Cyclic Adrenaline Derivatives. Aryl-2-Piperidyl-Carbinols.

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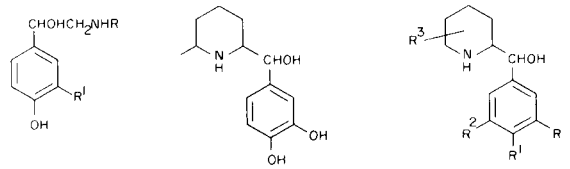
A synthetic route to 3,4-dihydroxyphenyl-(2-piperidyl)carbinols is described. These novel catecholamines may be regarded as derivatives of adrenaline containing a cyclic side-chain moiety. Their biological action appears to be more selective than that of adrenaline or isoprenaline and the more active of these compounds show promise as powerful bronchodilators with minimum cardiac effect.

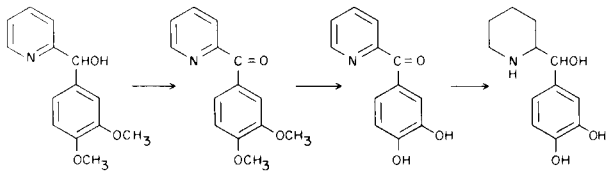
Adrenaline (**1**; R = CH_3, R^1 = OH) has been a valuable drug in the treatment of reversible airway obstructive disorders, and very many analogues of it have been screened (1). It, however, acts upon the α-, β_1- and β_2-adrenergic receptor sites (2), and this lack of selectivity has led to the predominant use of isoprenaline (**1**; R = Pr^1, R^1 = OH) as a bronchodilator, owing to its much reduced α-stimulant activity. Isoprenaline however, retains undesirable β_1-stimulant action upon the heart, which is less pronounced in its derivative isoetharine (**2**) containing an α-ethyl substituent (3).

Our interest in sympathomimetic amines possessing a "cyclised" side chain moiety, in contrast to the more recent emphasis on nuclear substitution (4-5), in this area, has led us to prepare a series of novel hydroxyphenyl-piperidylcarbinols, bearing this formal relationship to isoetharine, in the hope of producing bronchodilators of greater efficacy.



1 2 3

The following reaction sequence shows the general synthetic route used in this series.



Methoxyphenyl-2-pyridylcarbinols were prepared by the Hammick (6) reaction between methoxybenzaldehydes and picolinic acids or by treatment of the aldehydes with 2-pyridyllithium derivatives (7). The latter method, although more elaborate, was preferred as it gave much higher yields and avoided the use of a large excess of aldehyde (see Table II). Other synthetic approaches to 2-pyridylcarbinols have been reviewed (8).

Oxidation of the carbinols to the corresponding ketones (60-90%) was effected with potassium permanganate, at 70° for the unsubstituted pyridine derivatives but at room temperature for methyl substituted pyridine alcohols. Aerial oxidation or the dimethylsulphoxide-acetic anhydride reagent (9) also afforded the desired ketones but less efficiently. Chromium trioxide (10) has also been employed for the oxidation of arylpyridylcarbinols. Alternatively the ketones could be synthesised by a Friedel-Craft reaction between a pyridine acid chloride and a methoxybenzene derivative, thus picolinyl chloride and veratole undergo reaction in the presence of aluminum chloride to give 3,4-dimethoxyphenyl-2-pyridyl ketone in 20% yield (see Table III).

Removal of the protecting groups with boiling hydrobromic acid gave the hydroxyphenyl-(2-pyridyl) ketones, which usually crystallised in good yield from the reaction mixture as their hydrobromide salts (Table IV). Otherwise the crystalline bases were subsequently isolated. Indeed the hydroxyphenyl-(2-pyridyl) ketones are such weak bases that attempts to recrystallise their salts from aqueous alcohol resulted in the separation of the crystalline bases from solution.

The hydroxyphenyl-(2-pyridyl) ketones were hydrogenated, as their salts, over a platinum catalyst at atmospheric pressure and temperature to give mixtures of the corresponding *erythro*- and *threo*- aryl 2-piperidylcarbinols, from which the *erythro*-racemates, which were, with one

TABLE I

Chemical Shifts and Coupling Constants for the *erythro*- and *threo*-Benzylic Protons in Aryl-(2-piperidyl)carbinols and the Relative Proportions of Each Isomer Formed from the Hydrogenation of Aryl-(2-pyridyl) ketone.

Compound	Chemical shift δ and coupling const. Hz)	Solvent (temp., °C)	*erythro:threo*
3; R, R^1 = OH, R^2, R^3 = H hydrobromide	e 4.94 (4.5) t 4.66 (8.5)	D_2O (95)	3:1
3; R = OMe, R^1 = OH, R^2, R^3 = H hydrochloride	e 5.01 (5.0) t 4.72 (9.0)	D_2O (80)	3:1
3; R, R^2 = OH, R^1, R^3 = H hydrochloride	e 4.98 (4.0) t 4.68 (8.5)	D_2O (37)	3:1
3; R, R^1, R^2 = OH, R^3 = H hydrobromide	e 4.85 (4.5) t 4.61 (9.5)	D_2O (95)	11:2.5
3; R, R^2, R^3 = H, R^1 = OH hydrobromide	e 5.05 (3.5) t 4.63 (9.0)	DMSO-d_6 (37)	7.5:2
3; R, R^1 = OH, R^2 = H, R^3 = 3-Me hydrochloride	e 5.07 (4.5) t 4.76 (9.0)	D_2O (90)	3:8
3; R, R^1 = OH, R^2 = H, R^3 = 4-Me hydrobromide	e 4.93 (4.5) t 4.6 (9.0)	D_2O (90)	5:2
3; R, R^1 = OH, R^2 = H, R^3 = 5-Me hydrobromide	e 4.98 (5.5) t 4.62 (9.0)	D_2O (90)	5:1
3; R, R^1 = OH, R^2 = H, R^3 = 6-Me hydrobromide	e 5.16 (3.0) t 4.5 (9.5) e 4.9 (4.0)	DMSO-d_6 (90) D_2O (37)	5:2
3; R, R^1 = OH, R^2 = H, R^3 = 6-$PhCH_2CH_2$ hydrobromide	e 5.13 (3.0) t 4.53 (9.5)	DMSO-d_6 (80)	7:3
3; R, R^1 = OH, R^2 = H, R^3 = 6-$(PhCH_2)_2CH$ hydrochloride	e 5.18 (2.0) t 4.2 (9.0)	DMSO-d_6 (80)	3:2
Isoetharine hydrochloride	e 5.02 (3.0)	DMSO-d_6 (37)	
Ephedrine	e - (3.6)[5]	D_2O	
	e - (4.0)[12]	$CDCl_3$	
ψ - Ephedrine	t - (9.5)[5]	D_2O	
	t - (8.0)[12]	$CDCl_3$	

exception, the major products, were isolated (see Tables I and V). Thus, reduction of 3,4-dihydroxyphenyl-(3-methyl-2-pyridyl) ketone afforded instead the *threo*-isomer as the main product (72%) and it was isolated in 39% yield. Isolation of other *threo*-racemates was probably hampered by their greater relative solubility (11).

Although the *threo*-racemates were not isolated, their presence in the hydrogenated mixtures was clearly revealed by nmr spectroscopy. Hyne (12) has shown that in ephedrine and ψ-ephedrine, which possess respectively *erythro* and *threo* configurations, the coupling constants for the corresponding benzylic protons have, respectively, values J = 4.0 Hz and J = 8.2 Hz. In our series coupling constants, J = 2.0 - 5.5 Hz, have been observed for the *erythro*-racemates, and J = 8.0-9.5 Hz for the corresponding *threo*-isomers. Also, the benzylic proton in each *erythro*-racemate was found to resonate at a lower field than the same proton in the corresponding *threo*-racemate. The relevant nmr data for our series is given in Table I, together with the approximate proportions of each isomer present in the crude hydrogenation mixtures as determined from their relative benzylic proton signal intensities. Other workers (5,13) in the sympathomimetic amine field have reported similar findings. In addition, it had long been established that catalytic reduction of this class of amino-ketone yields predominantly the *erythro*-race-

mate (14).

The methyl substituted piperidylcarbinols (**3**; R, R^1 = OH, R^2 = H, R^3 = 3Me, 4Me, 5Me and 6Me) contain an additional asymmetric centre, but in each case only one *erythro*- and one *threo*-form was detected in the nmr spectra of the total hydrogenation products. Overlapping signals in the nmr spectra of isolated major products made it impossible to determine the relative dispositions of the methyl and benzylic alcohol groupings.

Attempts to use the alternative *O*-benzyl protecting groups in this synthetic route were thwarted by the concomitant hydrogenolysis of the benzylic hydroxyl group during their removal. Thus, 3,4-dibenzyloxyphenyl-(2-pyridyl)carbinol gave 3,4-dihydroxyphenyl-(2-pyridyl)-methane on hydrogenation over a palladium catalyst whereas 4-benzyloxy-3-methoxyphenyl-(2-pyridyl)carbinol, under the same conditions, afforded the desired 4-hydroxy-3-methoxyphenyl-(2-pyridyl)carbinol.

The preliminary pharmacology of these aryl-(2-piperidyl)carbinols encouraged us to extend our programme toward other sympathomimetics of biological potential, including 3,4-dihydroxyphenyl-(6-phenylethyl-2-piperidyl)-carbinol (**3**; R, R^1 = OH, R^2 = H, R^3 = $6PhCH_2CH_2$).

Condensation of 3,4-dimethoxyphenyl-(6-methyl-2-pyridyl) ketone and propane-1,3-diol in the presence of *p*-toluenesulphonic acid gave the crystalline ketal in 70% yield. Successive treatment of this derivative with phenyllithium and benzyl chloride, with subsequent chromatography on silica gel afforded the crystalline products 2-(3,4-dimethoxyphenyl)-2-(6-phenylethyl-2-pyridyl)-1,3-dioxan, and 2-(3,4-dimethoxyphenyl)-2-(6-dibenzylmethyl-2-pyridyl)-1,3-dioxan in low yield. Simultaneous demethylation and deketalisation occurred in boiling hydrobromic acid, and hydrogenation of the

TABLE II

Preparation and Properties of Arylpyridylcarbinols

Compound	Method	Yield %	M.p. (lit) °C	Analyses Found C	H	N	Cl	Calculated C	H	N	Cl
4-Methoxyphenyl-(2-pyridyl)carbinol[18]	A	30	132-134 (133-134)	-----	-----	-----	-----	-----	-----	-----	-----
3,4-Dimethoxyphenyl-(2-pyridyl)carbinol[19]	A B	30 72	93-95 (92-93)	-----	-----	-----	-----	-----	-----	-----	-----
3,5-Dimethoxyphenyl-(2-pyridyl)carbinol	A	69	98-100	68.3	6.2	5.5	-----	68.55	6.2	5.7	-----
3,4,5-Trimethoxyphenyl-(2-pyridyl)carbinol	A	27	106-108	65.0	6.1	5.0	-----	65.4	6.2	5.1	-----
3,4-Dibenzyloxyphenyl-(2-pyridyl)carbinol hydrochloride	A	13.5	121-123	71.9	5.45	3.2	8.25	72.0	5.6	3.2	8.2
4-Benzyloxy-3-methoxyphenyl-(2-pyridyl)carbinol	B	51.5	126-127	74.7	6.1	4.3	-----	74.7	6.0	4.4	-----
4-Hydroxy-3-methoxyphenyl-(2-pyridyl)carbinol	C	84	136-137	67.35	5.5	6.0	-----	67.5	5.7	6.1	-----
3,4-Dimethoxyphenyl-(3-methyl-2-pyridyl)-carbinol hydrochloride	B	72	187-189	60.8	6.0	4.9	11.9	60.9	6.1	4.7	12.0
3,4-Dimethoxyphenyl-(4-methyl-2-pyridyl)-carbinol hydrochloride	B	82.5	179-181	60.55	6.2	4.9	11.9	60.9	6.1	4.7	12.0
3,4-Dimethoxyphenyl-(5-methyl-2-pyridyl)-carbinol hydrochloride	B	83	164-165	60.6	6.1	4.9	11.6	"	"	"	"
3,4-Dimethoxyphenyl-(6-methyl-2-pyridyl)-carbinol	A B	7.3 87	88-90	69.3	6.3	5.6	-----	69.5	6.6	5.4	-----

Methods: (A) Hammick reaction; (B) From 2-pyridyllithium derivatives; (C) Prepared by the hydrogenolysis of it's 4-benzyloxy derivative.

resulting catechol derivative gave, as before, *erythro-threo* mixtures. Fractional crystallisation was successful in separating the mono-substituted product, affording *erythro*-3,4-dihydroxyphenyl-(6-phenylethyl-2-piperidyl)-carbinol (**3**; R, R^1 = OH, R^2 = H, R_3 = 6$PhCH_2CH_2$).

Two compounds in this series (**3**; R, R^1 = OH, R^2, R^3 = H, **3**; R, R^1 = OH, R^2 = H, R^3 = 6CH_3) were potent bronchodilators, comparable with isoprenaline and they possessed a negligible effect upon the heart. The full pharmacology (16) and preliminary human studies (17) will be reported separately.

EXPERIMENTAL

Nmr spectra were obtained on a 60 Hz Varian A60 instrument and infra-red spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer for potassium chloride discs.

Preparation of Arylpyridylcarbinols. General methods.

(A) Hammick Reaction.

Picolinic acid (10 g.) was added to a boiling solution of araldehyde (50 g.) in *p*-cymene (50 ml.). Heating was continued for three hours after the addition and then the cooled reaction solution was extracted with 2*N* hydrochloric acid (2 x 50 ml.). The acid layers were washed with ether (100 ml.), basified with ammonia and the liberated base was extracted into ether (4 x 50 ml.). Concentration of the dried extracts gave the crude carbinol which could usually be crystallised from aqueous ethanol or acetone-petroleum ether (b.p. 60-80°) mixtures.

(B) From 2-Pyridyllithium Derivatives.

Lithium shavings (1.27 g., 0.18 mole) were added to dry ether (50 ml.) under nitrogen. The suspension was stirred at -10 to 0° while 1-bromobutane (12.3 g., 0.09 mole) in anhydrous ether (50 ml.) was added. After the addition (0.5 hour) the reaction mixture was stirred at -10 to 0° until dissolution of the metal was complete (about 1 hour) and then the suspension was cooled to -20°. 2-Bromopyridine (9.55 g., 0.06 mole) in dry ether (10 ml.) was then added dropwise. The resulting chocolate brown solution was kept at -20° for 15 minutes and then araldehyde (0.06 mole) in ether (100 ml.) was added dropwise, maintaining the temperature below -10°. The thick suspension was allowed to warm to room temperature and it was then extracted with 2*N* hydrochloric acid (2 x 50 ml.). Isolation of the carbinol was performed as before.

All compounds prepared by the described procedures had ir and nmr spectra consistent with their assigned structures. Details of these experiments are given in Table II.

TABLE III

Preparation and Properties of Arylpyridylketones

Compound	Method	Yield %	M.p. (lit) °C	Analyses Found C	H	N	Calculated C	H	N
4-Methoxyphenyl-(2-pyridyl) ketone[20]	A	95	93-95 (93)						
3,4-Dimethoxyphenyl-(2-pyridyl) ketone	A D	66.5 20	93-94	69.3	5.4	5.9	69.1	5.4	5.8
3,5-Dimethoxyphenyl-(2-pyridyl) ketone	A	34	66-67	69.0	5.35	5.5	"	"	"
3,4,5-Trimethoxyphenyl-(2-pyridyl) ketone	A	87.5	111-112	66.1	5.5	5.1	65.9	5.5	5.1
3,4-Dimethoxyphenyl-(3-methyl-2-pyridyl) ketone	A	62	121-122	70.2	5.85	5.5	70.0	5.9	5.4
3,4-Dimethoxyphenyl-(4-methyl-2-pyridyl) ketone	A	57	84-85	70.2	5.8	5.6	"	"	"
3,4-Dimethoxyphenyl-(5-methyl-2-pyridyl) ketone	A	55	81	70.0	6.1	5.4	"	"	"
3,4-Dimethoxyphenyl-(6-methyl-2-pyridyl) ketone	A B C	69 60 50	84-86	69.7	5.7	5.2	"	"	"
3-Nitrophenyl-(2-pyridyl) ketone	C	23	120-121 (122)						
3-Nitrophenyl-(6-methyl-2-pyridyl) ketone	C	5	102-104	64.5	4.3	11.5	64.5	4.2	11.6

Methods: (A) Permanganate oxidation; (B) Dimethylsulphoxide - acetic anhydride; (C) Aerial oxidation; (D) Friedel-Craft.

Preparation of Arylpyridyl Ketones. By the Oxidation of Arylpyridylcarbinols.

(A) With Potassium Permanganate. General Procedure.

Arylpyridylcarbinol (x g.) was suspended in water (20 x ml.) and warmed to 70°. Potassium permanganate (0.5 x g.) was added portionwise as the colour was discharged. Excess of permanganate was destroyed by the addition of ethanol and the manganese dioxide was removed by filtration. The filter cake was extracted with boiling acetone and the filtrate was concentrated until crystallisation of the product began.

Oxidations of arylpicolylcarbinols was carried out at 20° in order to avoid attack on the methyl groups.

(B, C) With other reagents.

Arylpyridylcarbinols are also readily oxidised by dimethylsulphoxide-acetic anhydride mixtures (B) or by air in boiling nitrobenzene (C). However, evil smelling by-products (9) accompany the former method and the greater isolation problems posed by these procedures renders them of less synthetic value.

(D) Friedel-Craft method. 3,4-Dimethoxyphenyl-(2-pyridyl) Ketone.

Picolinic acid (10 g.) in pure thionyl chloride (50 ml.) was heated under reflux for 1.5 hours and the excess of reagent was removed under reduced pressure. The residue was dissolved in nitrobenzene (150 ml.) and veratrole (25 ml.). Aluminum chloride (11 g.) was then added and the mixture was heated at 100° for 1 hour. The cooled reaction mixture was diluted with ether (200 ml.) and shaken with 5*N* sodium hydroxide solution (200 ml.). The organic phase was filtered through kieselguhr, washed with water, and then extracted with 2*N* hydrochloric acid (3 x 100 ml.). Basification of the acid extracts with ammonia solution gave the crude ketone (3.9 g., 20%; recrystallised from aqueous acetone), m.p. 93-94° (see Table III).

All compounds prepared had nmr spectra consistent with the assigned structures; the carbonyl absorption in their ir spectra was at 1650 to 1670 cm^{-1}. Physical properties and experimental details are given in Table III.

Hydroxyphenylpyridyl Ketones. General Methods.

Methoxyphenyl-(2-pyridyl) ketone in constant boiling hydrobromic acid (5 ml./g.) was heated under reflux for 16 hours. The product usually crystallised from the cooled solution as its hydrobromide, which was recrystallised from methanol-ethyl acetate. In cases where a crystalline salt was not obtained, the acid was removed and the residue was treated with ammonia solution to give the crystalline base or, alternatively, the residue was dissolved in warm aqueous methanol from which the base crystallised.

TABLE IV

Properties of Hydroxyphenylpyridylketones

Compound	Yield %	M.p. °C	Analyses Found C	H	N	Br	Calculated C	H	N	Br
4-Hydroxyphenyl-(2-pyridyl) ketone hydrobromide	94	225 dec.	51.5	3.5	4.9	28.7	51.45	3.6	5.0	28.5
3,4-Dihydroxyphenyl-(2-pyridyl) ketone hydrobromide	80	225 dec.	48.7	3.3	4.5	26.7	48.7	3.4	4.7	27.0
3,5-Dihydroxyphenyl-(2-pyridyl) ketone	91	208 dec.	67.1	4.2	6.6	-----	67.0	4.2	6.5	-----
3,4,5-Trihydroxyphenyl-(2-pyridyl) ketone hydrobromide	83	240 dec.	46.2	3.4	4.3	25.5	46.2	3.2	4.5	25.6
3,4-Dihydroxyphenyl-(3-methyl-2-pyridyl) ketone	64	197-199	68.0	4.9	6.3	-----	68.1	4.8	6.1	-----
3,4-Dihydroxyphenyl-(4-methyl-2-pyridyl) ketone hydrobromide	87	210 dec.	50.3	4.0	4.4	25.7	50.3	3.9	4.5	25.8
3,4-Dihydroxyphenyl-(5-methyl-2-pyridyl) ketone hydrobromide	89	209-220	50.35	4.0	4.5	25.7	"	"	"	"
3,4-Dihydroxyphenyl-(6-methyl-2-pyridyl) ketone hydrobromide	75.5	224 dec.	50.5	4.1	4.6	25.6	50.3	3.9	4.5	25.8
3,4-Dihydroxyphenyl-(6-phenylethyl-2-pyridyl) ketone	53	181	60.2	4.7	3.6	20.35	60.0	4.5	3.5	20.0
3,4-Dihydroxyphenyl-(6-dibenzylmethyl-2-pyridyl) ketone	74	141-143	78.95	5.9	3.2	-----	79.2	5.7	3.4	-----

All compounds prepared in this way had nmr and ir spectra consistent with their assigned structures. Physical properties and yields are recorded in Table IV.

Preparation of Hydroxyphenyl-(2-piperidyl) Carbinols. General Procedure.

The hydroxyphenyl-(2-pyridyl) ketone hydrobromides dissolved in methanol (20 ml./g.) were hydrogenated under atmospheric pressure and room temperature in the presence of Adams catalyst (0.2 g./g. substrate). Free bases were hydrogenated in the presence of an equivalent amount of hydrochloric acid. Hydrogen (4 mole) was consumed in each experiment, and after removal of the catalyst and solvent, the residue was crystallised from methanol-ethyl acetate. The isolated product was in all cases isomerically pure as determined by nmr spectroscopy. Examination of the unfractionated products by the same technique allowed the *erythro-threo* isomer ratio to be calculated from the relative intensities of the benzylic proton resonances.

Experimental details and physical properties are given in Table V.

3,4-Dihydroxyphenyl-(2-pyridyl)methane Hydrochloride.

3,4-Dibenzyloxyphenyl-(2-pyridyl) carbinol hydrochloride (5 g.) was hydrogenated in ethanol (200 ml.) under atmospheric pressure and at room temperature in the presence of palladium on charcoal catalyst (5 g., 10%). After hydrogen (5 moles) had been consumed, the catalyst and solvent were removed and the residue gave, on crystallisation from ethanol-ethyl acetate, the catechol derivative (1.1 g., 40%), m.p. 152-154°.

Anal. Calcd. for $C_{12}H_{12}ClNO_2$: C, 60.6; H, 5.1; Cl, 14.9; N, 5.9. Found: C, 60.4; H, 5.1; Cl, 14.6; N, 6.0.

The nmr spectrum (DMSO-d_6) showed the presence of 2 benzylic, 7 aromatic and 2 phenolic hydroxyl protons. This compound was also prepared from 3,4-dimethoxyphenyl-(2-pyridyl) carbinol by treatment with thionyl chloride followed by a zinc-acetic acid reduction (7), demethylation and conversion into the hydrochloride.

2-(3,4-Dimethoxyphenyl)-2-(6-methyl-2-pyridyl)-1,3-dioxan.

3,4-Dimethoxyphenyl-(6-methyl-2-pyridyl) ketone (77.1 g.), *p*-toluenesolphonic acid (74.1 g.) and propane-1,3-diol (22.8 ml.) in toluene (600 ml.) were heated under reflux with stirring for 17 hours, the water evolved during the reaction being removed azeotropically. The cooled solution was neutralised with saturated sodium hydrogen carbonate solution and the phases were separated. The organic layer was washed with water and dried over magnesium sulphate. Removal of the solvent gave a solid residue which, on recrystallisation from acetone-petroleum ether (b.p. 60-80°), yielded the ketal (66.3 g., 70.1%), m.p. 124-126°.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.7; N, 4.4. Found: C, 68.9; H, 6.6; N, 4.4.

TABLE V

Arylpiperidylcarbinols

Compound	Yield %	M.p. °C	Analyses Found C	H	N	X	Calculated C	H	N	X
3; R, R^1 = OH, R^2, R^3 = H hydrobromide	64 (a)	212-214	47.5	6.1	4.6	26.1	47.4	6.0	4.6	26.3
3; R, R^2 = OH, R^1, R^3 = H hydrochloride	(b)		53.5	7.2	5.2	13.45	55.5	7.0	5.4	13.6
3; R, R^1, R^2 = OH, R^3 = H hydrobromide	60 (c)	130-140	47.1	6.6	3.6	20.7	45.0	5.7	4.4	24.95
3; R, R^1 = OH, R^2 = H, R^3 = 3-Me hydrochloride	37 (d)	231-235	57.0	7.3	5.2	12.7	57.0	7.4	5.1	13.0
3; R, R^1 = OH, R^2 = H, R^3 = 4-Me hydrobromide	40 (a)	148-150	49.2	6.2	4.6	24.9	49.1	6.3	4.4	25.1
3; R, R^1 = OH, R^2 = H, R^3 = 5-Me hydrobromide	33 (a)	207-212	49.2	6.2	4.5	25.3	"	"	"	"
3; R, R^1 = OH, R^2 = H, R^3 = 6-Me hydrobromide	38 (a)	216 dec.	49.2	6.3	4.2	25.1	"	"	"	"
3; R = OMe, R^1 = OH, R^2, R^3 = H hydrochloride	68 (a)	242-245	57.1	7.4	5.1	13.3	57.0	7.4	5.1	12.95
3; R, R^1 = OH, R^2 = H, R^3 = 6-$PhCH_2CH_2$ hydrobromide	59 (a)	204	58.6	6.6	3.5	19.9	58.8	6.4	3.4	19.6

(a) *Erythro form.* (b) Analysis of a freeze dried syrup, *erythro:threo* (3:1). (c) Contains solvent of crystallisation. (d) *Threo form.*

2-(3,4-Dimethoxyphenyl)-2-(6-phenylethyl-2-pyridyl)-1,3-dioxan and 2-(3,4-Dimethoxyphenyl)-2-(6-dibenzylmethyl-2-pyridyl)-1,3-dioxan.

Bromobenzene (8.66 ml.) in dry ether (20 ml.) was added over a period of 30 minutes to a stirred suspension of lithium shavings (1.0 g.) in anhydrous ether (50 ml.) under a nitrogen atmosphere. After the addition, the mixture was stirred for 1.5 hours and then 2-(3,4-dimethoxyphenyl)-2-(6-methyl-2-pyridyl)-1,3-dioxan (18.9 g.) in the minimum quantity of dry tetrahydrofuran was added. Benzyl chloride (8 g.) in dry tetrahydrofuran (10 ml.) was then added at such a rate than gentle boiling occurred. Stirring was continued for 30 minutes after the addition and then the complex was decomposed with saturated ammonium chloride solution and the phases were separated. The organic layer was diluted with ether (200 ml.) and extracted with 2*N* hydrochloric acid (2 x 100 ml.). The acid extract was basified with ammonia solution and the liberated base was extracted into chloroform (2 x 60 ml.). Concentration of the dried extracts gave a syrup which was absorbed on a column of silica gel (30 x 4 cm.) from chloroform-ethyl acetate (4:1). Elution with the same solvent gave successively (i) 2-(3,4-dimethoxyphenyl)-2-(6-dibenzylmethyl-2-pyridyl)-1,3-dioxane (3.38 g.), m.p. 124° (from ethanol), (ii) 2-(3,4-dimethoxyphenyl)-2-(6-phenylethyl-2-pyridyl)-1,3-dioxan (3.0 g.), m.p. 86-87° (from ethanol) and (iii) starting material which was very slowly eluted.

Anal. (i) Calcd. for $C_{32}H_{33}NO_4$: C, 77.55; H, 6.7; N, 2.8. Found: C, 77.65; H, 6.8; N, 3.0. (ii) Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.7; N, 3.45. Found: C, 74.1; H, 6.6; N, 3.45.

Details of the demethylation with concomitant deketalisation, and the hydrogenation of these compounds is given in Tables IV and V.

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