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Original paper

Synthesis and preliminary study of some ring-substituted arylpropanonamines and their quaternary salts

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Summary — The synthesis and biological examination of 1-phenyl- and 1-(4-bromophenyl)-3-(*N*-2-hydroxyethyl-*N*-methylamino) propan-1-one methiodides and 1-(4-bromophenyl)-3-(*N*-2-hydroxyethyl-*N*-methylamino)propan-1-ol methiodide as model potential intravenous anesthetics are described. A series of 1-alkyl-3-aroyl-4-arylpiperidin-4-ols, their mesylate salts and quaternary iodides has been also prepared and examined.

Résumé — **Synthèse et étude préliminaire de quelques arylpropanonamines substitués sur le cycle et leurs sels quaternaires.** *Synthèse et étude biologique d'iodométhylates de phényl-1 et (bromo-4-phényl)-1 (*N*-hydroxy-2-éthyl-*N*-méthylamino)3 propanone-1 ou propanol-1 sont décrits. Également une série d'alkyl-1 aroyl-3 aryl-4 pipéridinols-4, des mésylates ainsi que les sels quaternaires correspondants ont été préparés et examinés.*

1-phenyl-3-aminopropanones / 1-alkyl-3-aroyl-4-arylpiperidin-4-ols / anesthetic

Introduction

In recent years increasing concern has been expressed about the toxic effects of inhalation anesthetics [1, 2] on both patients and operating theatre staff. Extraction of expired anesthetic gases to the external atmosphere is not always efficient, particularly in recovery areas, posing a toxic hazard to staff. Additionally, inhalation anesthetics are disadvantageous in some clinical situations, such as neurosurgery, where for example they may effect cerebral blood flow adversely, and also in cardiac and obstetric surgery where the optimum air–gas mixture for anesthesia can provide inspired oxygen concentrations that are otherwise inappropriate for patient care.

Several intravenous anesthetics have been introduced into clinical practice in recent years. Those capable of being administered in aqueous solution, such as diazepam, have proved reasonably successful. Others with much lower water-solubilities have proved difficult to formulate, and products, such as Althesin^{R} based on alphadolone acetate and alphaxalone solubilised with Cremophor EL have eventually been withdrawn because of doubts about the safety of the solubilising agent. More recently, propofol has been successfully formulated as an injectable lipid emulsion with soybean oil and purified egg phosphatide. The search for new agents is therefore beset with the fundamental problem of finding either a readily water-soluble, injectable, and dissociable base–conjugate acid to ensure rapid uptake into the central nervous system of an inherently lipid parent acid or base, or for alternative means of carrying an essentially lipid active neutral compound in a water-soluble form.

One solution to this latter problem may lie in the preparation of a stable water-soluble pro-drug capable of undergoing rapid biodegradation under physiological conditions to release a lipid-soluble anesthetic. Studies leading to the successful introduction of the neuromuscular blocking agent, atracurium [3, 4], the half-life of which is controlled by just such a biodegradation mechanism, suggest that this might be possible. We have therefore sought to develop model water-soluble compounds that are stable *in vitro* but capable of undergoing biodegradation under physiological conditions of pH and temperature by either Hofmann elimination or a reverse Michael addition to release an agent capable of effecting speedy anesthesia.

In this paper, we report the preparation of some simple water-soluble arylpropanonamine salts **1** and their quaternary ammonium derivatives **3**, substituted in the aromatic ring with powerful electron-attracting substituents to promote expulsion of lipid-soluble model anesthetic moieties *in vivo*. *N*-Hydroxyethyl substituents in the compounds **1** and **3** were chosen to enhance water-solubility and, in the case of the quaternary ammonium compounds, to eliminate cholinergic activity.

These quaternary ammonium salts are analogues of two related series of β-benzoylethyltrialkylammonium salts [3] that are rapidly decomposed within minutes by Hofmann elimination *in vitro* under physiological conditions of pH (7.4) and temperature (37°C). Decomposition leads to the usual destruction of the quaternary ammonium function and formation of an olefine in accord with the well-esta-

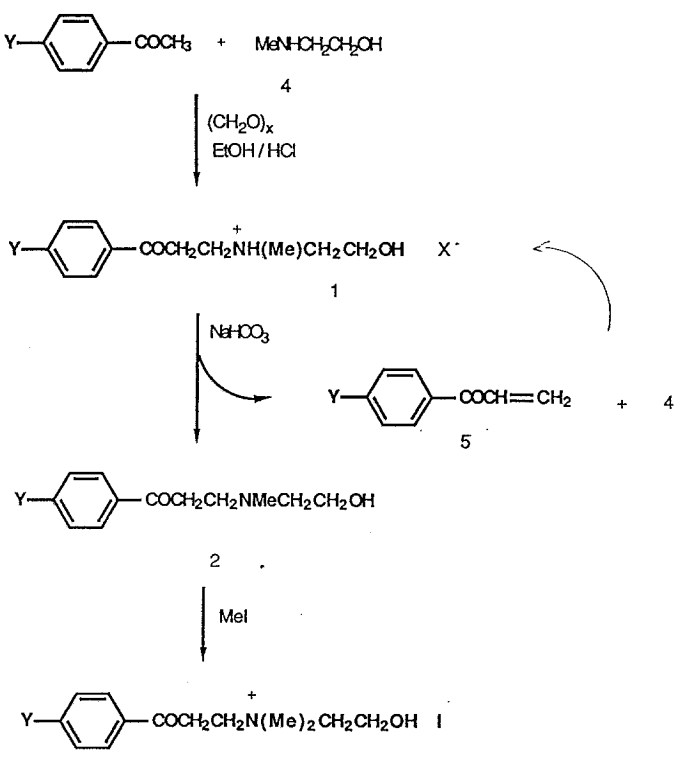
blished reaction pathway. Olefine formation, which can be followed by UV spectrophotometry, occurs at rates that are determined by the nature and position of the substituents in the aromatic ring. Half-lives for olefine formation decreased in order from 11 to 1.5 min in the 3,4-dimethoxybenzoyl-, 4-methoxybenzoyl-, benzoyl- and 4-chlorobenzoyl-ethylammonium compounds respectively, *i.e.*, in parallel with the reduction of electron repulsion and, in the case of the last compound, increase of electron withdrawal in the series. Other relevant decompositions of quaternary salts, β-substituted with activating carbonyl substituents, both under physiological conditions of pH and temperature *in vitro* in buffer systems, human plasma and whole blood [4, 7–9] and *in vivo* [4, 10–12] have also been described in detail.

We also report the preparation of a chemically related series of 1-alkyl-3-aroyl-4-aryl-piperidin-4-ols, **9**, and their derivative, **15–19**. Their water-soluble quaternised esters retain the potential for pH-dependent biodegradation with the formation of lipid-soluble moieties. Additionally, although this property is deficient in the parent unquaternised piperidinols, their water-soluble salts and those of the corresponding esters are also of interest because of their structural relationship to the neuroleptic haloperidol, **20**, [5], and the pethidine type analgesics.

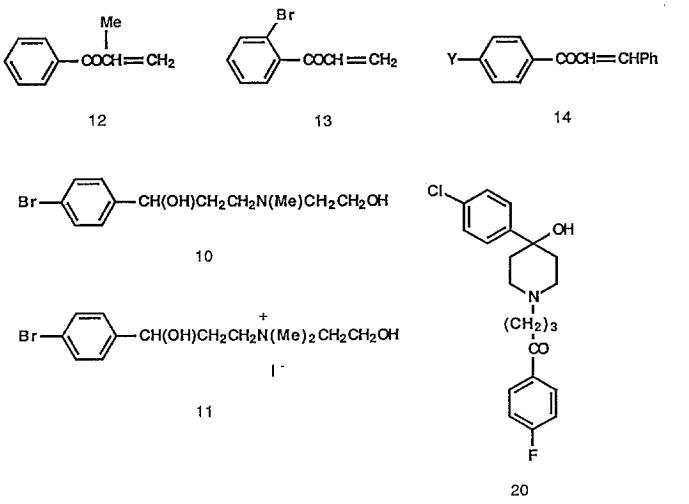
Chemistry

Synthesis of the benzoylethylamine, **2 (Y = Br)**, and its quaternary salt, **3 (Y = Br)**, was attempted by the route outlined in Scheme 1. The Mannich reaction, however, proceeded slowly and in poor yield (20%) to give the hydrochloride salt, **1 (Y = Br, X = Cl⁻)**, contaminated with *N*-methylaminoethanol hydrochloride. Purification by crystallisation was not successful. When treated with sodium hydrogen carbonate the product gave a mixture of the free base **2 (Y = Br)**, and *N*-methylaminoethanol **4** which proved impossible to separate by crystallisation, chromatography, or vacuum distillation. The product was finally crystallised as the oxalate **1 (Y = Br, X = HOOC·COO⁻)** and maleate **1 (Y = Br, X = HOOC·CH = CH·COO⁻)** salts, *ca* 98–99% pure. Neutralisation of the oxalate to yield the free base, however, resulted in a product containing *ca* 10% of *N*-methylaminoethanol, suggesting that the suspected reverse Michael reaction may indeed occur fairly readily, though no attempt was made to identify the vinyl ketone **5 (Y = Br)**.

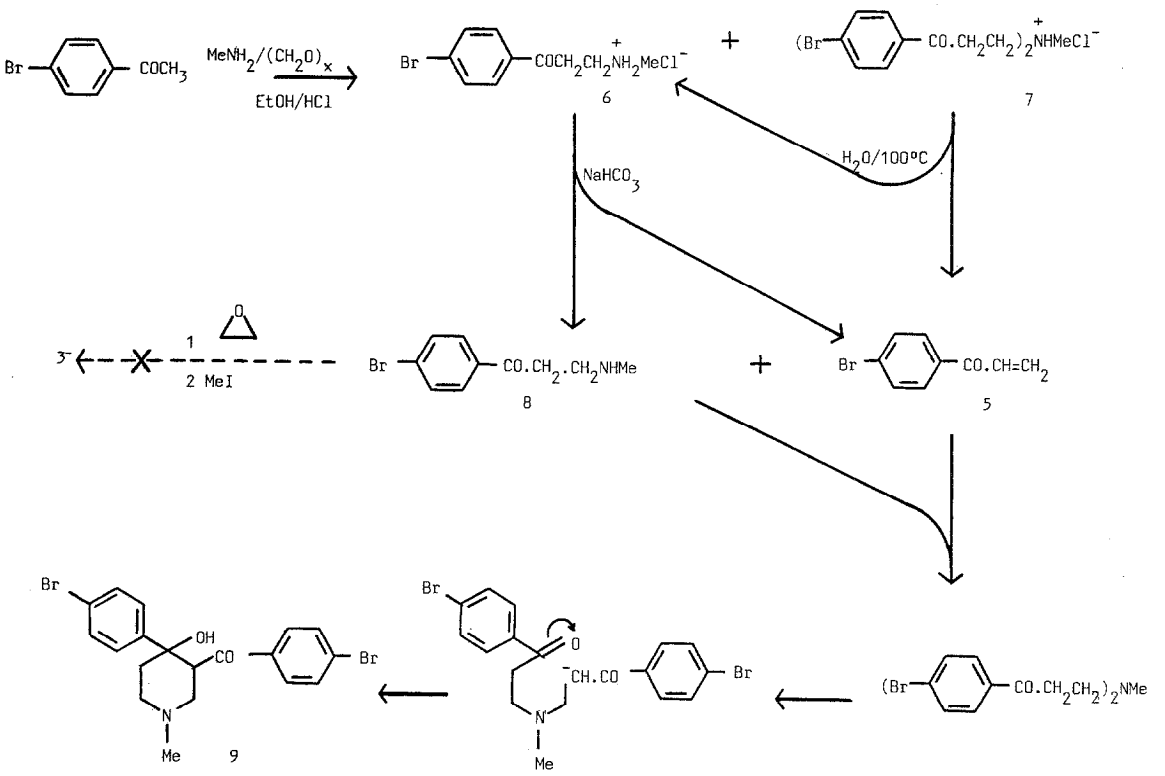
An alternative approach to the base **2 (Y = Br)** and quaternary salt **3 (Y = Br)** was attempted as shown in Scheme 2. In this, the Mannich reaction produced a mixture of the mono- and bis-substituted methylamine hydrochlorides **6** and **7** respectively, which were separated by fractional crystallisation. The bis-substituted methylamino hydrochloride **7** could also be converted to the mono-substituted base hydrochloride **6** by steam distillation due to the volatility of the vinyl ketone **5**, a reaction which further demonstrates the hydrolytic instability of compounds in this series. Treatment of the base **6** hydrochloride with cold aqueous sodium hydrogen carbonate and subsequent solvent extraction failed to yield the free base **8**, but gave instead the cyclised base **9** as visualised in Scheme 2.



Scheme 1.



In a third approach to the synthesis of the quaternary salt **3**, it was considered that reduction of the ketamine **1** oxalate would allow isolation of the pure aminodiol **10** without breakdown *via* a reverse Michael reaction. The latter product was readily obtained and succesfully converted into the methiodide **11**. Oxidation of the methiodide with manganese dioxide, however, was unsuccessful, and further work on the oxidation was abandonned in the light of the success achieved with the alternative route to **3 (Y = Br)** in which 4-bromophenyl



Scheme 2.

vinyl ketones **5 (Y = Br)**, prepared by the method of Domborovskii and Shevchuk [6], was condensed directly with *N*-methylaminoethanol **4** and the product **2 (Y = Br)** quaternised with methyl iodide. The quaternary salt **3 (Y = H)** was obtained similarly.

The aryl vinyl ketones, **12** and **13** were also condensed with *N*-methylethanolamine, but the product bases failed to yield the corresponding methiodides in a purified form. The aryl ketones **14 (Y = H** and **Y = Br)** failed to condense with *N*-methylethanolamine.

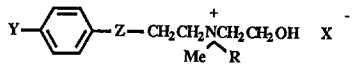
The 1-alkyl-3-aroyl-4-aryl-piperidin-4-ols **9** were prepared from the appropriately substituted acetophenones, as shown in Scheme 2, and were obtained for the most part as their water-soluble mesylate salts **15 (R^2 = H)**. Corresponding esters **16** and quaternary salts **15 (R^2 = Me)** were obtained by standard procedures. Reduction of **9 (Y = Br)** and **9 (Y = F)** with sodium borohydride gave the corresponding diols **17** and **18**. The latter was converted into the diacetate **19**.

Ring closure leading to the compounds **9** generates two chiral centres giving rise to a product consisting of one or more of the four possible optical isomers. In the absence of evidence to the contrary, the products are assumed to be mixtures of the two possible racemates. This apart, it was considered for the following reasons that availability of the separate racemates would not assist the present study. Thus, prolongation of pentobarbitone-induced sleeping time is a central effect, and intravenously administered quaternary ammonium compounds do not pass the blood–brain barrier. Also, it has been established [13] that central effects arising from administration of biodegradable quaternary salts are due to their non-quaternary breakdown products. In the present study, formation of the relevant breakdown products by the predicted Hofmann degradation results in the destruction of the chiral centre at position 3 and also of any additional chiral centre in those compounds with asymmetry on quaternary nitrogen.

Pharmacological Results and Discussion

The products listed in Tables I–IV were tested for their potential as intravenous anesthetics by measuring their effects on pentobarbitone-induced sleeping in mice. All the compounds were water-soluble and were administered intravenously in aqueous solution. As already indicated and shown in Scheme 1, the tertiary amine **1** is susceptible to Hofmann elimination under mildly alkaline conditions, and it would be expected that this potential instability would be enhanced in the quaternary ammonium salt **3b**. Neither shows any enhancement of pentobarbitone-induced sleeping time over controls, but there is some evidence that the electron-withdrawing effect of the *p*-bromo ring substituant in **3b** enhances availability of anesthetic-inducing fragments. Thus onset of pentobarbitone-induced sleeping is significantly faster in the *p*-bromo-substituted quaternary salt **3b** than in its unsubstituted analogue **3a**. The diol **11** in which the carbonyl group is reduced to the corresponding secondary alcohol, however, shows an even greater reduction in onset time and increase in sleeping time, though only at the 20 mg/kg level.

Table I. Effects of ring-substituted-*N*-hydroxyethyl-*N*-methyl-arylpropanoramine derivatives on pentobarbitone-induced sleeping time in mice.



Compd.	Y	Z	R	X[a]	Dose[b]	Pentobarbitone-induced sleeping[c]			
						Onset (min) mean ± SEM	(*n*)[d]	Duration (min) mean ± SEM	(*n*)[d]
1	Br	CO	H	M	30	NR[e]		54.1 ± 6.0	(10)
3a	H	CO	Me	I	30	5.0 ± 0.6	(8)	44.3 ± 4.6	(8)
3b	Br	CO	Me	I	30	3.0 ± 0.2***	(10)	38.4 ± 2.7	(10)
11	Br	CHOH	Me	I	20	0.8 ± 0.7***	(9)	80.0 ± 13.0**	(9)
Control						5.3 ± 0.3	(56)	30.1 ± 1.9	(60)

[a]M = maleate; I = iodide. [b]mg/kg. [c]Dose 40 mg/kg, i.p. [d]No. of animals. [e] = not recorded. $^{**}P < 0.01$. $^{***}P < 0.001$.

Few of the 1-alkyl-3-aroyl-4-arylpiperidin-4-ols **15** and esters **16**, and none of their quaternary salts showed comparable effects on onset and duration of sleeping time (Table II). The *N*-2-hydroxyethyl compounds **15l** and **15m** were inactive, and only the *N*-alkyl chloro- and bromo-substituted compounds showed increased sleeping times. The *N*-ethyl compounds **15g** and **15k** were more effective than the corresponding *N*-methyl compounds **15e** and **15h**. Acetylation of the 4-hydroxy group (Table III) only marginally influenced activity, whilst reduction of the 3-carbonyl group (Table IV) had no positive effect.

Experimental protocols

Chemistry

Unless stated otherwise, melting points were recorded on a Koffler Heizbach 184321 melting point apparatus, and are uncorrected. Infrared spectra were obtained on either a Perkin–Elmer 710B or a Perkin–Elmer 781 infrared spectrometer using liquid films or KCl discs (for solids). Routine proton magnetic resonance spectra were recorded on a Perkin–Elmer R32 (90 MHz) or a Bruker (250 MHz) using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Mass Spectrometry Services Ltd. MS9 spectrometer. IR, NMR, and MS data were in accord with the structures given. Microanalytical results (C, H, N, except where stated otherwise) were within ± 0.4% of theoretical. Thin–layer chromatography (TLC) was run on Merck silica gel 250 μm plates in ethyl acetate/formic acid/water, 7:2:1. Plates were air-dried and sprayed with a 1:1 mixture of nitroprusside (5%, w/w) and acetaldehyde (10%, w/v) in water, and sodium carbonate (2%) in water.

N-*2-Hydroxyethyl*-N-*methylamino*-p-*bromopropiophenone* ***2* (Y = Br)**
N-Methylaminoethanol (7.85 g, 105 mmol) in absolute ethanol (30 ml) was acidified with dry hydrogen chloride. *p*-Bromoacetophenone (19.9 g, 100 mmol) and *para*formaldehyde (20 g) were added and the mixture refluxed overnight with vigorous stirring. A further portion of *para*-formaldehyde (10 g) was added and the mixture stirred under reflux for 24 h. Ethanol was removed under vacuum to give an oil which was triturated with ether. The oil was dissolved in water, the solution cooled in ice, treated with sodium hydrogen carbonate, and extracted with chloroform (×3). The combined chloroform extracts were dried with $MgSO_4$, filtered and concentrated to give the free base as an oil. Crystallisation from hexane gave needles (12.9 g, 45%), shown by TLC to be contaminated with *N*-aminoethanol. The base (12 g, 42 mmol) was dissolved in acetone (200 ml), and mixed with oxalic acid (3.8 g, 42 mmol) to give a product (12.3 g), which was recrystallised from acetone–ethanol to yield the oxalate **1 (Y = Br, X = HO·OC·CO·O⁻)** (8.7 g, 55%), mp: 141–145°C, NMR (D_2O) 3.01 (s, 3H); 3.37–3.57 (m, 2H); 3.69 (br·s, 4H); 3.92–4.17 (m, 2H); 7.78 (d, J = 5 Hz, 2H); 7.96 (d, J = 9 Hz, 2H). The oxalate (3.94 g, 10.5 mmol) was suspended in water (50 ml) at 0°C and treated with cold aqueous sodium hydrogen carbonate (1.0 g, 12 mmol), then with cold aqueous sodium carbonate (2.2 g, 21 mmol). The solution was extracted with chloroform (×6), the extracts dried ($MgSO_4$), filtered and dried to give the free base (3 g). The base (1.3 g, 4.5 mmol) in acetone was treated with maleic acid (4.5 mmol) in acetone. The solvent was removed under vacuum and the residue crystallised from ethanol to give the maleate **1 (Y = Br, X = HO·OC·CH=CH·CO·O⁻)**, mp: 105–106°C. Anal. $C_{16}H_{20}NO_6Br$, (C, H, Br, N), IR, NMR. TLC showed *N*-methylaminoethanol maleate *ca* 1% to be present.

Aryl vinyl ketones ***5* (Y = H *and* Y = Br)**
1-Aryl-2-propen-1-ones were prepared as described by Dombrorskii and Schevchuk [6].

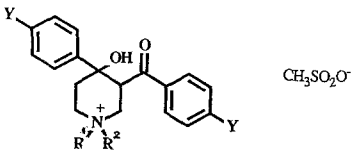
N-*2-Hydroxyethyl*-N,N′-*dimethylamino*-p-*bromopropiophenone iodide* ***3* (Y = Br)**
All operations were protected from light. Freshly distilled aryl vinyl ketone **5 (Y = Br)** (10 mmol) was dissolved in dry tetrahydrofuran (2 ml). The flask was flushed with nitrogen, sealed and cooled in an ice bath. *N*-Methylaminoethanol (5mmol) was added dropwise with stirring to the cold solution over a period of 5–10 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 30–40 min before adding dropwise over a period of 40–50 min to a stirred solution of methyl iodide (25 mmol) in dry tetrahydrofuran (6 ml) with cooling and under nitrogen. The mixture was stirred at 0°C for 30–60 min, filtered, and washed first with dry tetrahydrofuran and then with dry ether, ensuring that the solvent level remained above the solid. Final drying was carried out, firstly by sucking dry under nitrogen, then *in vacuo* over P_2O_5. Crystallisation from ethanol gave the iodide **3 (Y = Br)** (yield 60%), mp: 155–157°C. Anal. $C_{13}H_{19}NO_2BrI$, (C, H, N, total halogen), IR, NMR.

N-*2-Hydroxymethyl*-N,N-*dimethylaminopropiophenone iodide* ***3* (Y = H)**
This compound (mp: 121.5–123.5°C) prepared similarly (yield 68%), gave Anal. $C_{13}H_{20}NO_2I$, (C, H, N, I), IR, NMR.

*1-(4′-Bromophenyl)-3(*N,N-*dimethyl*-N-*2-hydroxyethyl)propan-1-ol iodide* ***11***
The oxalate **1 Y = Br X = HO·OC·COO⁻** (5 mmol) was suspended in ethanol (50 ml). Sodium borohydride (12.6 mmol), dissolved in ethanol, was added dropwise at room temperature with stirring. The mixture was stirred for 1 h, acidified with HCl, extracted with chloroform, then basified at 0°C with Na_2CO_3 and extracted with chloroform (×3). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give the base **10** as an oil. The oil was dissolved in dry tetrahydrofuran (30 ml), methyl iodide added with stirring, and the mixture stirred overnight at room temperature. The resulting precipitate was crystallised from propan-2-ol to give the iodide **11** (1.65 g, 77%), mp: 126–129°C. IR, NMR.

1-Alkyl-3-aroyl-4-aryl-piperidin-4-ols ***9*** *and analogues*
The substituted acetophenone (100 mmol), *para*formaldehyde (120 mmol), and dialkylamine hydrochloride (Me_2NH or Et_2NH) (100 mmol) were refluxed in ethanol (30 ml) with vigorous stirring for 4–5 h. The mixture was allowed to cool and stand overnight at 4°C, and the resulting precipitate triturated with ether. The product was shaken with a mixture of aqueous sodium hydroxide (5%) and chloroform, and the aqueous layer further extracted with chloroform (×2). The combined chloroform extracts were dried ($MgSO_4$) and filtered to give an oil. Repeated solution in absolute ethanol, evaporation of solvent,

Table II. Effects of 1-alkyl-3-aroyl-4-arylpiperidin-1-ols, **15**, and their derivatives on pentobarbitone-induced sleeping time in mice.



No.	Y	R'	R^2	Salt	mp (°C)	Yield (%)	Solvent	Formula	Anal.	NMR	IR	Dose[a]	Pentobarbitone-induced sleeping[b] onset (min) mean ± SEM	(n)[c]	duration (min) mean ± SEM	(n)[c]
15a	H	Me	H	Mesylate	152–155	90	EtOAc	$C_{20}H_{25}NO_5S$	N	+	+	10	3.8 ± 0.5	(10)	24.0 ± 4.3	(10)
15b	H	Et	H	"	167–172	80	^{i}PrOH	$C_2H_{27}NO_5S$	CHNS	+	+	10	6.1 ± 0.8	(9)	29.3 ± 6.3	(9)
15c	F	Me	H	"	173–175	62	EtOAc	$C_{20}H_{23}NF_2O_5S$	CHNFS	+	+	10	9.1 ± 1.9	(8)	31.3 ± 5.6	(8)
15d	F	Et	H	"	189–193	92	^{i}PrOH	$C_{21}H_{25}NF_2O_5S$	CHNS	+	+	10	6.3 ± 0.8	(6)	29.5 ± 4.9	(6)
15e	Cl	Me	H	"	176–177	76	EtOAc	$C_{20}H_{23}NCl_2O_5S$	CHNClS	+	+	30	3.3 ± 0.5	(9)	55.1 ± 7.3**	(10)
15f	Cl	Me	Me	"	223–225	75	MeOH	$C_{21}H_{25}NCl_2O_5S$	CHNClS	+	+	10	4.9 ± 0.4	(10)	26.4 ± 2.2	(10)
15g	Cl	Et	H	"	184–197	93	EtOH	$C_{21}H_{25}NCl_2O_5S$	CHNClS	+	+	10	3.6 ± 0.5	(10)	44.8 ± 1.7***	(10)
15h	Br	Me	H	"	173–176	59	THF	$C_{20}H_{23}NBr_2O_5S$	CHNBrS	+	+	30	NR[d]		55.0 ± 6.2*	(10)
	Br	Me	H	Maleate	127–135	83	EtOH	$C_{23}H_{23}NBr_2O_6$		+	+	NT[e]				
15j	Br	Me	Me	Mesylate	209–211	60	EtOH	$C_{21}H_{25}NBr_2O_5S$	CHNBrS		+	10	NR		31.2 ± 3.0	(10)
	Br	Me	Me	Iodide	190–199	95	MeOH	$C_{20}H_{22}NBr_2IO_2$		+	+	NT				
	Br	Me	Me	Besylate	205–212	95	EtOH	$C_{26}H_{27}NBr_2O_5S$	CHNBrS	+	+	NT				
	Br	Me	Me	Tosylate	210–215	63	EtOH	$C_{27}H_{29}NBr_2O_5S$	CHNBrS	+	+	NT				
15k	Br	Et	H	Mesylate	193–195	92	EtOH	$C_{21}H_{25}NBr_2O_5S$	CHNBrS	+	+	30	2.1 ± 0.5*	(9)	86.1 ± 5.8***	(9)
15l	Br	CH_2CH_2OH	H	"	196–199	65	^{i}PrOH/PrOH	$C_{21}H_{25}NBr_2O_6S$	CHNBrS	+	+	10	NR		37.0 ± 11.6	(10)
	Br	CH_2CH_2OH	H	HCl	151–158	65	EtOH	$C_{20}H_{23}NBr_2ClO_3$		+	+	NT				
15m	Br	CH_2CH_2OH	Me	Mesylate	180–192	90	PrOH	$C_{22}H_{27}NBr_2O_6S$	CHNBrS		+	10	NR		38.5 ± 7.3	(10)
	Br	CH_2CH_2OH	Me	Iodide	180	65	PrOH	$C_{21}H_{24}NBr_2IO_3$		+	+	NT				
15n	NO_2	Me	H	Mesylate	197–200	59	$CHCl_3$/MeOH/H_2O	$C_{20}H_{23}N_3O_9S$	CHNS	+	+	30	4.2 ± 0.7	(10)	20.4 ± 3.8	(9)
15o	NO_2	Me	Me	"	196–199	65	MeOH/H_2O	$C_{21}H_{23}N_3O_9S$	CHNS	+	+	30	5.4 ± 0.6	(10)	27.4 ± 1.9	(10)
Control													5.3 ± 0.3	(56)	30.1 ± 1.9	(60)

[a]mg/kg. [b]Dose 40 mg/kg i.p. [c]No. of animals. [d]NR = not recorded. [e]NT = not tested. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

followed by drying *in vacuo*, and crystallisation from ethanol gave the required piperidin-4-ol **9** characterised in Table V.

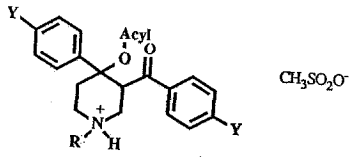
1-Alkyl-3-aroyl-4-arylpiperidin-4-ol mesylates ***15 (R^2 = H)***
These compounds were prepared by dissolving the free base in methanol containing methanesulphonic acid (1 eq), concentrating, and recrystallising the product from the stated solvent. Other salts were prepared similarly. Their characteristics are given in Table II.

1-Alkyl-3-aroyl-4-aryl-4-piperidin-4-ol quaternary salts, ***15 (R^2 = alkyl)***
The 4-piperidinol **9** or analogue (1.0 g) was treated with methylating agent (methyl metanesulphonate, iodide, besylate or tosylate; 2 eq in dry tetrahydrofuran and stirred overnight at room temperature under nitrogen. The resulting precipitate was crystallised from the stated solvent. Their characteristics are given in Table II.

1-Alkyl-3-aroyl-4-acyloxy-4-arylpiperidines ***16***
The 4-piperidinol **9** or analogue (1.0 g) and redistilled acid chloride (2 eq) in dry chloroform (20 ml; passed through alumina grade 0) was stirred at 50°C overnight, protected from moisture. The reaction solution was cooled in an ice bath and washed with ice-cold sodium hydrogen carbonate solution (×2) then with ice-cold water, dried ($MgSO_4$) and concentrated to give the crude ester. Their characteristics are given in Table IV.

3-Bromobenzyl-4-bromophenyl-1-methylpiperidin-3,4-diol mesylate ***17***
The *N*-methylpiperidin-4-ol **9** (15 mmol) was dissolved in chloroform-ethanol (1:1, 200 ml). Sodium borohydride (2.2 eq) in ethanol was added at room temperature with swirling to give a cloudy solution which was stirred at room temperature overnight. The resulting precipitate was filtered and crystallised from ethanol to give the expected diol. The diol

Table III. Effects of 1-alkyl-3-aroyl-4-acyloxy-4-arylpiperidones, **16**, on pentobarbitone-induced sleeping time in mice.



No.	Y	R	Acyl	Salt	mp (°C)	Yield (%)	Solvent	Formula	Anal.	NMR	IR	Dose[a]	Pentobarbitone-induced sleeping[b] onset (min) mean ± SEM	(*n*)[c]	duration (min) mean ± SEM	(*n*)[c]
16a	H	Me	$CO{\cdot}CH_3$	fumarate	165–167	53	^{i}PrOH	$C_{25}H_{27}NO_7$	CHN	+	+	30	3.8 ± 0.9	(9)	55.0 ± 5.4***	(9)
16b	F	Me	$CO{\cdot}CH_3$	mesylate	110–118	45	^{i}PrOH	$C_{22}H_{25}NF_2O_6S$	CHN	+	+	30	5.7 ± 0.5	(10)	61.8 ± 15.4	(9)
16c	F	Me	$CO{\cdot}CH_2CH_3$	"	165–169	67	EtOAc	$C_{23}H_{27}NF_2O_6S$	CHNFS	+	+	10	7.9 ± 1.1	(8)	42.0 ± 7.8	(8)
16d	F	Me	$CO{\cdot}CH_2CHMe_2$	"	170–195	70	^{i}PrOH	$C_{25}H_{31}NF_2O_6S$	CHNS	+	+	10	2.6± 0.4	(10)	42.6 ± 5.1	(10)
16e	F	Et	$CO{\cdot}CH_3$	"	216–217	42	^{i}PrOH	$C_{23}H_{27}NF_2O_6S$	CHNS	+	+	10	2.1 ± 0.2	(10)	15.2 ± 5.0	(10)
16f	Cl	Me	$CO{\cdot}CH_3$	"	199–204	70	^{i}PrOH	$C_{22}H_{25}NCl_2O_6S$	CHNClS	+	+	30	1.3 ± 0.3	(3)[d]	90.7 ± 20.9*	(3)
16g	Cl	Me	$CO{\cdot}CH_2CH_3$	"	203–207	79	EtOAc	$C_{23}H_{27}NCl_2O_6S$	CHNClS	+	+	10	3.4 ± 0.3	(10)	39.4 ± 7.6	(10)
16h	Cl	Me	$CO{\cdot}CH_2CH_2CH_3$	"	167–170	89	toluene / petrol 60–80	$C_{24}H_{29}NCl_2O_6S$	CHNClS	+	+	10	2.8 ± 0.4	(10)	55.8 ± 6.2**	(10)
	Cl	Me	$CO{\cdot}CH_2CHMe_2$	"	185–191	20	toluene / petrol 60–80	$C_{25}H_{31}NCl_2O_6S$	CHNClS	+	+	NT[e]				
16j	Cl	Et	$CO{\cdot}CH_2CH_3$	"	169–173	35	^{i}PrOH	$C_{24}H_{29}NCl_2O_6S$	CHNClS	+	+	10	4.9 ± 0.7	(10)	27.1 ± 6.7	(10)
	Cl	Et	$CO{\cdot}CH_2CHMe_2$	"	100–119	26	^{i}PrOH	$C_{26}H_{33}NCl_2O_6S$	CHNClS	+	+	NT				
16k	Br	Me	$CO{\cdot}CH_2CH_3$	"	197–204	60	EtOAc	$C_{23}H_{27}NBr_2O_6S$	CHNBrS	+	+	30	3.3 ± 0.6	(8)	64.0 ± 5.9**	(8)
16l	Br	Me	$CO{\cdot}CH_2CH_2CH_3$	"	183–187	17	toluene	$C_{24}H_{29}NBr_2O_6S$	CHNBrS	+	+	10	4.2 ± 0.8	(10)	38.0 ± 4.6	(10)
	Br	Me	CO·Ph	HCl	225–226	79	PrOH	$C_{26}H_{24}NBr_2ClO_3$	CHNBrCl	+	+	NT				
16m	Br	Et	$CO{\cdot}CH_3$	mesylate	119–125	46	^{i}PrOH	$C_{23}H_{27}NBr_2O_6S$	CHNBrS	+	+	30	3.5 ± 0.6	(10)	53.2 ± 8.0	(10)
16n	Br	Et	$CO{\cdot}CH_2CH_3$	"	153–162	54	toluene	$C_{24}H_{29}NBr_2O_6S$	CHNBrS	+	+	30	4.4 ± 0.7	(8)	31.3 ± 5.6	(10)
16o	Br	Et	$CO{\cdot}CH_2CH_2CH_3$	"	174–185[f]	18	^{i}PrOH	$C_{29}H_{39}NBr_2O_8S$	CHNBr[g]	+	+	10	4.5 ± 0.3	(8)	28.4 ± 3.5	(8)
16p	Br	CH_2CH_2OAc	H	"	158–161	48	^{i}PrOH	$C_{23}H_{27}NBr_2O_7S$	CHNBrS	+	+	10	9.1 ± 1.1	(8)	40.6 ± 7.6	(8)
16q	NO_2	Me	$CO{\cdot}CH_3$	"	185–210	73	PrOH	$C_{22}H_{25}N_3O_{10}S$	CHNS	+	+	30	2.5 ± 0.3	(10)	43.3 ± 4.7*	(10)
Control													5.3 ± 0.3	(56)	30.1 ± 1.9	(60)

[a]mg / kg. [b]Dose 40 mg / kg. [c]No. of animals. [d]7 / 10 died. [e]Not tested. [f]Salt + 1 eq $CH_3CH_2CH_2COOH$. [g]Butyrate. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

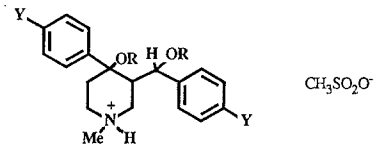
mesylate (mp: 192–200°C) from ^{i}PrOH/toluene/petrol (60–80°C) was prepared as described previously. (Yield 32%). Anal. $C_{20}H_{25}Br_2NO_5S$, (C H Br N S), NMR, IR.

3-Fluorobenzyl-4-fluorophenyl-1-methylpiperidin-3,4-diol mesylate ***18***
This compound was prepared similarly (Yield 18%), mp: 240–245°C from ^{i}PrOH. Anal. $C_{20}H_{25}F_2NO_5S$, (C H N S), NMR IR. Hydrochloride : mp: 273.5–275°C from ethanol. (Yield 18%). Anal. $C_{19}H_{22}ClF_2NO_2$, (C H Cl F N).

3,4-Diacetocy-3-fluorobenzyl-4-fluorophenyl-1-methylpiperidine mesylate ***19***
The difluorodiol (2.0 g), obtained as above, in dry dimethylformamide (20 ml) was heated with acetyl chloride (3.5 eq) at 50°c overnight. The solution was added to ice, treated with cold sodium hydrogen carbonate solution, and extracted with ethyl acetate (×3). The combined extracts were washed twice with water, dried ($MgSO_4$), filtered and concentrated to give the diester, which was crystallised from ethanol. The product in ethyl acetate (10 ml) was treated at room temperature with methanesulphonic acid (1 eq) added dropwise with swirling. Recrystallisation from isopropanol gave the mesylate, mp: 222–224°C. (Yield 26%). Anal. $C_{24}H_{29}F_2NO_7S$, (C H N S), NMR, IR.

1-(2-Acetoxyethyl)-3-(4-bromobenzoyl)-4-(4-bromophenyl)-piperidin-4-ol mesylate ***16p***
1-(2-Hydroxyethyl)-3-(4-bromobenzoyl)-4-(4-bromophenyl)piperidin-4-ol hydrochloride was treated with sodium hydrogen carbonate solution and extracted with ether (×3). Aqueous sodium hydroxide was then added and the solution further extracted with ether (×6). The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to give a fluffy solid (1.8 g). The solid was dissolved in chloroform (40 ml) which had been passed through a column of alumina 0 grade. Acetyl chloride (1.1 ml, 15.5 mmol) was added and the solution stirred at 50°C overnight protected from moisture. The solution was cooled in an ice bath, washed twice with ice-cold sodium hydrogen carbonate solution, then water, dried ($MgSO_4$), filtered and evaporated to give a solid (1.5 g). The solid in ethyl acetate (30 ml), cooled in an ice bath, was treated with methanesulphonic acid (272 mg) in ethyl acetate added dropwise with swirling. The mixture was allowed to stand at room temperature, and the resulting precipitate crystallised from isopropanol to give 1-(2-acetoxyethyl)-3-(4-bromobenzoyl)4-(4-bromophenyl)piperidin-4-ol mesylate: mp: 158–161°C. (Yield 48%). Anal. $C_{23}H_{27}Br_2NO_7S$, (C H Br N S), NMR, IR.

Table IV. Effects of 4-aryl-3-benzyl-1-methylpiperidin-3α, 4-diols, **17** and **18**, and the diacetate, **19**, on pentobarbitone-induced sleeping time in mice.



Compound	Y	R	Dose[a]	Pentobarbitone-induced sleeping[b]			
				onset (min) mean ± SEM	(*n*)[c]	duration (min) mean ± *SEM*	(*n*)[c]
17	Br	H	30	4.1 ± 0.5	(8)	32.6 ± 5.7	(8)
18	F	H	30	4.7 ± 0.5	(10)	20.0 ± 2.4	(10)
19	F	CO·CH_3	10	7.0 ± 1.4	(10)	26.8 ± 2.8	(10)
Control				5.3 ± 0.3	(56)	30.1 ± 1.9	(60)

[a]mg/kg. [b]40 mg/kg i.p. [c]No. of animals.

Table V. Characterisation of piperidin-4-ols **9.**

Y	R^1	mp (°C)	Yield (%)	Formula	Anal.	NMR	MS	IR
H	Me	130–133	93	$C_{19}H_{21}NO_2$	C H N	+	+	
F	Me	148–156	54	$C_{19}H_{19}NF_2O_2$	C H N F	+		+
Cl	Me	168–169	42	$C_{19}H_{19}NCl_2O_2$	C H N Cl	+		+
Br	Me	170–173	85	$C_{19}H_{19}NBr_2O_2$	C H N	+	+	+
NO_2	Me	159–161	44	$C_{19}H_{19}N_3O_6$	C H N	+		+
H	Et	102–113	14	$C_{20}H_{23}NO_2$		+		
F	Et	128–137	17	$C_{20}H_{21}NF_2O_2$	C H N	+		
Cl	Et	152–153	63	$C_{20}H_{21}NCl_2O_2$	C H N Cl	+		+
Br	Et	162–164	51	$C_{20}H_{21}NBr_2O_2$	C H N Br	+		+

Pharmacology

Male albino mice (Glaxo CR/H, 18–30 g) were used. Test compounds were dissolved in sterile water immediately before use, and injected intravenously (10 ml/kg) *via* the tail vein. Groups of 10 mice received test compound (10–30 mg/kg), immediately followed by intraperitoneal injection of pentobarbitone (40 mg/kg). Recordings were made of the onset and duration of loss of righting reflex.

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