**33a**) into the *N*-cyclopropylmethyl analogue (**34**) for testing was achieved using the standard methodology described earlier. Irradiation of the 1-methyl group of (**34**) caused an n.O.e. enhancement of the 2′-Ar*H* and 6′-Ar*H* signals thereby establishing a *cis*-disposition of the methyl group and the aromatic ring and confirming the tentative stereochemical assignment made on the ester (**31**).

Pharmacology.—The pharmacological evaluation of the compounds described herein involved the methodology used in the accompanying paper.[1] However, for the *in vitro* determination of μ/κ selectivity (guinea-pig ileum), the competitive μ-antagonist M8008[7] was used in place of β-FNA in some instances.

For the pyrano[2,3-*c*]pyridines (**12a**—**d**) the antinociceptive activity of the *N*-cyclopropylmethyl (**12b**) and *N*-cyclobutylmethyl (**12d**) derivatives is similar to the corresponding derivatives in the pyrano[4,3-*c*]pyridine series (Table 2). However, the *N*-methyl (**12a**) and *N*-allyl (**12c**) compounds showed higher and lower activity, respectively, compared to

Table 3. *In vitro* activities of *trans*-3-(octahydro-2*H*-pyrano[2,3-*c*]pyridin-4a-yl)phenols

Compound[a]	R^1	R^2	IC_{50} (μM) in rabbit vas deferens	IC_{50} (μM) in guinea-pig ileum	β-FNA Dose ratio	β-CNA Dose ratio
(**12a**)	H	Me	8	0.49	81 (34)[b]	NT
(**12b**)	H	$CH_2CHCH_2CH_2$	Antagonist, pA_2 = 5.7	0.45	2.2 (10.7)[b]	3.8 (1.9)
(**12d**)	H	$CH_2CHCH_2CH_2CH_2$	3.2	0.28	5.7 (19.6)[c]	1.0 (3.3)[c]
(**12e**)	Me	Me	Antagonist, pA_2 = 5.9	0.22	20 (11.9)[b]	3.1(1.8)[c]
(**12f**)	Me	$CH_2CHCH_2CH_2$	Antagonist, pA_2 = 5.5	0.30	5.2 (19.6)[c]	2.1 (3.3)[c]
(**12g**)	Me	$CH_2CHCH_2CH_2CH_2$	*d*	0.044	10.5 (35.4)[c]	NT

[a] Compounds are racemic. [b] Data for the μ-agonist normorphine. [c] Data for the μ-agonist DAGO. [d] No significant agonist or antagonist activity at 10^{-5}M.

Table 4. Pharmacological data for 3-substituted *trans*-3-(octahydro-2*H*-pyrano[2,3-*c*]pyridin-4a-yl)phenols

Compound[a]	R	Antinociceptive[h] ED_{50}	IC_{50} (μM) in rabbit vas deferens	IC_{50} (μM) in guinea-pig ileum	Dose-ratio produced by M8008 (10^{-7}M)
(**20a**)	Me	0.16 (0.09—0.27)	*b*	0.31	84 ± 15 (61 ± 25)[c] (1.3 ± 0.2)[d]
(**20b**)	$CH_2CHCH_2CH_2$	0.8 (0.5—1.5)	Antagonist, pA_2 = 5.3	0.21	2,[e] 11[f]
(**20c**)	$CH_2CHCH_2CH_2CH_2$	0.53 (0.17—0.92)	*g*	0.16	31 ± 6 (33 ± 8)[c] (1.5 ± 0.2)[d]
(**21**)	$CH_2CHCH_2CH_2$	1.23 (0.94—1.62)	*g*	0.48	4.5 ± 1.5 (30 ± 9)[c] (2.2 ± 0.7)[d]
(**22**)	$CH_2CHCH_2CH_2$	66% inibition at 10	NT	NT	NT

[a] Compounds are racemic. [b] $E_{max.}$ = 15% at 1 μM. [c] Data for the μ-agonist DAGO. [d] Data for the κ-agonist U-50488. [e] β-FNA Dose ratio (value for DAGO = 11). [f] β-CNA Dose ratio (value for DAGO = 5, value for U-50488 = 67). [g] No significant agonist or antagonist activity at 3 × 10^{-5}M. [h] Acetylcholine mouse abdominal constriction test, mg/kg, s.c. (confidence limits).

Table 5. Pharmacological data for *trans*-3-(octahydro-1*H*-pyrano[3,4-*c*]pyridin-4a-yl)phenols

Compound[a]	Antinociceptive[e] ED_{50}	IC_{50} (μM) in rabbit vas deferens	IC_{50} (μM) in guinea-pig ileum	Dose ratio produced by M8008 (10^{-7}M)
(**28a**)	69% Inibition at 10	NT	NT	NT
(**28b**)	1.47 (1.11—1.87)	*b*	0.36	34 ± 11 (74 ± 29)[c] (1.8 ± 0.2)[d]
(**34**)	0.21 (0.11—0.35	30	0.01	2 ± 1 (99 ± 48)[c] (2.0 ± 0.2)[d]

[a] Compounds are racemic. [b] No significant agonist or antagonist activity at 10^{-5}M. [c] Data for the μ-agonist DAGO. [d] Data for the κ-agonist U-50488. [e] Acetylcholine mouse abdominal constriction test, mg/kg, s.c. (confidence limits).

their pyrano[4,3-*c*]pyridine counterparts (**1**; R = Me, $CH_2CH{=}CH_2$).

Introduction of the ring junction 8a-methyl group (**12e—g**) increased the antinociceptive activity relative to the unsubstituted analogues (**12a, b, d**). This was particularly striking with the *N*-methyl analogue (**12e**) which was *ca.* 20 times more potent than (**12a**).

In the guinea-pig ileum large β-FNA dose ratios were observed for the *N*-methyl derivatives (**12a**) and (**12e**), indicating a predominantly μ-agonist profile for these compounds. A similar profile can be assigned to (**12d**) on the basis of a modest but significant β-FNA shift and lack of βCNA shift. It is particularly interesting to compare the opioid receptor profiles of the *N*-cyclopropylmethyl derivatives (**12b**) and (**12f**) with the corresponding pyrano[4,3-*c*]pyridine (**1**; R = $CH_2CHCH_2CH_2$). Whereas (**1**; CH_2–$CHCH_2CH_2$) possesses a selective κ profile, both *in vitro* (β-FNA, β-CNA data) and *in vivo* (urine output) experiments show (**12b**) and (**12f**) as non-selective agonists.

Introduction of 3-methylene and 3-oxo substituents has little effect on antinociceptive activity (Table 4). Again the *N*-cyclopropylmethyl derivatives (**20b**) and (**21**) displayed a significant μ-agonist component.

The *N*-cyclopropylmethyl (**28a**) and *N*-cyclobutylmethyl (**28b**) analogues in the pyrano[3,4-*c*]pyridine series are *ca.* 3 times less active in the antinociceptive test relative to the other two series (Table 5). The large M8008 shift observed for (**28b**) indicates this compound has a predominantly μ-agonist profile. One notable result is that introduction of a 1α-methyl substituent (**34**) provided a 50-fold increase in antinociceptive activity. The observation parallels the effect of introducing the 4α-methyl group in the pyrano[4,3-*c*]pyridines and underlines the significance of this modification.

Experimental

For general experimental details see ref. 1.

trans-4-(3-*Methoxyphenyl*)-1-*methylpiperidin*-3-*ol* (**5**).—Freshly distilled boron trifluoride–diethyl ether (17.4 ml, 135 mmol) was added dropwise to a stirred mixture of 1,2,3,6-tetrahydro-4-(3-methoxyphenyl)-1-methylpyridine* (**4**) (13.21 g, 65 mmol), sodium borohydride (3.9 g, 104 mmol) and diglyme (65 ml) with cooling to maintain the internal temperature below 20 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h before water (5 ml) was added

* **CAUTION** is recommended in the use of (**4**) which has been shown to possess neurotoxic properties. It is suggested that the corresponding *N*-ethyl derivative, which is considerably less toxic, now be employed in place of (**4**).[9]

dropwise, with cooling in an ice-bath, to quench excess of hydride. 5M Aqueous sodium hydroxide (18 ml) was added and the reaction mixture was warmed to 65 °C. Hydrogen peroxide (15.9 ml; 30% w/v) was added over 30 min, the internal temperature being maintained between 60—70 °C. The resulting mixture was heated at 65 °C for a further 1 h, cooled, and acidified with concentrated hydrochloric acid (20 ml). This mixture was evaporated to give a white foam which was dissolved in 1M hydrochloric acid (300 ml). The resultant solution was washed with dichloromethane (2 × 50 ml), basified to pH 14 with 5M aqueous sodium hydroxide, and extracted with dichloromethane (3 × 80 ml). The latter extracts were combined, dried (Na_2SO_4), and concentrated to give a colourless oil which crystallized with time to give the *title compound* (11.8 g, 82%), m.p. 74—76 °C (Found: C, 70.35; H, 9.0; N, 6.25. $C_{13}H_{19}NO_2$ requires C, 70.5; H, 8.65; N, 6.35%); $\nu_{max.}$($CHBr_3$) 3 580 cm^{-1} (OH); δ_H($CDCl_3$) 1.80—2.10 (5 H, m), 2.29—2.40 (1 H, m, ArC*H*), 2.34 (3 H, s, NCH_3), 2.97 (1 H, br d, *J* 12 Hz), 3.14 (1 H, dd, *J* 11, 5 Hz), 3.77—3.89 (1 H, m, C*H*OH), 3.79 (3 H, s, OCH_3), 6.77—6.9 (3 H, m, ArH), and 7.26 (1 H, t, *J* 8 Hz, ArH).

The dichloromethane washings (above) were dried (Na_2SO_4) and concentrated to give a colourless oil. This was dissolved in 2M hydrochloric acid (100 ml) and washed with dichloromethane (2 × 40 ml). The aqueous layer was basified to pH 14 with 5M aqueous sodium hydroxide and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give further title compound (1.15 g, 8%) as a white solid.

4-(3-*Methoxyphenyl*)-1-*methylpiperidin*-3-*one* (**6**).—A solution of dimethyl sulphoxide (8.81 g, 113 mmol) in dichloromethane (30 ml) was added dropwise during 15 min to a stirred solution of oxalyl chloride (7.17 g, 56.5 mmol) in dichloromethane (120 ml) under nitrogen maintained at an internal temperature below −50 °C. The resulting solution was stirred for 5 min before a solution of *trans*-4-(3-methoxyphenyl)-1-methylpiperidin-3-ol (11.32 g, 51.2 mmol) in dichloromethane (50 ml) was added over a period of 10 min. The solution was then stirred for 15 min at −60 °C before triethylamine (25.91 g, 257 mmol) was added. The reaction mixture was then allowed to warm to −20 °C and quenched with water (200 ml). After shaking, the layers were separated and the aqueous layer was washed with dichloromethane (2 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a light brown solid. This solid was dissolved in hot hexane (600 ml, 50 °C) and decanted from the brown residue. The hexane solution was cooled to −30 °C for 1 h and filtered cold to give the *title compound* (9.07 g, 80%), as a light yellow solid, m.p. 66—67 °C (Found: C, 71.35; H, 7.7; N, 6.3. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%). This material was stored at −30 °C; $\nu_{max.}$($CHBr_3$) 1 712 cm^{-1} (C=O); δ_H($CDCl_3$) 2.21—2.34 (2 H, m, $NCH_2CH_AH_B$), 2.42 (3 H, s, NCH_3), 2.50—2.64 (1 H, m, $NCH_AH_BCH_2$), 2.89 (1 H, d, *J* 14 Hz, NCH_AH_BC=O), 2.98—3.10 (1 H, m, *J* 12, 2, 4 Hz, $NCH_AH_BCH_2$), 3.36 (1 H, dd, *J* 14, 2 Hz, NCH_AH_BC=O), 3.48 (1 H, t, *J* 9 Hz, ArC*H*), 3.80 (3 H, s, OCH_3), 6.68—6.88 (3 H, m, ArH), and 7.28 (1 H, t, *J* 8 Hz, ArH).

4-*Allyl*-4-(3-*methoxyphenyl*)-1-*methylpiperidin*-3-*one* (**7**).—4-(3-Methoxyphenyl)-1-methylpiperidin-3-one (2.0 g, 9.1 mmol) in DMF (5 ml) was added dropwise to a stirred suspension of sodium hydride (80% dispersion in oil; 300 mg, 10.01 mmol) in DMF (10 ml), under nitrogen, with ice-cooling. The resulting mixture was stirred at room temperature for 3 h and cooled to −25 °C, followed by dropwise addition of allyl bromide (1.1 g, 0.79 ml, 9.1 mmol). The reaction mixture was allowed to warm to room temperature, and then stirred at room temperature for 45 min. The mixture was poured into 0.5M sodium carbonate (120 ml) and the aqueous layer was extracted with ether (2 × 100 ml). The combined ether extracts were washed with water (3 × 75 ml), dried (Na_2SO_4) and evaporated to afford an orange oil. This was dissolved in 1M hydrochloric acid (50 ml) and washed with ether (2 × 25 ml). The aqueous layer was basified with 5M sodium hydroxide and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the *title compound* (1.96 g, 83%) as a brown oil. This compound was characterized as its hydrochloride salt, m.p. 114—116 °C (Found: C, 64.85; H, 7.55; N, 4.7. $C_{16}H_{21}NO_2$·HCl requires C, 64.85; H, 7.5; N, 4.75%); $\nu_{max.}$($CHBr_3$) 1 726 cm^{-1} (C=O); δ_H[$CDCl_3$ (free base)] 2.05 (1 H, m), 2.25 (3 H, s), 2.4—2.65 (4 H, m), 2.72 (1 H, d), 2.84 (1 H, m), 3.10 (1 H, dd), 3.80 (3 H, s, OCH_3), 4.89—5.00 (2 H, m, CH=CH_2), 5.47 (1 H, m, C*H*=CH_2), 6.7—6.85 (3 H, m, ArH), and 7.27 (1 H, t, ArH).

cis-4-(3-*Hydroxypropyl*)-4-(3-*methoxyphenyl*)-1-*methylpiperidin*-3-*ol* (**8a**).—Borane solution in tetrahydrofuran (THF) (103 ml, 103 mmol; 1M) was added dropwise to a cooled solution of 4-allyl-4-(3-methoxyphenyl)-1-methylpiperidin-3-one (**7**) (7.21 g, 27.8 mmol) in dry THF (45 ml) under nitrogen at −10 °C. The resulting mixture was stirred at −10 °C for 3 h, followed by warming at 40 °C for 18 h. Sodium methoxide (11.0 g, 205 mmol) was added portionwise and stirring at 40 °C continued for a further 1 h. After cooling, 5M sodium hydroxide (17 ml) was added followed by hydrogen peroxide (3.2 ml; 30% w/v). The reaction mixture was stirred at room temperature for 3 h and then extracted with chloroform (3 × 140 ml). The organic extracts were dried ($MgSO_4$) and evaporated to afford a yellow oil which was dissolved in ethylene glycol (35 ml) and warmed at 100 °C for 1 h. The solution was diluted with water (75 ml), basified with 5M sodium hydroxide, and extracted with chloroform (3 × 140 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford a yellow oil. This material was purified by column chromatography on alumina, with dichloromethane–methanol (95:5) as eluant, to provide the *title compound* (**8a**) (4.52 g, 58%) which was used directly in the next stage; $\nu_{max.}$($CHBr_3$) 3 600 cm^{-1} (OH); δ_H($CDCl_3$) 0.87—1.05 (1 H, m), 1.21—1.40 (1 H, m), 1.53 (1 H, dt, *J* 4 Hz, 13 Hz, $NCH_2CH_AH_B$), 1.86 (1 H, br d, *J* 13 Hz), 1.89 (1 H, dt, *J* 4, 13 Hz), 2.19—2.38 (2 H, m), 2.30 (3 H, s, NCH_3), 2.50—2.90 (4 H, m), 3.46 (2 H, t, *J* 7 Hz, CH_2OH), 3.80 (3 H, s, OCH_3), 3.99 (1 H, br s, C*H*OH), 6.75 (1 H, dd), 6.87 (1 H, t), 6.92 (1 H, d), and 7.27 (1 H, t).

4-(3-*Hydroxypropyl*)-4-(3-*methoxyphenyl*)-1,3-*dimethylpiperidin*-3-*ol* (**8b**).—Borane solution in THF (75 ml, 75 mmol; 1M) was added dropwise to a cooled solution of *cis*-4-allyl-4-(3-methoxyphenyl)-1,3-dimethylpiperidin-3-ol (5.32 g, 19.3 mmol) in dry THF (35 ml) at −10 °C under nitrogen. The resulting solution was stirred at −10 °C for 3 h, followed by stirring at room temperature for 19 h. The reaction mixture was cooled to 10 °C, when water (12.5 ml) was added cautiously, followed by 5M sodium hydroxide (12.5 ml), and hydrogen peroxide (2.4 ml; 30% w/v). The resulting solution was allowed to warm to room temperature, followed by stirring at room temperature for 3 h. The two layers were separated and the aqueous layer was further extracted with chloroform (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford a yellow foam. This was dissolved in ethylene glycol (55 ml) and warmed at 100 °C for 1 h. The cooled reaction mixture was diluted with water (100 ml), basified with 5M sodium hydroxide and extracted with chloroform (3 × 50 ml).

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

The combined organic extracts were dried and evaporated to afford a yellow foam. This material was applied to an alumina column and elution with dichloromethane–methanol (49:1) afforded the *title compound* (**8b**) (4.28 g, 75%) which was used directly in the next stage; $\delta_H(CDCl_3)$ 1.02 (3 H, s, CH_3COH), 1.1—1.61 (4 H, m), 2.00 (2 H, m), 2.26—2.38 (1 H, m), 2.32 (3 H, s, NCH_3), 2.45—2.80 (4 H, m), 2.88 (1 H, br s), 3.60 (2 H, t, *J* 7 Hz, CH_2OH), 3.80 (3 H, s, OCH_3), 6.77 (1 H, dd), 6.99—7.05 (2 H, m), and 7.25 (1 H, t).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-2H-*pyrano*-[2,3-c]*pyridine* (**9a**).*—A solution of methanesulphonyl chloride in dry dichloromethane (4 ml, 4.0 mmol; 1M) was added dropwise to a stirred solution of *cis*-4-(3-hydroxypropyl)-4-(3-methoxyphenyl)-1-methylpiperidin-4-ol (**8a**) (1.0 g, 3.58 mmol) and triethylamine (0.74 ml) in dry dichloromethane (10 ml) at −10 °C under nitrogen. The resulting suspension was stirred at −10 °C for 0.5 h and then poured into water (100 ml). The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the intermediate methanesulphonate as a yellow oil. This material (1.05 g, 3.08 mmol) was dissolved in dry DMF (6 ml) and sodium hydride (50% dispersion; 296 mg, 6.17 mmol) was added portionwise with stirring. The resulting mixture was warmed at 70 °C for 3 h under nitrogen. The cooled reaction mixture was poured into water (50 ml), basified to pH 14 using 5M sodium hydroxide and extracted with dichloromethane (3 × 40 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the *title compound* (**9a**) (0.85 g, 91%) as a yellow oil. This was characterized as its hydrochloride salt, m.p. 180—182 °C (Found: C, 62.85; H, 8.2; N, 4.2. $C_{16}H_{23}NO_2{\cdot}HCl{\cdot}0.37H_2O$* requires C, 63.1; H, 8.2; N, 4.6%); δ[$CDCl_3$ (free base)] 1.21—1.30 (1 H, m), 1.51—1.92 (5 H, m), 2.21 (3 H, s, NCH_3), 2.24 (1 H, dt, *J* 12, 2 Hz, 5α-H), 2.51 (1 H, dt, *J* 12, 2 Hz, 6β-H), 2.62 (1 H, t, *J* 11 Hz, 8α-H), 2.83 (1 H, dd, *J* 4, 11 Hz, 8β-H), 3.55—3.70 (2 H, m, 2β- and 8aβ-H), 3.80 (3 H, s, OMe), 4.09 (1 H, br d, *J* 11 Hz, 2α-H), 6.73 (1 H, dt, *J* 6, 2 Hz, ArH), 7.18—7.32 (3 H, m, 3 × ArH). Irradiation at δ 4.09 caused the signals at δ 1.51—1.92 and 3.55—3.70 to simplify. Irradiation at δ 3.65 caused the signals at δ 2.62 and 2.83 to simplify.

trans-7-(*Cyclopropylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-2H-*pyrano*[2,3-c]*pyridine* (**9b**).—(Bromomethyl)cyclopropane (332 mg, 2.46 mmol) was added dropwise to a stirred suspension of (**11a**) (608 mg, 2.46 mmol) and sodium hydrogen carbonate (428 mg, 5.09 mmol) in DMF (7 ml). The resulting mixture was heated at reflux for 1.5 h. After cooling, the solvent was evaporated and the residue was purified by column chromatography on alumina with hexane–ethyl acetate (3:1) ⟶ ethyl acetate eluant, to afford the *title compound* (**9b**) (535 mg, 72%) as a pale yellow oil. This compound was characterized as its maleate salt, m.p. 126—128 °C (Found: C, 66.2; H, 7.55; N, 3.4. $C_{19}H_{27}NO_2{\cdot}C_4H_4O_4$ requires C, 66.15; H, 7.5; N, 3.35%).

trans-7-*Allyloctahydro*-4a-(3-*methoxyphenyl*)-2H-*pyrano*-[2,3-c]*pyridine* (**9c**).—This compound was prepared from (**11a**) using the method described for the preparation of (**9b**). The *title compound* (**9c**) (56%) was characterized as its maleate salt, m.p. 108—109 °C (Found: C, 65.5; H, 7.35; N, 3.35. $C_{18}H_{25}NO_2{\cdot}C_4H_4O_4$ requires C, 65.5; H, 7.25; N, 3.45%).

trans-7-(*Cyclobutylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-2H-*pyrano*[2,3-c]*pyridine* (**9d**).—Cyclobutanecarboxylic acid chloride (0.5 ml, *ca.* 4.4 mmol) was added dropwise to a stirred solution of (**11a**) (939 mg, 3.8 mmol) and triethylamine (1.1 ml) in dry dichloromethane (25 ml) under nitrogen at room temperature. The resulting mixture was stirred at room temperature for a further 2 h, followed by quenching with 2M hydrochloric acid (50 ml). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (Na_2SO_4) and evaporated to afford the intermediate amide as a yellow oil. A solution of this material (1.16 g, 3.52 mmol) in dry THF (20 ml) was added to a stirred suspension of lithium aluminium hydride (0.5 g, 13.2 mmol) in dry THF (20 ml) under nitrogen. The resulting suspension was heated at reflux overnight. After cooling, saturated aqueous sodium sulphate (2 ml) was added, followed by 5 drops of 2M sodium hydroxide. This mixture was heated further until all the solid had turned white. Sodium sulphate was added and the mixture was filtered through Hyflo. The Hyflo was washed with ethyl acetate (100 ml) and the total filtrate dried ($MgSO_4$) and evaporated to give the *title compound* (**9d**) (1.09 g, 91%) as a yellow oil. The title compound was characterized as its maleate salt, m.p. 138—140 °C (Found: C, 66.5; H, 8.1; N, 3.2. $C_{20}H_{29}NO_2{\cdot}C_4H_4O_4$ requires C, 66.8; H, 7.7; N, 3.25%).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-7,8a-*dimethyl*-2H-*pyrano*[2,3-c]*pyridine* (**9e**).—This compound was prepared from (**8b**) using the method described for the preparation of (**9a**). The *title compound* (**9e**) (89%) was characterized as its hydrochloride salt, m.p. 170—173 °C (Found: C, 64.4; H, 8.6; N, 4.5. $C_{17}H_{25}NO_2{\cdot}HCl{\cdot}0.19H_2O$ requires C, 64.8; H, 8.4; N, 4.45%); δ_H[$CDCl_3$ (free base)] 1.18—1.29 (1 H, m, 3β-H), 1.43—1.65 (2 H, m, 3α- and 4β-H), 1.74 (3 H, s, *Me*C), 1.80—2.10 (4 H, m), 2.13 (3 H, s, NCH_3), 2.40 (1 H, d, *J* 11 Hz, 8β-H), 2.50—2.57 (1 H, m, 6β-H), 2.93 (1 H, d, *J* 11 Hz, 8α-H), 3.77 (1 H, dd, *J* 6, 12 Hz, 2α-H), 3.81 (3 H, s, OCH_3), 4.04 (1 H, dt, *J* 3, 12 Hz, 2β-H), 6.72 (1 H, dd, *J* 2, 8 Hz, ArH), 7.21 (1 H, t, *J* 8 Hz, ArH), and 7.32—7.57 (2 H, m, 2 × ArH). Irradiation at δ 7.45 caused n.O.e. enhancement of the signals at δ 1.43—1.65, 2.04, and 2.93. Irradiation at δ 1.74 caused n.O.e. enhancement of the signals at δ 2.40 and 4.04.

trans-7-(*Cyclopropylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-8a-*methyl*-2H-*pyrano*[2,3-c]*pyridine* (**9f**).—This compound was prepared from (**11b**) using the method described for the preparation of (**9b**). The *title compound* (**9f**) (77%) was characterized as its hydrochloride salt, m.p. 164 °C (decomp.) (Found: C, 68.05; H, 8.5; N, 3.8. $C_{20}H_{29}NO_2{\cdot}HCl$ requires C, 68.25; H, 8.6; N, 4.0%).

trans-7-(*Cyclobutylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-8a-*methyl*-2H-*pyrano*[2,3-c]*pyridine* (**9g**).—This compound was prepared from (**11b**) using the method described for the preparation of (**9d**). The *title compound* (**9g**) (56%) was purified by column chromatography on alumina, with diethyl ether–hexane (1:3) as eluant, and was obtained as a pale yellow oil (Found: C, 76.8; H, 9.7; N, 4.35. $C_{21}H_{31}NO_2$ requires C, 76.55; H, 9.5; N, 4.25%).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-2H-*pyrano*[2,3-c]-*pyridine* (**11a**).—Vinyl chloroformate (1.1 ml, 1.25 g, 11.74 mmol) was added dropwise to a stirred suspension of (**9a**) (1.92 g, 7.4 mmol) and potassium carbonate (1.97 g, 14.25 mmol) in dry 1,2-dichloroethane (20 ml) at −25 °C under nitrogen. The resulting suspension was heated at reflux for 1.5 h. A further amount of vinyl chloroformate (0.5 ml, 5.3 mmol) was added and the mixture was heated at reflux for a further 2 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on alumina, using ethyl acetate as the eluant, to afford the intermediate vinyl carbamate

* Fractional water content where given was experimentally determined.

(**10a**). A solution of the carbamate in 2M methanolic hydrogen chloride was heated at reflux for 3.5 h, cooled, and evaporated to dryness. The residue was dissolved in water (10 ml) and the resulting solution washed with dichloromethane (2 × 5 ml). The aqueous phase was basified with 5M sodium hydroxide and extracted with dichloromethane (4 × 5 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the *title compound* (**11a**). This was characterized as its maleate salt, m.p. 130—133 °C (Found: C, 62.5; H, 7.1; N, 3.85. $C_{15}H_{21}NO_2 \cdot C_4H_4O_4$ requires C, 62.8; H, 6.95; N, 3.85%).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-8a-*methyl*-2H-*pyrano*[2,3-c]*pyridine* (**11b**).—Phenyl chloroformate (9.26 g, 6.8 ml, 59.1 mmol) was added dropwise to a cooled suspension of the pyrano[2,3-*c*]pyridine (**9e**) (2.96 g, 10.8 mmol) and anhydrous potassium carbonate (3.77 g, 27.3 mmol) in dry 1,2-dichloroethane (40 ml) under nitrogen, the temperature being maintained between 5—10 °C. The reaction mixture was heated at reflux for 24 h. The cooled reaction was quenched with 1M sodium hydroxide (150 ml) and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford a dark oil which solidified. This material was purified by flash chromatography on silica gel, eluting initially with ethyl acetate–hexane (1:3) and then with ethyl acetate–hexane (1:2) to yield the intermediate phenyl carbamate (**10b**) as a white foam. This material (2.62 g, 6.9 mmol) in a mixture of ethanol (200 ml) and 50% potassium hydroxide (50 ml) was heated at reflux under nitrogen for 20 h. After cooling, the solvent was evaporated and the residue was treated with water (250 ml). The mixture was extracted with dichloromethane (3 × 150 ml) and the combined organic extracts were dried ($NaSO_4$) and evaporated to afford the *title compound* (**11b**) (1.62 g, 91%) as a pale yellow oil (Found: C, 73.5; H, 8.95; N, 5.0. $C_{16}H_{23}NO_2$ requires C, 73.55; H, 8.85; N, 5.35%).

trans-3-(*Octahydro*-7-*methyl*-2H-*pyrano*[2,3-c]*pyridin*-4a-*yl*)*phenol* (**12a**).—A solution of sodium ethanethiolate in dry DMF (1M; 10 ml, 10 mmol) was added to (**9a**) (520 mg, 1.99 mmol) and the resulting mixture heated at reflux under nitrogen for 3 h. After cooling, ammonium acetate (771 mg, 10 mmol) was added and the solvent was evaporated. The residue was purified by column chromatography on alumina, with methanol–dichloromethane (1:19) as eluant, to afford the *title compound* (**12a**) which was characterized as its maleate salt; $\delta_H(D_2O)$ 1.32—2.00 (5 H, m), 2.52—2.75 (2 H, m), 2.79 (3 H, s, NCH_3), 3.28—3.89 (5 H, m), 4.16 (1 H, dd, *J* 12, 5 Hz), 6.31 (2 H, s, maleate), 6.84 (1 H, br d, *J* 9 Hz, ArH), and 7.20—7.39 (3 H, m, 3 × ArH).

trans-3-[7-(*Cyclopropylmethyl*)*octahydro*-2H-*pyrano*[2,3-c]-*pyridin*-4a-*yl*]*phenol* (**12b**).—Lithium methanethiolate (450 mg, 8.3 mmol) was added to a solution of (**9b**) (460 mg, 1.5 mmol) in dry DMF (6 ml). The resulting suspension was heated at reflux under nitrogen for 3 h. After cooling, ammonium chloride (433 mg, 8.1 mmol) was added and the solvent was evaporated. The residue was subjected to column chromatography on alumina, with dichloromethane–methanol (19:1) ⟶ (9:1) as eluant, to afford the title compound as a cream solid. This material required further purification and was dissolved in 1M hydrochloric acid (10 ml) and washed with ether (2 × 10 ml). The aqueous layer was adjusted to pH 7.5 and extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford a white solid which was recrystallized from ethyl acetate–methanol (with a trace of hexane) to give pure *title compound* (**12b**) (167 mg, 38%); $\delta_H[CDCl_3 + (CD_3)_2SO]$ 0.0—0.20, 0.40—0.60, 0.71—0.90 [5 H, m, c(C_3H_5)], 1.18—1.33 (1 H, m, 3β-H), 1.49—1.72 (2 H, m, 3α- and 4β-H), 1.66 (1 H, dt, *J* 3, 13 Hz, 5β-H), 1.85 (1 H, br t, *J* 11 Hz, 6α-H), 1.87 (1 H, br d, *J* 11 Hz, 4α-H), 2.12 [1 H, dd, *J* 13, 7 Hz, $NCH_AH_Bc(C_3H_5)$], 2.25 [1 H, dd, *J* 13, 7 Hz, $NCH_AH_Bc(C_3H_5)$], 2.23 (1 H, br d, *J* 13 Hz, 5α-H), 2.63 (1 H, t, *J* 11 Hz, 8α-H), 2.75 (1 H, br d, *J* 11 Hz, 6β-H), 3.10 (1 H, dd, *J* 11, 4 Hz, 8β-H), 3.62 (1 H, br t, *J* 11 Hz, 2β-H), 3.68 (1 H, dd, *J* 11, 4 Hz, 8aβ-H), 4.03—4.13 (1 H, m, 2α-H), 6.62—6.72 (1 H, m, ArH), and 7.08—7.23 (3 H, m, 3 × ArH). A similar procedure was used for the preparation of the phenols (**12c—g**), (**20a—c**), and (**28a, b**) from the corresponding methyl ethers (see Table 1).

cis-4-*Allyl*-4-(3-*methoxyphenyl*)-1,3-*dimethylpiperidin*-3-*ol* (**13**).—4-Allyl-4-(3-methoxyphenyl)-1-methylpiperidin-3-one (**7**) (4.0 g, 15.4 mmol) in dry THF (40 ml) was added dropwise to a stirred solution of methyl-lithium (1.6M; 20 ml, 32 mmol) in dry THF (120 ml) at 0 °C under nitrogen. The resulting mixture was allowed to warm to room temperature over 45 min and then quenched with water (320 ml). The resultant mixture was extracted with dichloromethane (2 × 250 ml, 1 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the *title compound* (**13**) (4.31 g, 100%) as an orange oil which crystallized on cooling (Found: C, 74.1; H, 9.3; N, 5.1. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.1%); $\nu_{max.}$(Nujol) 3 460 cm^{-1} (OH); $\delta_H(CDCl_3)$ 1.03 (3 H, s, CH_3COH), 1.61 (1 H, dt, *J* 13, 2.5 Hz), 2.22—2.42, 2.55—2.90 (7 H, m), 3.00 (1 H, br s), 2.33 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 4.90—5.10 (2 H, m, $CH{=}CH_2$), 5.30—5.49 (1 H, m, $CH{=}CH_2$), 6.72—6.80 (1 H, dd, *J* 8, 2 Hz, ArH), 7.01—7.12 (2 H, m, ArH), and 7.26 (1 H, t, *J* 8 Hz, ArH).

trans-[4-(3-*Methoxyphenyl*)-1-*methylpiperidin*-3-*yl*]*phenyl Carbonate* (**17a**).—Phenyl chloroformate (14.6 g, 93.5 mmol) was added dropwise, over a 15 min period, to a stirred solution of *trans*-4-(3-methoxyphenyl)-1-methylpiperidin-3-ol (**5**) (18.81 g, 85 mmol) in dichloromethane (340 ml) under nitrogen at −5 to 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 75 min before cooling to 5 °C and quenching with water (170 ml). The mixture was basified to pH 14 (2M sodium hydroxide) and after shaking the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 100 ml) and the combined dichloromethane layers were washed with 0.5M sodium hydroxide (2 × 100 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give the *title compound* (**17a**) (27.17 g, 94%), m.p. 51—54 °C (Found: C, 69.95; H, 6.8; N, 4.0. $C_{20}H_{23}NO_4$ requires C, 70.35; H, 6.8; N, 4.1%); $\nu_{max.}(CHBr_3)$ 1 702 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.8—2.16 (4 H, m), 2.38 (3 H, s, NCH_3), 2.67 (1 H, dt, *J* 7, 11 Hz, ArC*H*), 2.91 (1 H, br d, *J* 11 Hz), 3.31 (1 H, br dd, *J* 11, 5 Hz), 3.80 (3 H, s, OCH_3), 5.06 (1 H, dt, *J* 5, 11 Hz, C*H*OC=O), and 6.75—7.34 (9 H, m, 9 × ArH).

trans-*Phenyl* 4-(3-*Methoxyphenyl*)-3-(*phenoxycarbonyloxy*)-*piperidine*-1-*carboxylate* (**17b**).—Phenyl chloroformate (24.7 g, 158 mmol) was added dropwise, over a 10 min period, to a stirred suspension of anhydrous potassium carbonate (27.6 g, 0.2 mol) and *trans*-[4-(3-methoxyphenyl)-1-methylpiperidin-3-yl]phenyl carbonate (**17a**) (27.0 g, 79 mmol) in dry 1,2-dichloroethane (340 ml) at 5 °C under nitrogen. The reaction mixture was heated at reflux for 2.5 h before being cooled and quenched with water (200 ml). After shaking, the layers were separated and the aqueous phase extracted with dichloromethane (2 × 100 ml). The combined organic fractions were washed with 0.5M sodium hydroxide (2 × 100 ml), and water (100 ml), dried (Na_2SO_4), and evaporated to give a pale yellow solid. This material was recrystallized from toluene–hexane (4:1) to give the *title compound* (**17b**) (26.82 g, 76%), m.p. 123—124 °C (Found: C, 69.7; H, 5.7; N, 3.05. $C_{26}H_{25}NO_6$ requires C, 69.8; H, 5.65; N, 3.15%); $\nu_{max.}(CHBr_3)$ 1 710 (C=O) and 1 760

cm^{-1} (C=O); δ($CDCl_3$) 1.87—2.10 (2 H, m, NCH_2CH_2), 2.93 (1 H, dt, *J* 5, 11 Hz, ArC*H*), 2.90—3.20 (2 H, br m), 3.82 (3 H, s, OCH_3), 4.30—4.47 (1 H, br m), 4.63—4.81 (1 H, br m), 5.01 (1 H, dt, *J* 5, 11 Hz, OC*H*), and 6.81—6.98 and 7.12—7.42 (14 H, m).

trans-*Phenyl* 3-*Hydroxy*-4-(3-*methoxyphenyl*)*piperidine*-1-*carboxylate* (**17c**).—A solution of *trans*-phenyl 4-(3-methoxyphenyl)-3-(phenoxycarbonyloxy)piperidin-1-carboxylate (**17b**) (58.2 g, 0.13 mmol) in methanol (2 l) at 50 °C, was added to a solution of potassium carbonate (35.9 g, 0.26 mol) in water (975 ml) at 50 °C. The resulting solution was then stirred at 57—58 °C for 40 min before concentration to *ca.* 1 l to remove methanol. The reaction mixture was extracted with dichloromethane (500 ml, 2 × 200 ml) and the combined extracts were washed with 0.5M sodium hydroxide (2 × 200 ml), dried (Na_2SO_4), and concentrated to give the *title compound* (**17c**) (34.05 g, 80%) as a light yellow oil. This material was purified by flash chromatography on silica gel, with ethyl acetate–hexane (1:1) as eluant, and was obtained as a colourless gum (Found: C, 69.85; H, 6.55; N, 3.95. $C_{19}H_{21}NO_4$ requires C, 69.7; H, 6.45; N, 4.3%); δ_H($CDCl_3$) 1.8—1.95 (3 H, m), 2.59 (1 H, dt), 2.65—3.10 (2 H, m), 3.7—3.85 (1 H, m), 3.82 (3 H, s), 4.30—4.43 (1 H, m), 4.47—4.60 (1 H, m), 6.8—6.9 (3 H, m), and 7.1—7.4 (6 H, m).

Phenyl 4-(3-*Methoxyphenyl*)-3-*oxopiperidine*-1-*carboxylate* (**14**; R = CO_2Ph).—A solution of *trans*-phenyl 3-hydroxy-4-(3-methoxyphenyl)piperidine-1-carboxylate (**17c**) (18.98 g, 58 mmol) in dichloromethane (175 ml) was treated with pyridinium dichromate (65.5 g, 174 mmol) and molecular sieve powder (3 Å; 29 g). The resulting suspension was stirred at ambient temperature for 20 h before addition of diethyl ether (175 ml). The reaction mixture was filtered through silica gel (Merck 9385, 100 g), and the silica gel washed with diethyl ether–dichloromethane (1:1; 1 l). The combined organic solutions were again filtered through silica gel (Merck 9385, 20 g) to remove final traces of chromate residues. The filtrate was evaporated to give a pale yellow solid. This material was recrystallized from ethyl acetate–hexane to give the *title compound* (**14**; R = CO_2Ph) (7.9 g, 42%) as a colourless crystalline solid, m.p. 83—84 °C (Found: C, 70.15; H, 5.85; N, 4.1. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3%); $\nu_{max.}$ ($CHBr_3$) 1 715 cm^{-1} (C=O); δ_H($CDCl_3$) 2.30—2.43 (2 H, m, NCH_2CH_2), 3.50—3.85 (1 H, br m), 3.70 (1 H, dd, *J* 8, 10 Hz, ArC*H*), 3.80 (3 H, s, OCH_3), 4.10—4.57 (3 H, br m), and 6.68—7.42 (9 H, m, 9 × ArH).

Phenyl 2,3,4,4a,5,6-*Hexahydro*-4a-(3-*methoxyphenyl*)-3-*methylene*-7H-*pyrano*[2,3-c]*pyridine*-7-*carboxylate* (**16a**).—A solution of phenyl 4-(3-methoxyphenyl)-3-oxopiperidine-1-carboxylate (**14**; R = CO_2Ph) (3.61 g, 11.0 mmol) in dry DMF (11 ml) was added dropwise, over a 10 min period, to a suspension of sodium hydride (80% dispersion in oil; 0.83 g, 27.5 mmol) in dry DMF (11 ml) at −50 °C under nitrogen. The reaction mixture was allowed to warm to −30 °C and stirring continued at this temperature for 1 h. After cooling to −50 °C 3-chloro-2-chloromethylprop-1-ene (1.40 ml, 1.51 g, 12.1 mmol) was added and the reaction mixture allowed to warm to room temperature. Stirring was continued for 2.5 h before quenching with saturated aqueous ammonium chloride (25 ml). Water (25 ml) was added and the mixture was extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with 0.1M aqueous sodium hydroxide (3 × 50 ml), saturated brine (50 ml), dried (Na_2SO_4) and concentrated to give a brown oil. This was triturated with ethyl acetate–hexane (1:1) and the solid filtered off. This solid was recrystallized from ethyl acetate–hexane to give the *title compound* (**16a**) (0.95 g, 23%). Concentration of the mother liquor afforded further (**16a**) (0.59 g, 14%), m.p. 107—109 °C (Found: C, 72.85; H, 6.2; N, 3.65. $C_{23}H_{23}NO_4$ requires C, 73.2; H, 6.15; N, 3.7%); $\nu_{max.}$($CHBr_3$) 1 710 cm^{-1} (C=O); δ_H($CDCl_3$) 2.00—2.28 (2 H, m, 2 × 5-H), 2.54 (1 H, d, *J* 12 Hz, 4-H), 2.80—3.08 (1 H, m, 6-H), 3.08 (1 H, d, *J* 12 Hz, 4-H), 3.84 (3 H, s, OCH_3), 3.94—4.12 (1 H, m, 6-H), 4.18 (1 H, d, *J* 12 Hz, 2-H), 4.31 (1 H, d, *J* 12 Hz, 2-H), 4.69 (1 H, s, C=CH_AH_B), 4.78 (1 H, s, C=CH_AH_B), and 6.74—7.43 (10 H, m, 9 × ArH and NC*H*=C).

3,4,4a,5,6,7-*Hexahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-3-*methylene*-2H-*pyrano*[2,3-c]*pyridine* (**16b**).—A solution of (**16a**) (0.75 g, 2 mmol) in dry THF (8 ml) was added to a stirred suspension of lithium aluminium hydride (0.46 g, 12 mmol) in THF (8 ml) under nitrogen. The reaction mixture was heated at reflux for 3 h, cooled, and then quenched by adding 2M aqueous sodium hydroxide (40 ml). The mixture was filtered through Hyflo and the solid washed with ethyl acetate (100 ml). After shaking the total filtrate, the layers were separated and the aqueous phase extracted with ethyl acetate (25 ml). The combined organic fractions were dried (Na_2SO_4) and concentrated to give the *title compound* (**16b**) (0.49 g, 91%), m.p. 75—78 °C (Found: C, 74.9; H, 7.9; N, 4.7. $C_{17}H_{21}NO_2$ requires C, 75.25; H, 7.8; N, 5.1%); δ_H($CDCl_3$) 1.98—2.13 (2 H, m, 2 × 5-H), 2.30 (1 H, dt, *J* 5, 11 Hz, 6-H), 2.45 (1 H, br d, *J* 13 Hz, 4-H), 2.52 (3 H, s, NCH_3), 2.67 (1 H, dt, *J* 11, 3 Hz, 6-H), 3.02 (1 H, d, *J* 13 Hz, 4-H), 3.80 (3 H, s, OCH_3), 4.03 (1 H, d, *J* 12 Hz, 2-H), 4.19 (1 H, d, *J* 12 Hz, 2-H), 4.60 (1 H, s, C=CH_AH_B), 4.70 (1 H, s, C=CH_AH_B), 6.00 (1 H, s, NC*H*=C), 6.69—7.03 (3 H, m, 3 × ArH), and 7.23 (1 H, t, *J* 8 Hz, ArH).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-3-*methylene*-2H-*pyrano*[2,3-c]*pyridine* (**18a**) *and* cis-*Isomer* (**19**).—Ammonium acetate (5.9 g) and sodium cyanoborohydride (2.22 g, 35.4 mmol) were added to a stirred solution of the enamine (**16b**) (1.6 g, 5.9 mmol) in dry methanol (29.5 ml) under nitrogen. After 3 h at ambient temperature the reaction mixture was quenched with 1M sodium hydroxide (75 ml) and extracted with dichloromethane (3 × 75 ml). The combined organic extracts were washed with saturated brine (75 ml), dried (Na_2SO_4), and evaporated to give a yellow oil (1.42 g). This was purified by column chromatography on alumina (activity II), using diethyl ether–methanol (99:1) as eluant, to give the *trans*-isomer (**18a**) (0.73 g, 45%) as a pale yellow gum. This compound was analysed as its hydrochloride salt, m.p. 112—117 °C (Found: C, 64.05; H, 8.1; N, 4.3. $C_{17}H_{23}NO_2$·HCl·0.5H_2O requires C, 64.05; H, 7.9; N, 4.4%); δ_H[$CDCl_3$ (free base)] 1.72 (1 H, dt, *J* 3, 13 Hz, 5β-H), 1.88 (1 H, ddd, *J* 2, 11.5, 12.5 Hz, 6α-H), 2.23 (3 H, s, NCH_3), 2.28—2.62 (5 H, m), 2.87 (1 H, ddd, *J* 1.5, 4, 10.5 Hz), 3.78 (1 H, dd, *J* 11, 4 Hz, 8aβ-H), 3.80 (3 H, s, OCH_3), 4.14 (1 H, br d, *J* 12 Hz, 2β-H), 4.31 (1 H, dd, *J* 1.5, 12 Hz, 2α-H), 4.38 (1 H, br t, *J* 2 Hz, C=CH_AH_B), 4.68 (1 H, br q, *J* 2 Hz, C=CH_AH_B), 6.68—6.73 (1 H, m, ArH), and 7.14—7.26 (3 H, m, 3 × ArH). Irradiation of 8aβ-H causes n.O.e. to signals at δ 4.14 and 1.72.

Further elution with diethyl ether–methanol (95:5) afforded the *cis*-isomer (**19**) (0.25 g, 16%) as a pale yellow gum. This compound was analysed as its hydrochloride salt, m.p. 119—125 °C (Found: C, 63.9; H, 8.2; N, 4.2. $C_{17}H_{23}NO_2$·HCl·0.67H_2O requires C, 63.5; H, 7.9; N, 4.35%); δ_H[$CDCl_3$ (free base)] 1.87 (1 H, dq), 2.05—2.26 (3 H, m), 2.38—2.52 (2 H, m), 2.65—2.82 (2 H, m), 2.12 (3 H, s, NCH_3), 3.83 (3 H, s, OCH_3), 4.07 (1 H, br d, *J* 12 Hz, 2-H), 4.19 (1 H, dt, *J* 3, 2 Hz, 8aα-H), 4.37 (1 H, dd, *J* 2, 12 Hz, 2-H), 4.76 (1 H, t, *J* 2 Hz, C=CH_AH_B), 4.89 (1 H, q, *J* 2 Hz, C=CH_AH_B), 6.67 (1 H, d), 6.92 (1 H, t), 6.77 (1 H, dd), and 7.30 (1 H, t, *J* 8 Hz, ArH).

trans-7-(*Cyclobutylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-3-*methylene*-2H-*pyrano*[2,3-c]*pyridine* (**18c**).—This compound was prepared from (**18e**) using the method described for the

preparation of (**9d**). The *title compound* (**18c**) (79%) was purified by column chromatography on alumina, with dichloromethane–ethyl acetate (2:1) as eluant, and characterized as its maleate salt, m.p. 164—167 °C (Found: C, 67.6; H, 7.55; N, 3.05. $C_{21}H_{29}NO_2 \cdot C_4H_4O_4$ requires C, 67.7; H, 7.5; N, 3.15%).

trans-7-(*Cyclopropylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-3-*methylene*-2H-*pyrano*[2,3-c]*pyridine* (**18b**).—Bromomethylcyclopropane (1.07 ml, 1.49 g, 11 mmol) was added to a stirred solution of *trans*-octahydro-4a-(3-methoxyphenyl)-3-methylene-2*H*-pyrano[2,3-*c*]pyridine (**18e**) (2.59 g, 10 mmol) and sodium hydrogen carbonate (1.93 g, 23 mmol) in DMF (25 ml) at room temperature under nitrogen. The reaction mixture was heated at 125 °C for 5 h. Evaporation of the solvent and purification by alumina chromatography, using dichloromethane–ethyl acetate (1:1) as the eluant, afforded the *title compound* (**18b**) (2.20 g, 70%) as a pale yellow oil (Found: C, 76.35; H, 8.75; N, 4.65. $C_{20}H_{27}NO_2$ requires C, 76.65; H, 8.7; N, 4.45%).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-3-*methylene*-2H-*pyrano*[2,3-c]*pyridine* (**18e**).—Phenyl chloroformate (5.02 ml, 6.26 g, 40 mmol) was added to a stirred solution of the pyrano[2,3-*c*]pyridine (**18a**) (5.47 g, 20 mmol) and *N*,*N*-diisopropylethylamine (1.74 ml, 1.29 g, 10 mmol) in dry 1,2-dichloroethane (80 ml) at room temperature under nitrogen. The stirred reaction mixture was heated at reflux for 3 h and then cooled and diluted with diethyl ether (320 ml). The resultant solution was washed successively with 1M hydrochloric acid (3 × 50 ml), 1M sodium hydroxide (2 × 50 ml), and saturated brine (50 ml). The organic phase was dried (Na_2SO_4) and evaporated to give the intermediate carbamate (**18d**) as a white crystalline solid. This solid was dissolved in ethanol (380 ml) and heated to reflux before addition of 50% w/w aqueous potassium hydroxide (100 ml). The stirred reaction mixture was heated at reflux for 6 h and then cooled and concentrated to remove the ethanol. 1M Hydrochloric acid (200 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 150 ml). The combined organic extracts were washed successively with 1M sodium hydroxide (2 × 100 ml) and saturated brine (100 ml), dried (Na_2SO_4), and evaporated to give the *title compound* (**18e**) (5.2 g, 100%) as a pale yellow oil (Found: C, 73.85; H, 8.15; N, 5.4. $C_{16}H_{21}NO_2$ requires C, 74.1; H, 8.15; N, 5.4%); $\nu_{max.}$(Nujol) 3 310 cm^{-1} (NH).

trans-3-[7-(*Cyclopropylmethyl*)*octahydro*-3-*oxo*-2H-*pyrano*-[2,3-c]*pyridin*-4a-*yl*]*phenol* (**21**).—Osmium tetroxide (32 mg, 0.125 mmol) was added in one portion to a stirred mixture of sodium periodate (2.7 g, 12.5 mmol) and *trans*-3-[7-(cyclopropylmethyl)octahydro-3-methylene-2H-pyrano[2,3-*c*]pyridin-4a-yl]phenol (**20b**) (749 mg, 2.5 mmol) in THF–water–acetic acid (3:1:1) (35 ml) at room temperature under nitrogen. The reaction mixture was stirred at ambient temperature for 2 h, filtered, and adjusted to pH 7 by addition of ammonia solution (10 ml). The resultant mixture was extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with water (20 ml) containing ammonia (*d* 0.880; 0.5 ml), dried (Na_2SO_4), and concentrated to a brown oil. This material was purified by flash chromatography on silica gel, using dichloromethane–methanol–ammonia (*d* 0.880) (100:8:1) as eluant, to give the *title compound* (**21**) (560 mg, 74%) as a colourless foam. This compound was characterized as its maleate salt (Found: $[M + H]^+$, 302.1761. $C_{18}H_{24}NO_3$ requires $[M + H]^+$, 302.1758); $\delta_H(D_2O)$ 0.20—1.13 [5 H, m, c-(C_3H_5)], 1.8—2.2, 2.4—3.1, 3.3—3.7, 3.8—4.0 (11 H, multiplets), 4.29 (1 H, d, *J* 16 Hz, 2-H), 4.44 (1 H, d, *J* 16 Hz, 2-H), 6.31 (2 H, s, maleate), 6.77—6.9 (1 H, m), and 7.1—7.4 (3 H, m).

trans-(3α,4aα,8aβ)-3-[7-(*Cyclopropylmethyl*)*octahydro*-3-*hydroxy*-2H-*pyrano*[2,3-c]*pyridin*-4a-*yl*]*phenol* (**22**).—A solution of the ketone (**21**) (362 mg, 1.2 mmol) in methanol (9 ml) was added dropwise to sodium borohydride (0.18 g, 4.8 mmol) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 30 min before quenching with saturated aqueous ammonium chloride (0.6 ml). After concentration the resulting gum was purified by flash silica chromatography, using dichloromethane–methanol–ammonia (*d* 0.880) (100:8:1) as the eluant, to give the *title compound* (**22**) (257 mg, 71%) as a colourless foam. This was characterized as its maleate salt, m.p. 133—135 °C (Found: C, 62.65; H, 6.95; N, 3.25. $C_{18}H_{25}NO_3 \cdot C_4H_4O_4$ requires C, 63.0; H, 6.95; N, 3.35%); δ_H[$CDCl_3$ (free base)] 0.0—0.92 [5 H, m, c-(C_3H_5)], 1.70 (1 H, dt, *J* 3, 13 Hz, 5β-H), 1.84 (1 H, t, *J* 13 Hz, 6α-H), 1.86 (1 H, dd, *J* 4, 13 Hz, 4β-H), 2.18 (1 H, br d, *J* 13 Hz, 5α-H), 2.35 (1 H, dt, *J* 2, 13 Hz, 4α-H), 2.16—2.33 [2 H, m, CH_2c-(C_3H_5)], 2.77 (1 H, br d, *J* 11 Hz, 6β-H), 2.83 (1 H, t, *J* 11 Hz, 8α-H), 3.28 (1 H, dd, *J* 11, 4 Hz, 8β-H), 3.73 (1 H, br s, 3β-H), 3.75 (1 H, dd, *J* 4, 11 Hz, 8aβ-H), 3.82 (1 H, dd, *J* 2, 12 Hz, 2β-H), 4.10 (1 H, br d, *J* 12 Hz, 2α-H), 6.65 (1 H, dd, *J* 2, 8 Hz, ArH), and 7.10—7.35 (3 H, m, 3 × ArH). Irradiation of δ 3.28 caused the signals at δ 2.83 and 3.75 to simplify to (1 H, d, *J* 11 Hz) and (1 H, d, *J* 11 Hz) respectively.

5-(3-*Methoxyphenyl*)-8-*methyl*-2-*oxa*-8-*azabicyclo*[3.3.1]-*nonane* (**23**).—A solution of the tetrahydropyridine (**4**) (1.25 g, 6.15 mmol) in dry THF (25 ml) at −20 °C to −30 °C was treated with a solution of butyl-lithium (1.55M in hexane; 4.5 ml, 6.9 mmol) dropwise over a 10 min period. The mixture was stirred at −30 °C for 10 min and cooled to −70 °C. A solution of ethylene oxide in toluene (22%; 3.0 ml, 6.0 mmol) was added over a 5 min period. The mixture was stirred at −70 °C for 1 h and then treated with saturated brine (50 ml). The product was extracted with diethyl ether (2 × 50 ml). The ethereal extracts were dried (Na_2SO_4), filtered and evaporated to give the *title compound* (1.5 g, 98%) which was of sufficient purity to be used directly in the next stage. An analytical sample was obtained after flash chromatography on silica gel, with dichloromethane–methanol–ammonia (*d* 0.880) (150:8:1) as eluant, as a pale yellow oil (Found: C, 72.5; H, 8.5; N, 5.75. $C_{15}H_{21}NO_2$ requires C, 72.85; H, 8.55; N, 5.65%); $\delta_H(CDCl_3)$ 1.88—2.22 (6 H, m), 2.29 (1 H, dt, *J* 12, 3 Hz), 2.54 (3 H, s, NCH_3), 2.89 (1 H, ddd, *J* 2, 6, 12 Hz), 3.78—3.88 (1 H, m, OCH_AH_B), 3.81 (3 H, s, OCH_3), 4.02 (1 H, ddd, *J* 6, 8, 12 Hz, OCH_AH_B), 4.69 (1 H, dd, *J* 2, 4 Hz, NC*H*O), 6.75 (1 H, dt), 6.85 (1 H, t), 6.90 (1 H, d), and 7.27 (1 H, t, *J* 8 Hz, ArH).

3,4,4a,5,6,7-*Hexahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-1H-*pyrano*[3,4-c]*pyridine* (**24**).—A solution of 5-(3-methoxyphenyl)-8-methyl-2-oxa-8-azabicyclo[3.3.1]nonane (**23**) (3 g, 0.012 mol) in 1M sulphuric acid (6 ml) was adjusted to pH 3 using triethylamine. The resulting solution was added to a solution of 36% aqueous formaldehyde (1.89 g, 0.017 mol) and triethylamine (1.82 g, 2.5 ml, 0.018 mol) in water (14 ml). The solution was adjusted to pH 3 and then stirred at 70 °C for 2.5 h under nitrogen. The resulting solution was basified with 5M sodium hydroxide and extracted with ether (3 × 20 ml). The combined ether extracts were washed with water (2 × 30 ml), dried ($MgSO_4$), and evaporated to afford a dark brown oil. This was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (*d* 0.880) (97:2:1) as eluant, to afford the *title compound* (1.67 g, 53%) (Found: C, 74.45; H, 8.4; N, 5.35. $C_{16}H_{21}NO_2$ requires C, 74.1; H, 8.15; N, 5.4%); $\delta_H(CDCl_3)$ 1.82—1.98 (3 H, m), 2.39 (1 H, br d, *J* 14 Hz), 2.45—2.54 (1 H, m), 2.63 (3 H, s, NCH_3), 2.69 (1 H, dt, *J* 12, 3.5 Hz), 3.24 (1 H, dt, *J* 1.5, 12 Hz), 3.76 (1 H, br d, *J* 12 Hz), 3.82 (3 H, s, OCH_3), 3.94 (1 H, d, *J* 12 Hz, 1-H), 4.10 (1 H, d, *J* 12 Hz, 1-

H), 6.06 (1 H, s, 8-H), 6.76 (1 H, dd, *J* 2, 8 Hz, ArH), 6.91—7.0 (2 H, m, 2 × ArH), and 7.27 (1 H, t, *J* 8 Hz, ArH).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-1H-*pyrano*-[3,4-c]*pyridine* (**25**).—A solution of the enamine (**24**) (2.58 g, 9.96 mmol) in ethanol (60 ml) was hydrogenated at 1 atm over Adams catalyst (490 mg) for 18 h. The catalyst was removed by filtration through Hyflo and the filtrate evaporated to afford the title compound (2.58 g, 99%).* The material was converted into its maleate salt and recrystallized from ethyl acetate to provide pure *title compound, maleate salt* as a colourless solid, m.p. 173—175 °C (Found: C, 63.25; H, 7.4; N, 3.65. $C_{16}H_{23}NO_2 \cdot C_4H_4O_4$ requires C, 63.65; H, 7.2; N, 3.7%); $\delta_H(CD_3OD)$ 1.83 (1 H, dt, *J* 4, 13 Hz, 4β-H), 1.93 (1 H, dt, *J* 3.5, 13 Hz, 5β-H), 2.11 (1 H, dt, *J* 13, 2 Hz, 4α-H), 2.42 (1 H, tt, *J* 4, 12 Hz, 8aβ-H), 2.46 (1 H, dt, *J* 14, 2.5 Hz, 5α-H), 2.61 (1 H, dt, *J* 2.5, 13 Hz, 6α-H), 2.82 (3 H, s, NCH_3), 3.22 (1 H, dt, *J* 2, 12.5 Hz, 3α-H), 3.32 (1 H, dt, *J* 13, 2.5 Hz, 6β-H), 3.44 (1 H, ddd, *J* 2, 4, 12 Hz, 8β-H), 3.55 (1 H, t, *J* 13 Hz, 8α-H), 3.70 (1 H, ddd, *J* 2, 4, 12 Hz, 3β-H), 3.78 (1 H, dd, *J* 4, 12 Hz, 1β-H), 3.80 (3 H, s, OCH_3), 4.20 (1 H, t, *J* 12 Hz, 1α-H), 6.65 (2 H, s, maleate), 6.88 (1 H, dd, *J* 2, 8 Hz, ArH), 7.04 (1 H, t, *J* 2 Hz, ArH), 7.12 (1 H, dd, *J* 2, 8 Hz, ArH), and 7.37 (1 H, t, *J* 8 Hz, ArH).

trans-*Octahydro*-4a-(3-*methoxyphenyl*)-1H-*pyrano*[3,4-c]-*pyridine* (**26**).—Vinylchloroformate (2.62 g, 2.25 ml, 24.6 mmol) was added dropwise to a stirred suspension of *trans*-octahydro-4a-(3-methoxyphenyl)-7-methyl-1*H*-pyrano[3,4-*c*]pyridine (**25**) (2.57 g, 9.83 mmol) and potassium carbonate (2.72 g, 19.7 mmol) in dry 1,2-dichloroethane (35 ml) at −30 °C under nitrogen. The resulting mixture was heated at reflux for 1 h. A further quantity of vinyl chloroformate (0.5 ml) was added and the reaction mixture was refluxed for an additional 2 h. After cooling, the solvent was evaporated and the residue purified by column chromatography on alumina. Elution with ethyl acetate afforded the intermediate carbamate as a yellow oil. This material was dissolved in 2M methanolic hydrogen chloride (60 ml) and the resulting solution heated at reflux under nitrogen for 3 h. The solvent was evaporated and the residue dissolved in water (50 ml) and washed with ether (2 × 20 ml). The aqueous phase was basified with 5M sodium hydroxide and extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the *title compound* (**26**) (1.40 g, 97%) as a pale yellow oil. This material was used directly in the subsequent stage without further purification; $\nu_{max.}$(Nujol) 3 310 cm^{-1} (NH); $\delta_H(CDCl_3)$ 1.70 (1 H, dt, *J* 4, 13 Hz, 5β-H), 1.89 (1 H, dt, *J* 4, 13 Hz, 4β-H), 1.97 (1 H, dt, *J* 3, 2.5 Hz, 4α-H), 2.10 (1 H, dt, *J* 13, 12 Hz, 5α-H), 2.31 (1 H, tt, *J* 4, 13 Hz, 8aβ-H), 2.47 (1 H, dt, *J* 2, 13 Hz, 6α-H), 2.8 (1 H, dt, *J* 13, 3 Hz, 6β-H), 2.86 (1 H, dd, *J* 4, 13 Hz, 8β-H), 3.28 (1 H, dt, *J* 2, 12 Hz, 3α-H), 3.35 (1 H, t, *J* 13 Hz, 8α-H), 3.63—3.76 (2 H, m, 3β- and 1β-H), 3.81 (3 H, s, OCH_3), 4.15 (1 H, t, *J* 12 Hz, 1α-H), 6.74 (1 H, dd, *J* 2, 8 Hz, ArH), 7.00 (1 H, t, *J* 2 Hz, ArH), 7.04 (1 H, br d, *J* 8 Hz, ArH), and 7.27 (1 H, t, *J* 8 Hz, ArH).

trans-7-(*Cyclobutylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-1H-*pyrano*[3,4-c]*pyridine* (**27b**).—Cyclobutanecarboxylic acid chloride (0.37 ml, 3.26 mmol) was added dropwise to a stirred solution of the pyrano[3,4-*c*]pyridine (**26**) (660 mg, 2.67 mmol) and triethylamine (0.29 ml) in dry dichloromethane (20 ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 2 h and then quenched with 2M hydrochloric acid (25 ml). The layers were separated and the aqueous phase was further extracted with dichloromethane (2 × 25 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the intermediate oily amide. A solution of this intermediate in dry THF (5 ml) was added to a stirred suspension of lithium aluminium hydride (354 mg, 9.32 mmol) in dry THF (20 ml) under nitrogen and the mixture heated at reflux under nitrogen for 19 h. After cooling, saturated aqueous sodium sulphate (2 ml) was added followed by 2M sodium hydroxide (1 ml). The mixture was heated for a further 30 min and then diluted with water (150 ml) and extracted with ethyl acetate (4 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford a yellow oil. This was purified by column chromatography on alumina, eluting with ethyl acetate–methanol (19:1), to give the *title compound* (**27b**) (520 mg, 62%). This compound was characterized as its maleate salt, m.p. 144—147 °C (Found: C, 66.95; H, 7.9; N, 3.15. $C_{20}H_{29}NO_2 \cdot C_4H_4O_4$ requires C, 66.8; H, 7.7; N, 3.25%).

trans-7-(*Cyclopropylmethyl*)*octahydro*-4a-(3-*methoxyphenyl*)-1H-*pyrano*[3,4-c]*pyridine* (**27a**).—Cyclopropylmethyl bromide (389 mg, 2.88 mmol) in dry DMF (2 ml) was added dropwise to a stirred suspension of (**26**) (679 mg, 2.75 mmol) and sodium hydrogen carbonate (461 mg, 5.49 mmol) in dry DMF (3 ml) under nitrogen. The resulting mixture was heated at 100 °C for 2 h. A further amount of cyclopropylmethyl bromide (190 mg, 1.4 mmol) was added and the mixture heated at 150 °C for 2 h. After cooling, the solvent was evaporated and the residue purified by column chromatography, with ethyl acetate–hexane (1:1) ⟶ ethyl acetate as eluant, to give the *title compound* (**27a**) (337 mg, 41%) as a gum. This material was used without further purification, in the next stage.

Ethyl 3,4,4a,5,6,7-*Hexahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-1H-*pyrano*[3,4-c]*pyridine*-1-*carboxylate* (**29**).—A solution of 5-(3-methoxyphenyl)-8-methyl-2-oxa-8-azabicyclo-[3.3.1]nonane (**23**) (5.0 g, 20.2 mmol) in 1M sulphuric acid (10 ml) was adjusted to ~pH 3 using triethylamine. The resulting solution was added to a solution of methyl glyoxylate (2.51 g, 43.09 mmol) and triethylamine (4.20 ml, 4.63 ml, 45.8 mmol) in water (23 ml). The pH of the solution was adjusted to ~3 and the mixture heated at 80 °C for 18 h, under nitrogen. The reaction mixture was evaporated to dryness and the residue was dissolved in toluene (100 ml) and again evaporated to dryness. The resulting oil was dissolved in a mixture of ethanol–toluene (1:1) (300 ml) and concentrated to afford a dark brown oil. This material (14.62 g, 48 mmol) was dissolved in a mixture of absolute ethanol (100 ml) and concentrated sulphuric acid (5 ml) and heated at reflux for 2 h. After cooling, the solvent was removed and the residue was basified with aqueous potassium carbonate. The resulting solution was extracted with diethyl ether (4 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford a dark brown oil. This oil was purified by flash column chromatography on silica gel, with dichloromethane–ethanol–ammonia (*d* 0.880) (150:12:1) as eluant, to afford the *title compound* (**29**) (3.47 g, 52%) as a mixture of epimers (Found: C, 68.85; H, 7.75; N, 4.45. $C_{19}H_{25}NO_4$ requires C, 68.85; H, 7.6; N, 4.25%); $\nu_{max.}(CHBr_3)$ 1 735 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.05 and 1.37 (3 H, 2 × t, *J* 7 Hz, CH_2CH_3), 1.58—2.10 (6 H, m), 2.65 and 2.76 (3 H, 2 × s, NCH_3), 3.27—4.13 (2 H, m), 3.77 and 3.82 (3 H, 2 × s, OCH_3), 4.32 (2 H, br q, CH_2CH_3), 4.54 and 4.68 (1 H, 2 × s, OC*H*), 5.91 and 6.31 (1 H, 2 × s, NC*H*=C), and 6.68—7.32 (4 H, m, 4 × ArH).

(1α,4aβ,8aα)-*Ethyl Octahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-1H-*pyrano*[3,4-c]*pyridine*-1-*carboxylate* (**30**) *and* (1α,4aα,8aβ)-*Ethyl Octahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-1H-*pyrano*[3,4-c]*pyridine*-1-*carboxylate* (**31**).—A solution of the enamine (**29**) (3.43 g, 10.4 mmol) in ethanol (35 ml) was

* Contains 5% of the *cis*-isomer by ^1H n.m.r.

hydrogenated at 60 p.s.i. over Adams catalyst (350 mg) for 19 h. A further quantity of Adams catalyst (370 mg) was added and the mixture was hydrogenated at 60 p.s.i. for a further 24 h. The reaction mixture was filtered through Hyflo and the catalyst was washed thoroughly with ethanol. The filtrate was evaporated to dryness to afford a yellow oil. This was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–ammonia (*d* 0.880) (98:1:1) ⟶ (96:3:1), to give the *title compound* (**30**) (0.89 g, 26%) as a pale yellow oil (Found: C, 68.8; H, 8.4; N, 4.05. $C_{19}H_{27}NO_4$ requires C, 68.45; H, 8.15; N, 4.2%); $\nu_{max.}$($CHBr_3$) 1 735 cm^{-1} (C=O); δ_H($CDCl_3$) 1.34 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.75—2.15 (5 H, m, 2 × 4-H, 2 × 5-H, and 8aα-H), 2.23 (3 H, s, NCH_3), 2.40 (1 H, dt, *J* 4, 12 Hz, 6β-H), 2.53 (1 H, dd, *J* 12, 3 Hz, 6α-H), 2.60 (1 H, dd, *J* 12, 4 Hz, 8α-H), 2.74 (1 H, t, *J* 12 Hz, 8β-H), 3.31 (1 H, dt, *J* 2, 12 Hz, 3β-H), 3.78—3.87 (1 H, m, 3α-H), 3.82 (3 H, s, OCH_3), 4.29 (2 H, ABX_3, CH_2CH_3), 4.81 (1 H, d, *J* 12 Hz, 1β-H), 6.75 (1 H, dd, *J* 2, 8 Hz, ArH), 7.00 (1 H, t, *J* 2 Hz, ArH), 7.09 (1 H, br d, *J* 8 Hz, ArH), and 7.29 (1 H, t, *J* 8 Hz, ArH). Irradiation at δ 4.81 caused an n.O.e. enhancement of the signals at δ 7.00, 7.09, and 3.31.

Further elution with dichloromethane–methanol–ammonia (*d* 0.880) (94:5:1) gave the *epimer* (**31**) (1.02 g, 30%) as a colourless foam (Found: C, 68.75; H, 8.4; N, 4.15. $C_{19}H_{27}NO_4$ requires C, 68.45; H, 8.15; N, 4.2%); δ_H($CDCl_3$) 1.20 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.73—2.30 (5 H, m, 2 × 4-H, 2 × 5-H, and 8aβ-H), 2.33 (3 H, s, NCH_3), 2.54 (1 H, br dt, *J* 12, 3 Hz, 6β-H), 2.75—2.85 (1 H, m, 6α-H), 2.93 (1 H, t, *J* 12 Hz, 8α-H), 3.02 (1 H, dd, *J* 4, 12 Hz, 8β-H), 3.68 (1 H, ddd, *J* 2, 4, 12 Hz, 3β-H), 3.79 (3 H, s, OCH_3), 3.86 (1 H, br t, *J* 12 Hz, 3α-H), 4.14 (2 H, ABX_3, CH_2CH_3), 4.42 (1 H, d, *J* 7 Hz, 1β-H), 6.71 (1 H, dd, *J* 2, 8 Hz, ArH), 6.89—6.95 (2 H, m, 2 × ArH), and 7.19 (1 H, t, *J* 8 Hz, ArH).

(1α,4aα,8aβ)-*Octahydro*-4a-(3-*methoxyphenyl*)-7-*methyl*-1H-*pyrano*[3,4-c]*pyridin*-1-*ylmethanol* (**32a**).—A solution of the ester (**31**) (4.47 g, 13.4 mmol) in dry THF (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (890 mg, 23.45 mmol) in dry THF (25 ml) under nitrogen. The resulting suspension was stirred at room temperature for 3.5 h. A saturated solution of sodium sulphate (6 ml) was added followed by 5M sodium hydroxide (1 ml). The mixture was heated until all the solid had turned white. Sodium sulphate was added and the mixture was filtered through Hyflo. The filtrate was dried ($MgSO_4$) and the solvent evaporated to afford the *title compound* (**32a**) (4.10 g, 100%) as a colourless oil which was used directly in the next stage.

(1α,4aα,8aβ)-*Octahydro*-4a-(3-*methoxyphenyl*)-1,7-*dimethyl*-1H-*pyrano*[3,4-c]*pyridine* (**33a**).—A solution of tris(dimethylamino)phosphine (1.23 g, 1.36 ml, 7.54 mmol) in THF (3 ml) was added dropwise to a cooled solution of (**32a**) (1.65 g, 5.67 mmol) and carbon tetrachloride (1.75 g, 11.3 mmol) in tetrahydrofuran (15 ml) at −45 °C under nitrogen. The resulting solution was stirred at −45 °C for 1 h. Lithium triethylborohydride (1M in THF; 51 ml, 51 mmol) was added dropwise and the resulting mixture was heated at reflux under nitrogen for 20 h. A further amount of lithium triethylborohydride (12 ml, 12 mmol) was added and the mixture was heated at reflux for a further 24 h. The reaction mixture was quenched with water (12 ml), the solvent was evaporated, and the residue partitioned between 1M hydrochloric acid (60 ml) and diethyl ether (40 ml). The aqueous layer was washed again with ether (40 ml), basified with 1M sodium hydroxide, and extracted with dichloromethane (4 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a yellow oil which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–ammonia (*d* 0.880) (150:8:1) to give the *title compound* (**33a**) (1.16 g, 74%) as a yellow oil (Found: C, 74.35; H, 9.3; N, 5.2. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.1%); δ_H($CDCl_3$) 1.22 (3 H, d, *J* 7.5 Hz, CH_3CH), 1.69—1.88 (3 H, m), 1.97—2.12 (1 H, m), 2.28—2.36 (1 H, m), 2.34 (3 H, s, NCH_3), 2.55 (1 H, dt, *J* 12, 3 Hz), 2.59—2.85 (3 H, m), 3.45—3.63 (2 H, m), 3.82 (3 H, s, OCH_3), 4.12 (1 H, br quintet, CH_3CH), 6.73 (1 H, br d, *J* 8 Hz, ArH), and 7.10—7.26 (3 H, m, ArH).

(1α,4aα,8aβ)-*Octahydro*-4a-(3-*methoxyphenyl*)-1-*methyl*-1H-*pyrano*[3,4-c]*pyridine* (**33b**).—Phenyl chloroformate (1.50 g, 1.2 ml, 9.6 mmol) was added to a stirred solution of (**33a**) (1.32 g, 4.8 mmol) and tri-isobutylamine (0.445 g, 0.6 ml, 2.4 mmol) in dry 1,2-dichloroethane (20 ml) at room temperature under nitrogen. The reaction mixture was heated at reflux for 3 h. The cooled reaction 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 phase was dried ($MgSO_4$) and evaporated to give the intermediate carbamate as a yellow oil. A solution of this intermediate in a mixture of ethanol (90 ml) and 50% aqueous potassium hydroxide (22 ml) was heated at reflux under nitrogen for 19 h. The solvent was evaporated and the residue diluted with water (75 ml) and extracted with dichloromethane (4 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the *title compound* (**33b**) (1.20 g, 96%) which was used directly in the next stage without further purification.

trans-(1α,4aα,8aβ)-3-[7-(*Cyclopropylmethyl*)*octahydro*-1-*methyl*-1H-*pyrano*[3,4-c]*pyridin*-4a-*yl*]*phenol* (**34**).—(Bromomethyl)cyclopropane (0.217 g, 0.16 ml, 1.61 mmol) was added to a stirred suspension of (1α,4aα,8aβ)-octahydro-4a-(3-methoxyphenyl)-1-methyl-1*H*-pyrano[3,4-*c*]pyridine (**33b**) (400 mg, 1.53 mol) and sodium hydrogen carbonate (142 mg, 1.69 mmol) in dry DMF (6 ml) under nitrogen. The resulting mixture was heated at 125 °C for 4 h. After cooling, lithium methanethiolate (497 mg, 9.20 mmol) was added and the reaction mixture was heated at 130 °C for 8 h. Ammonium chloride (533 mg, 9.96 mmol) was added to the cooled reaction mixture and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (*d* 0.880) (150:8:1) ⟶ (100:8:1) as eluant, to give the free base of the *title compound* (**34**) as an off-white foam (355 mg). This material was dissolved in ethyl acetate and treated with a solution of maleic acid (151 mg, 1.30 mmol) in diethyl ether. The resulting gum was triturated four times with diethyl ether. The solvent was decanted off and the solid dried to afford the maleate salt of *title compound* as a cream solid (408 mg, 64%), m.p. 94—97 °C; δ_H[$CDCl_3$ (free base)] 0.1—1.0 [5 H, m, c(C_3H_5)], 1.23 (3 H, d, *J* 7 Hz, CH_3CH), 1.68—1.91 (3 H, m), 2.06—2.20 (1 H, m), 2.24—2.45 (3 H, m), 2.69 (1 H, dt, *J* 12, 5 Hz, 8aβ-H), 2.8—3.0 (3 H, m), 3.45—3.65 (2 H, m, 3α-, 3β-H), 4.14 (1 H, dq, *J* 5, 7 Hz, 1β-H), 6.62 (1 H, m, ArH), 6.98 (1 H, br s, ArH), and 7.05—7.17 (2 H, m, ArH).

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