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Chemistry and Pharmacology of 4-Alkoxypiperidines Related to Reversed Esters of Pethidine

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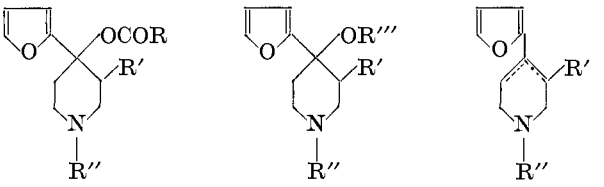
Previously Beckett, Casy and Phillips[1] reported that esters of 4-(2-furyl)-4-piperidinols (Ic; R = CH_3 or C_2H_5, R′ = CH_3) upon treatment with excess of hydrogen chloride in ethanol were readily converted into the 4-ethoxy counterpart (IIc; R′ = CH_3, R‴ = C_2H_5). It was proposed that these transformations proceeded



(I) (II) (III)

R″ = (*a*) H, (*b*) $CH_2C_6H_5$, (*c*) $(CH_2)_2C_6H_5$, (*d*) $(CH_2)_2COC_6H_5$, (*e*) $(CH_2)_3COC_6H_5$, (*f*) $(CH_2)_2CHOH\ C_6H_5$

via carbonium ions, generated by acid-catalysed alkyl-oxygen fission of the ester groups; a study of the factors affecting carbonium ion generation and fate in such compounds has been reported elsewhere.[2] The analgesic properties of esters (Ic) and ethers (IIc) made in the course of this work are presently reported together with an account of their structure–action relationships.

All ethers previously prepared carried a 2-phenethyl substituent on the piperidine nitrogen atom and, since certain members possess

significant analgesic activity, attempts have been made to enhance potency by preparing the analogues (IId, e and f) that bear N-substituents known to give high activities in the pethidine series.

Chemistry

Crude 4-acetoxy-1-benzyl-4-(2-furyl) piperidine (Ib; R = CH_3, R′ = H) in ethanol, upon treatment with excess of hydrogen chloride, gave the corresponding ether (IIb; R′ = H, R‴ = C_2H_5) hydrochloride which was smoothly debenzylated at room temperature and pressure by hydrogen in the presence of palladized charcoal. The 'nor' compound (IIa; R′ = H, R‴ = C_2H_5) on being refluxed in toluene with 4-chlorobutyrophenone and a catalytic amount of potassium iodide gave the analogue (IIe; R′ = H, R‴ = C_2H_5). Attempts to prepare the Mannich base (IId) from the secondary base (IIa; R′ = H, R‴ = C_2H_5), acetophenone and paraformaldehyde by the usual procedures failed; 4-(2-furyl)-1,2,5,6-tetrahydropyridine (IIIa; R′ = H) was isolated from one run. Application of an exchange reaction between the base (IIa; R′ = H, R‴ = C_2H_5) and β-dimethylaminopropiophenone methiodide, as used by Fry and May[3] in the morphine series, gave the desired product (IId; R′ = H, R‴ = C_2H_5) in good yield. The latter was reduced with lithium aluminium hydride to the secondary alcohol (IIf; R′ = H, R‴ = C_2H_5).

Considerable difficulty was met in preparing the 3-methyl ether (IIb; R′ = CH_3, R‴ = C_2H_5). The corresponding propionoxy ester, derived from 1-benzyl-3-methyl-4-piperidone and lithium 2-furyl and used (as in previous cases) without further purification, failed to give a crystalline product with excess of ethanolic hydrogen chloride; it gave the alcohol (IIb; R′ = CH_3, R‴ = H) hydrobromide with ethanolic hydrogen bromide. The ether (IIb; R′ = CH_3, R‴ = C_2H_5) was finally isolated when purified ester, obtained by recrystallization of its hydrochloride, was treated in the usual manner. The corresponding olefin (IIIb; R′ = CH_3) was detected in the mother liquors (ultraviolet absorption evidence). The ether was debenzylated and converted to the Mannich base (IId; R′ = CH_3, R‴ = C_2H_5) as described above.

Pharmacology

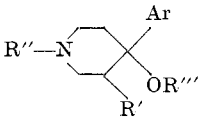
Analgesic Activity

The analgesic activities of the compounds were determined by a hot-plate method based on that described by Eddy and Leimbach.[4] All compounds that were found to be active in preliminary tests were administered subcutaneously at four dose levels to groups of five male albino mice weighing 16 to 20 g each. A dose ratio of 2·0 was employed and the doses were made up in 5 per cent acacia, all volumes being adjusted to 0·5 ml/20 g body weight. At 30, 60 and 90 min after injection, each animal was placed on a hot plate maintained at a temperature of 55–56°. Analgesia was regarded as present if the animal failed to show any signs of discomfort as judged by raising, shaking or licking of the hind paws within 30 sec. The median effective doses were estimated by Kärber's formula[5] from the numbers of animals showing analgesia at any of the observation times. The median effective dose of pethidine hydrochloride was determined in a like manner on each occasion and the results are summarized in Table I.

The most active member of the series, 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine (No. 4, Table I) was selected for a more detailed comparison with pethidine and morphine, the analgesic activity being determined by hot-plate, tail-pinch and phenylquinone-induced writhing methods in mice and by a radiant-heat method in rats.

In the hot-plate test, the procedure was as described above, except that twenty female mice were used at each dose level and the presence of analgesia was only determined at 30 min after injection, this being the time of peak effect. Apart from the actual pain stimulus, the experimental design was essentially the same in the other two tests using mice. The tail-pinch test was a modification of that described by Bianchi and Franceschini,[6] in which the criterion of analgesia was absence of attempts to remove a bulldog artery clip (covered with thin rubber tubing) when it was applied for 30 sec 1 cm from the base of the tail. (N.B. the animals were selected prior to the test on the basis of making repeated attempts to remove the clip within 15 sec.) The writhing test was similar to that of Siegmund, Cadmus and Lu,[7] and analgesia was judged to be present

Table I. Analgesic activities of 4-alkoxylpiperidines and related compounds



No.	Ar	R′	R″	R‴	ED_{50} mg/kg		Potency ratio, Pethidine = 1·0
					Compound	Pethidine	
1	2-furyl	H	$(CH_2)_2C_6H_5$	CH_3	Inactive		
2	,,	,,	,,	C_2H_5	Inactive		
3	,,	CH_3	,,	CH_3	81	21	0·3
4	,,	,,	,,	C_2H_5	5·6	20	3·6
5	,,	,,	,,	n-C_3H_7	93	27	0·3
6	,,	,,	,,	n-C_4H_9	Inactive		
7	,,	,,	,,	$(CH_2)_2Cl$	35	18	0·5
8	,,	H	$(CH_2)_2COC_6H_5$	C_2H_5	12	20	1·6
9	,,	,,	$(CH_2)_3COC_6H_5$	,,	9·3	18	1·9
10	,,	,,	$(CH_2)_2CHOH \cdot C_6H_5$	,,	13	23	1·8
11	,,	CH_3	$(CH_2)_2COC_6H_5$	H	Inactive		
12	,,	,,	,,	C_2H_5	9·3	23	2·5
13	,,	,,	$(CH_2)_2C_6H_5$	$COCH_3$	Inactive		
14	,,	,,	,,	COC_2H_5	Inactive		
15	2-thienyl	,,	,,	C_2H_5	20[a]		

[a] Thanks are due to Dr. Paul Janssen for this result.

if the animal failed to writhe within 15 min of an intraperitoneal injection of phenylquinone. The phenylquinone was dissolved in 5 per cent ethanol to give an 0·02 per cent solution which was maintained at 37° and protected from light. The volume injected was 0·02 ml/20 g body weight and the mice were placed in a constant temperature cabinet maintained at 34° immediately after the injection.

The radiant-heat method in rats was based on that described by D'Amour and Smith.[8] Immediately before the experiment, male albino rats weighing 130–180 g were screened for sensitivity. The beam of light from a 6-V, 36-W lamp placed in front of a metal reflector was focused by means of a condenser lens on a point 1 cm from the tip of the tail previously blackened with marking ink. Those animals in which the typical tail flick

response occurred between 4 and 6 sec from the commencement of exposure were used for the test. The compounds were then administered subcutaneously at four dose levels with a dose ratio of 2·0, all volumes being adjusted to 2·5 ml/100 g body weight. Ten animals were used at each dose level. At 60 min after injection, the tail of each animal was again exposed to the light beam. Analgesia was regarded as present if the tail flick response did not occur within 10 sec (i.e. twice the mean initial reaction time).

The results of these determinations of analgesic activity are summarized in Table II, the median effective doses and their

Table II. Summary of pharmacological data on 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine, pethidine and morphine

Test	Route of administration	4-Ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine	Pethidine HCl	Morphine HCl
Analgesia, hot-plate method, ED_{50}, mg/kg	s.c.	5·6 (4·1–7·6)	23·5 (17·4–31·7)	
		5·3 (3·9–7·2)		11·0 (7·9–15·4)
Analgesia, tail-pinch method, ED_{50}, mg/kg	s.c.	2·6 (1·9–3·5)	13·0 (10·0–16·9)	
		2·8 (2·2–3·6)		7·0 (4·7–10·5)
Analgesia, writhing method, ED_{50}, mg/kg	s.c.	0·97 (0·75–1·24)	6·2 (4·3–9·2)	
		0·80 (0·61–1·04)		0·97 (0·72–1·31)
Analgesia, radiant-heat method, ED_{50}, mg/kg	s.c.	0·41 (0·30–0·56)	4·8 (3·6–6·4)	
		0·41 (0·30–0·55)		1·20 (0·82–1·75)
Mydriasis, ED_{50}, mg/kg	s.c.	6·8 (5·0–9·2)	12·5 (9·5–16·5)	3·8 (2·8–5·1)
Straub Tail effect, ED_{50}, mg/kg	i.v.	2·0 (1·2–3·0)	9·9 (7·6–12·9)	12·5 (9·3–16·9)
Toxicity, LD_{50}, mg/kg	i.v.	41	50 (47–53)	310 (277–347)
Toxicity, LD_{50}, mg/kg	s.c.	1446	208	627

N.B. Confidence limits ($P = 0·95$) are shown in brackets.

confidence limits ($P = 0 \cdot 95$) being estimated by Litchfield and Wilcoxon's method.[9] 4-Ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine is 4·4 to 6·4 times as active as pethidine and 1·2 to 2·5 times as active as morphine in mice, depending on the method used, and according to the radiant-heat method is 12 times as active as pethidine and 3 times as active as morphine in rats.

Analgesic Activity—Effect of Nalorphine

As an aid to the characterization of the analgesic activity of 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine, the possibility of antagonism by nalorphine was examined.

The compound was administered subcutaneously to 100 mice at a dose level of 12 mg/kg. The mice were divided into five equal groups, four of which were also injected with nalorphine at dose levels of 2·5, 5, 10 or 20 mg/kg. Thirty minutes after injection, the presence of analgesia was determined by the hot-plate test as described above. The results are summarized in Table III and they

Table III. Effect of nalorphine on analgesic properties of 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine and morphine

Compound	Dose of nalorphine, mg/kg	No. with analgesia
4-Ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine, 12 mg/kg	—	15/20
	2·5	0/20
	5	1/20
	10	0/20
	20	0/20
Morphine hydrochloride, 20 mg/kg	—	17/20
	2·5	0/20
	5	0/20
	10	0/20
	20	0/20

clearly demonstrate that nalorphine at low dose levels antagonizes the analgesic effect of the compound. Similar results were obtained with morphine hydrochloride given at a dose level of 20 mg/kg.

Analgesic Activity—Development of Tolerance

The development of tolerance in animals repeatedly treated with 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine has been compared with that in animals receiving pethidine hydrochloride.

The compound was administered subcutaneously at a dose level of 12 mg/kg/day to 20 female albino mice whilst a similar group was injected with pethidine hydrochloride at a dose level of 40 mg/kg/day. The injections were made on five days a week

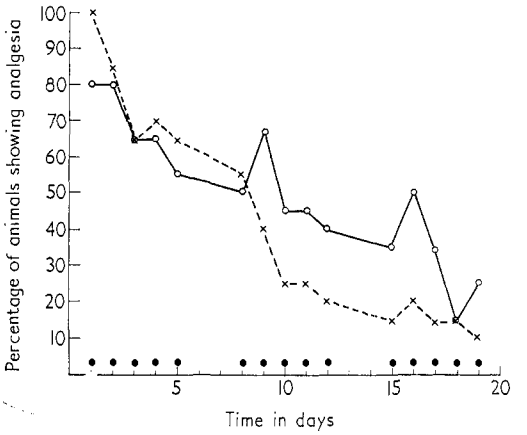


Fig. 1. The development of tolerance to 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine (o—o), 12 mg/kg/day, and pethidine hydrochloride, 40/mg/kg/day (x---x), injected subcutaneously on days marked ●.

for three weeks, and at 30 min after each injection the presence of analgesia was determined by the hot-plate test as described above. The results are illustrated in Fig. 1 and they suggest that tolerance develops with both substances, but possibly more rapidly in the case of pethidine.

Mydriatic Activity

Since an additional property of potent analgesics is the production of mydriasis, it was of interest to determine to what degree it was possessed by 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine. The experimental design was similar to that used for

the comparisons of analgesic activity and the pupil diameter of the right eye of each mouse was measured prior to and 60 min after injection, this being the time of peak effect. The measurement was performed under constant illumination using a binocular dissecting microscope with a graticule fitted in one eyepiece. On the basis of past experience, an increase in pupil diameter of 6 or more scale divisions was regarded as a positive response. The median effective doses were estimated by the method of Litchfield and Wilcoxon.[9]

The results are included in Table II and it is evident that although 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine causes mydriasis at low doses, it is only 1·8 times as active as pethidine and 0·6 times as active as morphine. Mydriatic activity therefore does not parallel analgesic activity.

Straub Tail Effect

4-Ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl)piperidine has also been examined for the production of the Straub tail effect, as this is a further action of potent analgesics. The compounds were administered intravenously at four dose levels to groups of 20 female mice. A dose ratio of 2·0 was used and all volumes were adjusted to 0·2 ml/20 g body weight. Raising the tail through at least 90° within two minutes was taken as the criterion of a positive Straub tail response. Median effective doses were estimated by Litchfield and Wilcoxon's method,[9] and are included in Table II.

4-Ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine is 5·0 times as active as pethidine and 6·3 times as active as morphine in this test, so that the relative activities do not parallel those with respect to analgesia. This may be due, however, to the use of different routes of administration.

Acute Toxicity—Intravenous Route

The compounds were injected intravenously at four dose levels using a dose ratio of 1·5 and 20 female mice/dose. The mortalities were recorded after 24 h and the median lethal doses were estimated by Litchfield and Wilcoxon's method.[9] The results are shown in Table II.

Acute Toxicity—Subcutaneous Route

The compounds were administered subcutaneously at three or four dose levels with a dose ratio of 1·5 to groups of 10 female mice. The numbers dead were recorded after seven days and the median lethal doses were estimated by Kärber's method.[5] These results are shown in Table II, and it is evident that by this route the compound is only 0·14 times as toxic as pethidine and 0·4 times as toxic as morphine.

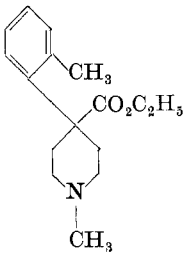
Discussion

An important, if not essential, structural feature in 4-aryl-piperidine analgesics is an oxygenated function at C-4, e.g. carbethoxy (in pethidine), acetoxy or propionoxy (in reversed esters of pethidine) and propionyl (in ketobemidone); the generally low activities of 4-phenyl-4-methylpiperidines accord with this statement.[11] However, oxygenated functions possessing acidic or alcoholic hydrogen atoms show weak activities or are inactive. Thus the acid derived from pethidine and 4-piperidinols from reversed esters of pethidine are far less potent than their precursors.[12, 13]

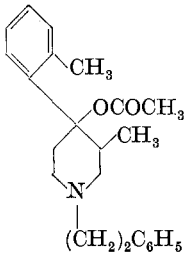
Hydrolysis has been established as a major metabolic pathway for pethidine, anileridine and ethoheptazine[14] and is probably implicated in the metabolism of reversed esters of pethidine although no relevant work has been reported. Since enzymic hydrolysis of pethidine and its reversed esters is a deactivation process, introduction of factors that hinder hydrolysis may give highly potent compounds with long duration of action. The effectiveness of steric factors, introduced in the vicinity of ester groups, in retarding hydrolysis under biological conditions is well illustrated by work on acetylcholine-type compounds.[15, 16]

Introduction of an *ortho* methyl group into 4-phenylpiperidines significantly increases steric factors near the C-4 ring carbon atom and the enhanced potencies of (IV) and (V) in mice over their 4-phenyl counterparts may be attributed, in part, to possibly slower rates of enzymic hydrolysis in the former compounds.

The observation that some of the presently reported 4-alkoxy-piperidines possess significant analgesic properties shows that an



(IV)
1·5 × activity of pethidine in mice[17]



(V)
3 × activity of 4-phenyl analogue in mice[13]

ether function at C-4 may also satisfy structural requirements for analgesia. Since alkyl ethers are more stable than esters and are probably less prone to enzyme attack[18] their substitution for ester groups represents a further potential means of retarding the metabolic deactivation of piperidine analgesics.

Structure–action relationships in the 2-furyl ethers (IIc; R‴ = alkyl) are summarized as follows:

(*a*) High activity is particularly associated with a 4-ethoxy group, lower and higher ethers being far less potent (*cf.* Table I, 3–7).

(*b*) In the 1-(2-phenethyl) series, a 3-methyl substituent adjacent to the 4-ethoxy group is essential for activity (*cf.* Table I, 2 and 4) while in the 1-(2-benzoylethyl) series the same group, although not essential, enhances activity (*cf.* Table I, 8 and 12).

The structural specificity for the ethers demonstrated in (*a*) and (*b*) is more extreme than that found in reversed esters of pethidine where acetoxy and propionoxy esters usually differ in potency only by a factor of 2–3 and where a 3-methyl substituent, although advantageous, is not essential for activity.[19,20]

(*c*) Replacement of 1-(2-phenethyl) in the inactive ether (IIc; R′ = H, R‴ = C_2H_5, Table I, 2) by 2-benzoylethyl,$(CH_2)_2COC_6H_5$, its reduced counterpart, $(CH_2)_2CHOHC_6H_5$, and 3-benzoylpropyl, $(CH_2)_3COC_6H_5$, considerably enhances activity, giving compounds that are all approximately twice as potent as pethidine (*cf.* Table I, 8–10).

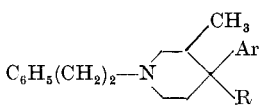
The advantageous effect of replacing *N*-alkyl by these groups was first reported in pethidine by Janssen and co-workers.[19,21]

(Fry and May[3] found 2-benzoylethyl-normorphine and -norcodeine to be less potent in mice than morphine and codeine respectively, while corresponding benzomorphans were somewhat more effective than the *N*-methyl compounds.)

The high activities of the Mannich base of pethidine and the ether (IId; R′ = H, R‴ = C_2H_5; Table I, 8) accord with the postulate that drug dealkylation at the receptor site, giving a nor derivative, initiates the analgesic response,[22] since the former compounds would be expected to undergo this reaction more readily than *N*-alkyl analogues. Replacement of 1-(2-phenethyl) by 1-(2-benzoylethyl) in the highly active ether (IIc; R′ = CH_3, R‴ = C_2H_5) led, however, to a less active compound (*cf.* Table I, 4 and 12); the corresponding alcohol (IId; R′ = CH_3, R‴ = H) was inactive.

It remains to consider the role of the 4-(2-furyl) group in the activities of the ethers (IIc; R‴ = alkyl). In reversed esters of pethidine, isosteric replacement of phenyl is generally disadvantageous (see Table IV). This is considered to be due to decreases in the degree of fit of the aryl group at the complementary flat portion of the receptor that result from the introduction of bulky heteroatoms (probably solvated) into the flat aryl ring.[1] The marked contrast in activities between the furyl esters (Ic; R = CH_3 or

Table. IV. Effect of isosteric replacement of phenyl in esters of 4-aryl-4-piperidinols[7, 13]



R	Ar	Activity (ED_{50}, hot plate), mg/kg	Activity of 4-phenyl counterpart (ED_{50}, hot plate), mg/kg
$OCOCH_3$	2-furyl	inactive	3·0
$OCOC_2H_5$	2-furyl	inactive	2·7
$OCOCH_3$	2-thienyl	18·0	3·0
$OCOCH_3$	2-pyridyl	37·5	3·0
$OCOC_2H_5$	2-pyridyl	26	2·7

C_2H_5, R′ = CH_3) (see Table IV) and the furyl ether (IIc ;R′ = CH_3, R‴ = C_2H_5) suggest that the 4-ethoxy structure is particularly favourable for association at the receptor site and compensates for any inadequacy in fit of the furyl ring at the site. The importance of these factors is, however, difficult to assess since the lack of analgesic activities in the 4-(2-furyl) esters may also be attributed to their probably undergoing *in vivo* hydrolysis more readily than the corresponding 4-phenyl counterparts.

The above discussion is subject to the limitation of being based upon the results of the hot-plate test for analgesia, a procedure which does not differentiate between morphine-type analgesics and other compounds that increase reaction time such as tranquillizers. However, 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine, the most active member of the series, fits the classical picture of a narcotic-type analgesic for the following reasons:

(*a*) It has a high order of potency in the usual tests for analgesic activity.

(*b*) The analgesic effect of the compound is antagonized by small amounts of nalorphine.

(*c*) Mydriasis occurs at low dose levels.

(*d*) Small doses of the compound cause a Straub tail effect.

(*e*) There is a development of tolerance, albeit at a somewhat slower rate than in the case of pethidine.

In conclusion, it is of interest to consider the possible addiction liability of 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine. Shemano and Wendel[10] have described a 'Straub Index' which they define as (the i.v. LD_{50})/(the i.v. ED_{50} for Straub tail effect). They claim that this index (but not the absolute Straub tail potencies *per se*) shows some correlation with the addiction liability of analgesic substances; they obtained the values 100 for heroin, 29 for morphine, 5 for pethidine and 2 for codeine, for example. From the results in Table II, Straub indices of 25 and 5 may be calculated for morphine and pethidine respectively, confirming those quoted above. The index for 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine is 21, which suggests that this compound may have addictive properties similar to those of morphine.

Experimental*

4-Acetoxy-1-benzyl-4-(2-furyl) piperidine (Ib; R = CH_3, R′ = H) *hydrochloride and 4-ethoxy analogue.* A mixture of freshly distilled furan (16·3 g) and lithium phenyl in ether, prepared from lithium (3·3 g) and bromobenzene (38 g), was refluxed for 2 h, cooled (ice-bath) and treated with 1-benzyl-4-piperidone (37 g) in ether. The product was stirred for 10 min at room temperature, the ice-bath was replaced and acetic anhydride (40 g) in ether was added. After a further period of stirring at room temperature, the mixture was poured onto crushed ice and acetic acid (40 ml). The solid which separated on storage at 5° was washed with ether, the base liberated with aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the solvent was removed to give the crude ester (40 g) as a dark brown oil. On careful neutralization with ethanolic hydrogen chloride, it gave a *hydrochloride*, m.p. 152°.

Anal. Calcd. for $C_{18}H_{22}ClNO_3$: C, 64·4; H, 6·6; N, 4·2. Found: C, 64·2; H, 6·4; N, 4·0.

The crude ester in ethanol with hydrogen chloride (2 moles) gave *1-benzyl-4-ethoxy-4-(2-furyl) piperidine* (IIb; R′ = H, R‴ = C_2H_5) *hydrochloride*, m.p. 206°.

Anal. Calcd. for $C_{18}H_{24}ClNO_2$: C, 67·2; H, 7·5; N, 4·0; equiv. wt., 322. Found: C, 67·25; H, 7·4; N, 4·2; equiv. wt., 325. It had a strong absorption peak at 1071 cm^{-1}, characteristic of ethers in this series.[2]

1-(3-Benzoylpropyl)-4-ethoxy-4-(2-furyl) piperidine (IIe; R′ = H, R‴ = C_2H_5) *hydrochloride.* A mixture of the ether (IIb; R′ = H, R‴ = C_2H_5) hydrochloride (10 g) in ethanol (150 ml) and 10 per cent palladized charcoal (1 g) was shaken with hydrogen at room temperature and pressure. After 10 h, when the approximately theoretical volume of hydrogen (650 ml) had been absorbed, the mixture was filtered and concentrated, when impure 4-ethoxy-4-(2-furyl) piperidine hydrochloride, m.p. 149–150°, separated. A mixture of the latter compound as free base (1 g), 3-chloropropyl

* Melting points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, and Mr. G. S. Crouch, School of Pharmacy, University of London. Equivalent weights of bases and salts were determined by titration with 0·02N perchloric acid in glacial acetic acid using Oracet Blue B as indicator. Salts were crystallized from ethanol–ether unless otherwise stated.

phenyl ketone (1 g) in toluene (20 ml) and a trace of powdered potassium iodide was refluxed for 10 h. Next morning the unreacted secondary base hydrochloride (0·86 g) that separated was collected and the toluene filtrate extracted with aqueous hydrochloric acid. *1-(3-Benzoylpropyl)-4-ethoxy-4-(2-furyl) piperidine*, recovered from the latter by basification with aqueous ammonia and ether extraction, gave a *hydrochloride*, m.p. 170° (d.).

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66·8; H, 7·4; equiv. wt., 378. Found: C, 67·1; H, 7·25; equiv. wt., 384.

1-(2-Benzoylethyl)-4-ethoxy-4-(2-furyl) piperidine (IId; R′ = H, R‴ = C_2H_5) *hydrochloride.* 2-Dimethylaminoethyl phenyl ketone methiodide (3·5 g) and sodium carbonate (1 g) were added to the secondary base (IIa; R′ = H, R‴ = C_2H_5) (1·6 g) in dimethylformamide (25 ml). Dry nitrogen was bubbled through the mixture for 4 h and the product diluted with water and kept at 5° overnight. Next morning the solvent was decanted from the oil that had separated which was washed with water and dissolved in ether. After drying (Na_2SO_4), the solvent was removed to give *1-(2-benzoylethyl)-4-ethoxy-4-(2-furyl) piperidine* which formed a *hydrochloride*, m.p. 171–172° (d.).

Anal. Calcd. for $C_{20}H_{26}ClNO_3$: C, 66·0; H, 7·15; equiv. wt., 364. Found: C, 66·4; H, 7·0; equiv. wt., 357. It had strong absorption peaks at 1681 cm^{-1} (aryl carbonyl) and 1075 cm^{-1} (ether).

A mixture of the secondary base (IIa; R′ = H, R‴ = C_2H_5) hydrochloride (2·3 g), acetophenone (1·2 g) and paraformaldehyde (0·45 g) in ethanol (27 ml) was heated on a steam bath for 1 h, when additional paraformaldehyde (0·3 g) was added and heating continued for a further 2 h. The product was cooled and diluted with ether (25 ml), when *4-(2-furyl)-1,2,5,6-tetrahydropyridine hydrochloride*, m.p. 231° (d.), separated on storage at 5°.

Anal. Calcd. for $C_9H_{12}ClNO$: C, 58·2; H, 6·5. Found: C, 57·9; H, 6·4. It had λ_{max} 263 mμ, ε 16,600 in H_2O.

4-Ethoxy-4-(2-furyl)-1-(3-hydroxy-3-phenylpropyl)piperidine (IIf; R′ = H, R‴ = C_2H_5) *hydrochloride.* The base (IId; R′ = H, R‴ = C_2H_5) (1·7 g) in ether was added to a stirred suspension of lithium aluminium hydride (0·4 g) in ether, the mixture refluxed for 1 h and excess of reagent decomposed with water. The product after filtration was dried (Na_2SO_4) and the solvent

removed to give *4-ethoxy-4-(2-furyl)-1-(3-hydroxy-3-phenylpropyl) piperidine*, which formed a hydrochloride, m.p. 153·5°.

Anal. Calcd. for $C_{20}H_{28}ClNO_3$: C, 65·7; H, 7·7; N, 3·8. Found: C, 64·8; H, 7·7; N, 3·8. It had strong absorption peaks at 3330 cm^{-1} (OH) and 1075 cm^{-1} (ether).

1-Benzyl-4-(2-furyl)-3-methyl-4-propionoxypiperidine (Ib; R = C_2H_5, R′ = CH_3) *hydrochloride and related compounds.* 1-Benzyl-3-methyl-4-piperidone (80 g) in ether was added to ice-bath-cooled lithium 2-furyl in ether prepared as above from lithium (6·6 g), bromobenzene (75·2 g) and furan (35 ml). The stirred mixture was treated with propionic anhydride (80 ml) and then refluxed for 1 h. The product was poured onto crushed ice and acetic acid (80 ml), and the organic phase exhaustively extracted with very dilute acetic acid. The aqueous extract was made alkaline with aqueous ammonia and the free base extracted with ether. After drying (Na_2SO_4), the solvent was removed to give the impure ester (Ib; R = C_2H_5, R′ = CH_3) (65 g) as a dark brown oil. Acetyl chloride (15·7 g) was added dropwise to a cooled mixture of the basic ester (65 g), acetone (35 ml) and ethanol (10 ml), when the *ester* (Ib; R = C_2H_5, R′ = CH_3) *hydrochloride*, m.p. 141–141·5°, separated on storage at 5°.

Anal. Calcd. for $C_{20}H_{26}ClNO_3$: C, 66·0; H, 7·15; N, 3·85; equiv. wt., 364. Found: C, 66·0; H, 7·4; N, 3·8; equiv. wt., 363.

The impure ester (Ib; R = C_2H_5, R′ = CH_3) with excess of ethanolic hydrobromic acid gave *1-benzyl-4-(2-furyl)-3-methyl-4-piperidinol hydrobromide*, m.p. 173–174° (d.).

Anal. Calcd. for $C_{17}H_{22}BrNO_2$: C, 57·95; H, 6·25; equiv. wt., 352. Found: C, 58·8; H, 6·6; equiv. wt., 354. It had a strong absorption peak near 3330 cm^{-1} (OH).

The 4-piperidinol (IIb; R′ = CH_3, R‴ = H) hydrobromide (10·8 g) in ethanol (150 ml) and 10 per cent palladized charcoal (1·08 g) was shaken with hydrogen at room temperature and pressure. After 10 h, when the approximately theoretical volume of hydrogen had been absorbed (670 ml), the mixture was filtered and concentrated. The residue in water was made alkaline with aqueous sodium hydroxide and extracted with ether. After drying (Na_2SO_4), the solvent was removed to give *4-(2-furyl)-3-methyl-4-piperidinol*, m.p. 99–100° after crystallization from acetone–ether.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66·3; H, 8·3. Found: C, 66·3; H, 8·3.

An exchange reaction between the secondary base (IIa; R′ = CH_3, R‴ = H) (3·95 g) in dimethylformamide (50 ml) and 2-dimethylaminoethyl phenyl ketone methiodide (8·7 g), carried out as applied above to 4-ethoxy-4-(2-furyl) piperidine, gave *1-(2-benzoylethyl)-4-(2-furyl)-3-methyl-4-piperidinol hydrobromide.*

Anal. Calcd. for $C_{19}H_{24}BrNO_3$; C, 57·9; H, 6·1; N, 3·55; equiv. wt., 394. Found: C, 57·7; H, 6·3; N, 3·4; equiv. wt., 397. It had strong absorption peaks at 3370 cm^{-1} (OH) and 1684 cm^{-1} (aryl C = O).

1-Benzyl-4-ethoxy-4-(2-furyl)-3-methylpiperidine (IIb; R′ = CH_3, R‴ = C_2H_5) *hydrochloride.* Acetyl chloride (2·3 g) was added dropwise to a cooled solution of the ester (Ib; R = C_2H_5, R′ = CH_3) hydrochloride (11 g) in ethanol (25 ml). The product was diluted with ether (70 ml) when the *ether* (IIb; R′ = CH_3, R‴ = C_2H_5) *hydrochloride* (3·7 g), m.p. 167–168°, separated on storage at 5°.

Anal. Calcd. for $C_{19}H_{26}ClNO_2$: C, 68·0; H, 7·75; N, 4·2; equiv. wt., 336. Found: C, 68·6; H, 7·8; N, 4·3; equiv. wt., 336. It had a strong absorption peak at 1073 cm^{-1} (ether).

1-(2-Benzoylethyl)-4-ethoxy-4-(2-furyl)-3-methylpiperidine (IId; R′ = CH_3, R‴ = C_2H_5) *hydrochloride* (by N. A. Armstrong). The ether (IIb; R′ = CH_3, R‴ = C_2H_5) hydrochloride (7 g) was catalytically debenzylated as described above to give *4-ethoxy-4-(2-furyl)-3-methylpiperidine hydrochloride* (4·5 g), m.p. 183°.

Anal. Calcd. for $C_{12}H_{20}ClNO_2$: C, 58·6; H, 8·2; N, 5·7; equiv. wt., 246. Found: C, 58·1; H, 8·4; N, 5·7; equiv. wt., 246.

An exchange reaction between the secondary base (IIa; R′ = CH_3, R‴ = C_2H_5) (2·5 g) and dimethylaminoethyl phenyl ketone methiodide (4·25 g), carried out as described above, gave *1-(2-benzoylethyl)-4-ethoxy-4-(2-furyl)-3-methylpiperidine hydrochloride,* m.p. 153°.

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66·7; H, 7·5; equiv. wt., 378. Found: C, 66·3; H, 7·5; equiv. wt., 380.

Infrared absorption measurements. Spectra were measured on a Grubb Parsons' GS 2A spectrophotometer with a grating of 1200 lines/in. Determinations were carried out in Nujol and calibration was accurate to ± 2 cm^{-1}.

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Summary. The synthesis of some 4-alkoxy-1-(benzoylalkyl)-4-(2-furyl) piperidines and related compounds is described. The analgesic activities of these compounds together with those of 1-(2-phenethyl) analogues are reported. Structure–action relationships in this series are discussed in terms of the 4-oxygenated function, the 1-substituent and the 4-aryl group. The results of a detailed study of the most active member, 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl) piperidine, show that it may be classified as a morphine-type analgesic.

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