magnesium bromide in 25 ml. of tetrahydrofuran. The reaction was run, and the product was isolated in the usual manner. The first aqueous acid extract was in this case allowed to stand for 2 hr. The product was dehydrated as above. The benzene solution was washed with sodium bicarbonate solution and taken to dryness. The residue was recrystallized twice from methanol to give 0.39 g. of the aminophenol, m.p. 154–155.5° (see Table IV).

Studies in Alkyl–Oxygen Heterolysis. Some 4-Alkoxypiperidines Related to Reversed Esters of Pethidine

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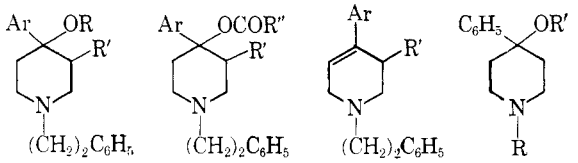
The preparation and pharmacological activity in the hot plate test of some 4-alkoxy-4-arylpiperidines is reported, and structure–activity relationships in this class of analgesics are discussed. Study has been made of the influence of the 4-aryl group upon alkyl–oxygen heterolysis in esters of 4-piperidinols.

A series of 4-alkoxy-4-(2-furyl)piperidines (**1a**, R = lower alkyl) has been reported previously, certain members being significantly active as analgesics in mice.[1] The results of a detailed study of the most active compound, 4-ethoxy-4-(2-furyl)-3-methyl-1-phenethylpiperidine (**1a**, R = C_2H_5; R' = CH_3) (4.4 times as active as pethidine and 1.2 times as active as morphine in the hot plate test) showed that it could be classified as a morphine-type analgesic. The object of the present work was to prepare 4-aryl analogs of the active 4-(2-furyl) ethers **1a** (R = CH_3 or C_2H_5) as part of a study of structure–activity relationships in this class of analgesics.



1 2 3 4

a, Ar = 2-C_4H_3O (2-furyl)
b, Ar = C_6H_5
c, Ar = *o*-$CH_3C_6H_4$
d, Ar = *p*-$CH_3C_6H_4$
e, Ar = *m*-$CH_3C_6H_4$
f, Ar = *m*-$CH_3OC_6H_4$
g, Ar = *p*-$CH_3OC_6H_4$
h, Ar = 2-(5-$CH_3C_4H_2O$) [2-(5-methylfuryl)]
i, Ar = *p*-$NO_2C_6H_4$
j, Ar = *p*-FC_6H_4

Since Williamson procedures (*e.g.*, reaction between lithium salts of 4-phenyl-4-piperidinols and alkyl halides) failed to give the desired ethers, resort was made to acid-catalyzed etherification reactions. Esters of 4-(2-furyl)-4-piperidinols give good yields of ethers (together with alkenes as by products) when treated in the cold with a molar excess of hydrogen chloride in a lower unbranched alcohol, transformations that have been interpreted as proceeding *via* carbonium ions generated by acid-catalyzed alkyl–oxygen fission of the ester groups.[2] The facile nature of these reactions was attributed to the high electron-releasing power of the 4-(2-furyl) substituent. Investigation was made previously of acid conditions necessary to induce carbonium ion reactions in analogous alcohols and esters containing a 4-phenyl substituent, an aryl group that less readily releases electrons.[2] Such compounds were stable in cold methanol containing up to 6% HCl or 16% sulfuric acid, but at the reflux temperature were converted, in these solvents, to methyl ethers. When methanol was replaced by ethanol or 1-propanol containing 16% sulfuric acid, elimination products were isolated, results indicating that, at high acid concentrations, the small unfavorable steric factors introduced by the latter change in nucleophile size are sufficient to make proton loss the predominant carbonium ion fate. Since esters of benzoic acid undergo alkyl–oxygen heterolysis more readily than those of saturated carboxylic acids,[3] the ethanolysis of 4-benzoyloxy-4-phenylpiperidines was investigated in the expectation that reaction could be induced at acid concentrations low enough to render elimination a minor pathway. Treatment of the 4-benzoyloxypiperidine **2b** (R' = H; R'' = C_6H_5) with 9% sulfuric acid in ethanol at the reflux temperature, conditions which had no effect on the corresponding 4-acetoxy analog,[4] gave the ethyl ether **1b** (R = C_2H_5; R' = H); the critical acid concentration for reaction was found to be between 2.4 and 1.4%. The 4-benzoyloxy-3-methylpiperidine **2b** (R' = CH_3; R'' = C_6H_5) was recovered after treatment with hot 9% sulfuric acid in ethanol, while use of 13% acid gave the alkene **3b** (R' = CH_3).[5] Unchanged substrate was also recovered when the corresponding 4-*p*-nitrobenzoyloxy-3-methylpiperidine was treated with 9% sulfuric acid in ethanol. These results are in contrast to the successful methanolysis of 3-methyl-4-phenyl-4-piperidinols and their esters[2] and illustrate the sensitivity of the described alkyl–oxygen heterolyses to steric factors in both substrate and nucleophile. 1-Benzyl-4-ethoxy-4-phenylpiperidine **4** (R' = C_2H_5; R = $CH_2C_6H_5$) was debenzylated reductively and the resultant secondary amine was converted to the 1-methyl derivative **4** (R' = C_2H_5; R = CH_3) by reductive methylation, the 1-(2-benzoylethyl) derivative **4** [R' = C_2H_5; R = $(CH_2)_2COC_6H_5$] by a Mannich base exchange process,[6] and the 1-(3-*p*-fluorobenzoylpropyl) deriva-

(1) A. F. Casy, A. H. Beckett, G. H. Hall, and D. K. Vallance, *J. Med. Pharm. Chem.*, **4**, 535 (1961).

(2) A. F. Casy, A. H. Beckett, and N. A. Armstrong, *Tetrahedron*, **16**, **85** (1961).

(3) V. R. Stimson, *J. Chem. Soc.*, 4020 (1955); G. J. Harvey and V. R. Stimson, *ibid.*, 3629 (1956).

(4) N. A. Armstrong, Ph.D. Thesis, University of London, 1962.

(5) The structure of the alkene was confirmed by n.m.r. spectroscopy, the key signals supporting the formulation **3b** (R' = CH_3), being an unresolved triplet at τ 4.19 (vinylic proton at C-5) and a doublet at 8.98, J = 7 c.p.s. (3 protons of 3-methyl substituent) (solvent, CCl_4).

(6) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).

tive **4** [R′ = C_2H_5; R = $(CH_2)_3COC_6H_4$-*p*-F] by a substitution reaction involving 4-chloro-*p*-fluorobutyrophenone.[7]

Further study of the influence of the 4-aryl group upon alkyl-oxygen heterolysis in 4-piperidinols and esters was made during this work. Most of the esters used were prepared by decomposing the lithium salt of the tertiary alcohol (obtained by reaction between a 4-piperidone and an organometallic reagent) with an acid anhydride or acid chloride; they were isolated as hydrochloride salts by careful neutralization of the basic products with ethanolic hydrogen chloride. Esters with aryl substituents of greater electron-releasing character than phenyl were first examined. Methyl groups substituted *ortho* or *para* in the 4-phenyl group promote carbonium ion formation in benzoyloxy esters, the 4-*o*- and 4-*p*-tolyl esters (**2c** and **2d**, R′ = H; R″ = C_6H_5) undergoing elimination when treated with 1 *M* excess of HCl in cold ethanol (corresponding acetoxy and propionoxy esters are stable in this medium).[8] The high degree of resonance stabilization obtaining in the alkene **3d** (R′ = H), as indicated by its ultraviolet adsorption characteristics ($\epsilon_{249.5}$ 16,950)], must be an important factor in determining carbonium ion fate in the reaction of the 4-*p*-tolyl ester. Alkene formation in the case of the *o*-tolyl ester **2c** (R′ = H; R″ = C_6H_5) appears to be a result of etherification being unfavored (on the grounds of the crowded nature of the molecule) rather than attainment of maximum resonance stabilization since the styrenoid adsorption peak near 240 mμ in the alkene **3c** (R′ = H) is suppressed through interactions between the *o*-methyl group and the 3,5-hydrogen atoms of the piperidine ring[9] (*cf.* the effect of acid upon the acetoxy esters of 4-*o*- and 4-*p*-methoxy-4-piperidinol).[2] In contrast, a *m*-methyl substituent does not promote carbonium ion formation in this series, the 4-*m*-tolyl ester **2e** (R′ = H; R″ = C_6H_5) being recovered when subjected to the same conditions of acidity. Treatment of this ester with 9% sulfuric acid in ethanol at the reflux temperature gave the 4-ethoxy derivative **1e** (R = C_2H_5; R′ = H); factors favoring alkene formation in this reaction are no greater than those obtained when the 4-phenyl ester **2b** (R′ = H; R″ = C_6H_5) is substrate, the two alkenes **3b** and **3e** (R′ = H) having similar ultraviolet absorption characteristics ($\epsilon_{243.5}$ 13,700 and ϵ_{245} 12,800, respectively).[9] However, use of larger nucleophiles (1- and 2-propanol) in the etherification procedure induced an elimination reaction. The *o*- and *p*-methoxy groups are more effective than *o*- and *p*-methyl in promoting carbonium ion formation since their influence may be demonstrated in 4-acetoxy esters.[2] Again a *meta* substituent fails to activate the substrate in this respect [the Hammett σ-values of *m*- and *p*-methoxy are +0.12 (indicating electron withdrawal) and −0.27 (indicating electron release), respectively].[10] The *m*-methoxyphenyl ester **2f** (R′ = H; R″ = CH_3) was unaffected by excess HCl in ethanol, and vigorous conditions (an acetic acid-hydrochloric acid mixture at the reflux temperature) were necessary to bring about its elimination. The extent of ultraviolet absorption shown by the alkene **3f** (R′ = H) (ϵ_{245} 8300, ϵ_{286} 1970) is much less than that of the *p*-methoxy analog **3g** (R′ = H) (ϵ_{256} 17,460).[2]

4-Acetoxy-4-[2-(5-methylfuryl)]-1-phenethylpiperidine (**2h**, R′ = H; R″ = CH_3) gave the alkene **3h** (R′ = H) when treated with 2 moles of HCl in ethanol; in contrast, the 4-(2-furyl) analog **2a** (R′ = H; R″ = CH_3) gives the 4-ethoxy derivative **1a** (R = C_2H_5; R′ = H) when treated similarly.[2] The stability of the 4-[2-(5-methylfuryl)]alkene **3h** (R′ = H) (ϵ_{273} 17,240) is greater than that of the 4-(2-furyl) congener **3a**, (R′ = H) ($\epsilon_{263.5}$ 15,300) and this factor is probably responsible in part for the difference in carbonium ion fate observed in the two cases. The structure of the alkene **3h** (R′ = H) was confirmed by n.m.r. spectroscopy (this was felt desirable since synthesis of this series involved use of 2-(5-methylfuryl)lithium prepared by a metalation process known to be of low efficiency[11]); the spectrum exhibited signals at τ 2.66 (5 phenyl protons), 3.8 (triplet, one vinylic proton), 3.96 (2 furyl protons), and 7.71 (singlet, 3 protons of the methyl substituent in the furyl ring), consistent with the formulation **3h** (R′ = H).

4-Piperidinols and esters substituted in the 4-position with the electron-withdrawing groups 2-pyridyl[2] and *p*-nitrophenyl failed to undergo carbonium ion reactions of the type described and could not be converted to alkenes by acid treatment. 1,3-Dimethyl-4-*p*-nitrophenyl-4-propionoxypiperidine was prepared by the nitration of α-prodine with cold fuming nitric acid–acetic acid (an attempt to metalate *p*-nitrobromobenzene with *n*-butyllithium, to be used in reaction with a 4-piperidone, was unsuccessful). Formulation of the product as a *p*-nitro derivative is based upon its n.m.r. aromatic protons signal which has a very similar form to that of *p*-nitrotoluene (and other *p*-nitro aromatic derivatives, *e.g.*, *p*-nitrobenzyl cyanide[12]); both signals consist of a pair of similar doublets of integral ratio 1:1 (*i.e.*, constitute an A_2B_2 spectrum) and differ from corresponding signals observed in the spectra of *o*- and *m*-nitrotoluene (see Figure 1).

A *p*-fluoro substituent in phenyl promotes carbonium ion formation, the 4-acetoxy-4-(*p*-fluorophenyl)-1-phenethylpiperidine **2j** (R′ = H; R″ = CH_3) being converted to the corresponding 4-ethoxy analog when heated with 9% sulfuric acid in ethanol (16% of the same acid in ethanol was required to effect alkyl-oxygen fission in esters of 4-phenyl-4-piperidinols and the products were alkenes rather than esters[2,4]). In this case carbonium ion stabilization by resonance contributors such as **5** (involving the lone pair p electrons of the halogen atom) is probably an important factor in the facilitation of the reaction.

5

Pharmacological Results and Discussion.—The analgesic activities of certain of the compounds reported were determined in mice by subcutaneous injection.

(7) P. A. J. Janssen, A. H. M. Jageneau, P. J. A. Demoen, C. van de Westeringh, J. H. M. de Cannière, A. H. M. Raeymaekers, M. S. J. Wouters, S. Sanczuk, and B. K. F. Heymans, *J. Med. Pharm. Chem.*, **2**, 271 (1960).

(8) A. H. Beckett, A. F. Casy, and G. Kirk, *ibid.*, **1**, 37 (1959).

(9) S. E. Fullerton, Ph.D. Thesis, University of London, 1960.

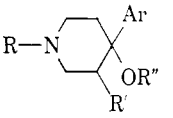
(10) H. M. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(11) H. Gilman and R. L. Bebb, *J. Am. Chem. Soc.*, **61**, 109 (1939).

(12) Varian Spectra Catalog, Varian Associates, Palo Alto, Calif., 1951, Spectrum No. 495.

TABLE I

ANALGESIC ACTIVITIES OF SOME 4-ALKOXYPIPERIDINES AND RELATED COMPOUNDS[1,2]

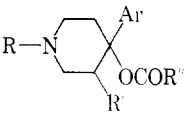


No.	Ar	R	R′	R″	ED_{50} mg./kg.	Potency ratio (pethidine = 1.0)[a]
1	C_6H_5	$(CH_2)_2C_6H_5$	H	C_2H_5	36	0.6
2	2-Furyl	$(CH_2)_2C_6H_5$	H	C_2H_5	Inactive[b]	...
3	C_6H_5	$(CH_2)_2C_6H_5$	CH_3	CH_3	20	1.0
4	2-Furyl	$(CH_2)_2C_6H_5$	CH_3	CH_3	81	0.25
5	C_6H_5	CH_3	CH_3	CH_3	Inactive	...
6	C_6H_5	$(CH_2)_2COC_6H_5$	CH_3	H	Inactive	...
7	2-Furyl	$(CH_2)_2COC_6H_5$	CH_3	H	Inactive	...
8	C_6H_5	$(CH_2)_2COC_6H_5$	H	C_2H_5	5.8	4.0
9	2-Furyl	$(CH_2)_2COC_6H_5$	H	C_2H_5	12	1.6
10	C_6H-*m*-CH_3	$(CH_2)_2C_6H_5$	H	C_2H_5	Inactive	...
11	C_6H_4-*p*-F	$(CH_2)_2C_6H_5$	H	C_2H_5	Inactive	...

[a] The data represent a series of assays in which the reference standard was tested repeatedly. [b] In cases of inactive compounds, the highest dose employed was in the order of 100 mg./kg.

TABLE II

ANALGESIC ACTIVITIES OF SOME 4-ACYLOXYPIPERIDINES[a]



No.	Ar	R	R′	R″	ED_{50} mg./kg.	Potency ratio (pethidine = 1.0)[b]
1	2-Pyridiyl	$(CH_2)_2C_6H_5$	H	CH_3	Inactive[c]	...
2	2-Pyridyl	$(CH_2)_2C_6H_5$	H	C_2H_5	13	1.2
3	C_6H_4-*o*-OCH_3	$(CH_2)_2C_6H_5$	H	CH_3	6.7	3.0
4	C_6H_4-*m*-OCH_3	$(CH_2)_2C_6H_5$	H	CH_3	48	0.5
5	C_6H_5	$(CH_2)_2C_6H_5$	H	C_6H_4-*p*-NO_2	Inactive[c]	...
6	C_6H_5	$(CH_2)_2C_6H_5$	H	CH_3	4.4	5.7
7	C_6H_5	$(CH_2)_2C_6H_5$	H	C_2H_5	1.5	17
8	C_6H_4-*p*-NO_2	CH_3	CH_3	C_2H_5	Inactive	...

[a] See ref. 2. [b] See footnote *a* to Table I. [c] See footnote *b* to Table I.

using a hot plate method based on that described by Eddy and Leimbach[1,13] (see Tables I and II). Our thanks are due to the staff of the pharmacology department of Smith Kline and French Laboratories, Welwyn Garden City, for carrying out the tests.

An important structural feature in 4-phenylpiperidine analgesics is an oxygen function at C-4[1,14]; it was of interest to determine whether a 4-alkoxy group may satisfy structural requirements for activity in this respect. Active 4-alkoxypiperidines previously reported[1] also possess a 4-(2-furyl) group and, in view of the possibility of their activities being due to a specific interaction between the two groups, it was important to study 4-alkoxy-4-phenylpiperidines in order to differentiate clearly the influence of the ether function. Comparison of the results obtained with the pairs 1–2, 3–4, and 7–8 (Table I) show that the 4-(2-furyl) group is not an essential feature of active 4-alkoxy-4-(2-furyl)piperidines since, in each case, the 4-phenyl derivatives are more active than the 4-(2-furyl) analogs. Hence, 4-alkoxy groups fulfill structural requirements for analgesic activity in 4-phenylpiperidines, although not so effectively as 4-acyloxy functions (*cf.* Table I, **1**, and Table II, **6** and **7**). In general, isosteric replacement of phenyl is disadvantageous

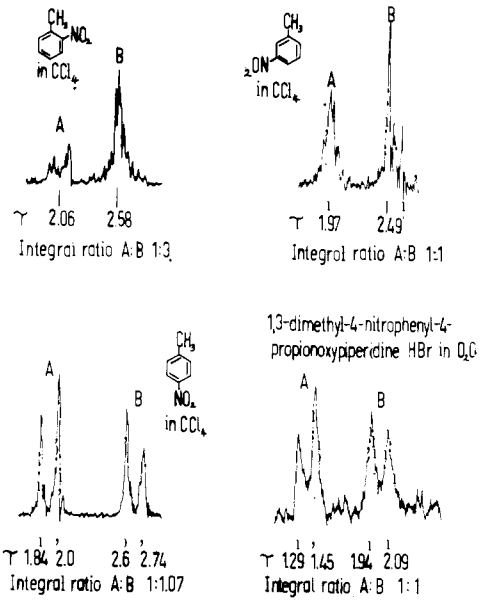


Figure 1.

(13) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(14) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

in analgesics[1,15] (in this respect note the results with the 4-(2-pyridyl) and 4-phenyl esters, Table II, **1**, **2**, **6**, and **7**). Few data upon 2-furyl isosteres are available; such isosteres of reversed esters of pethidine lack activity[1] but this result may be due to their undergoing *in vivo* hydrolysis more readily than the 4-phenyl counterparts rather than to an inherent inability of 2-furyl groups to associate with the receptor site at which analgesia is mediated.

In 4-alkoxy-4-(2-furyl)piperidines highest activity was associated with the 4-ethoxy-3-methyl system; lower and higher ethers and 4-ethoxypiperidines lacking the 3-methyl group were either inactive or of low potency.[1] 4-Phenyl derivatives of 4-ethoxypiperidines and 4-methoxy-3-methylpiperidines have been prepared but so far 4-ethoxy-3-methyl-4-phenyl analogs (which, from the results of Table I, may be anticipated to be highly active) have eluded synthesis; further work is in progress in this respect.

The most active 4-phenyl ether reported (Table I, **8**) possesses an N-2-benzoylethyl group, a substituent known to enhance markedly the activities of piperidine analgesics.[16]

The adverse effect of introducing substituents into the phenyl group of 4-phenylpiperidine analgesics[8,14,17] is further demonstrated by the results of Tables I and II (*cf.* Table I, **1**, **10**, and **11**, and Table II, **3**, **4**, **6**, and **8**). In the case of the *o*-methoxy derivative (Table II, **3**) the disadvantageous effect of aryl group enlargement may be offset by the shielding action that *ortho* groups have upon the ester function.

Experimental

Melting point values determined by capillary tube method are uncorrected (Townson and Mercer apparatus, type IV). Analyses by Drs. Weiler and Strauss, Oxford. Equivalent weights of bases determined by titration with 0.02 *N* perchloric acid in glacial acetic acid using oracet blue B as indicator (hydrohalide salts titrated in the presence of mercuric acetate). Salts crystallized from ethanol–ether unless otherwise stated. Free bases recovered from acidic reaction products by treatment with aqueous ammonia and ether extraction.

4-Benzoyloxy-1-phenethyl-4-phenylpiperidine (2b, R′ = H; R″ = C_6H_5).—A solution of 1-phenethyl-4-phenyl-4-piperidinol (5 g.) and benzoyl chloride (8.5 g.) in benzene (20 ml.) was heated under reflux for 5 hr., the product was evaporated under reduced pressure, and the recovered base (6.4 g.) was neutralized with C_2H_5OH–HCl to give the ester **2b** (**R′ = H; R″ = C_6H_5**) **hydrochloride,** m.p. 198°.

Anal. Calcd. for $C_{28}H_{28}ClNO_2$: C, 74.1; H, 6.7; N, 3.3; equiv. wt., 422. Found: C, 74.1; H, 6.9; N, 3.1; equiv. wt., 418.

The following ester hydrochlorides were prepared similarly. **2b (R′ = CH_3; R″ = C_6H_5) hydrochloride** had m.p. 95°.

Anal. Calcd. for $C_{27}H_{30}ClNO_2 \cdot C_2H_6O$: C, 72.1; H, 7.5; N, 2.9; equiv. wt., 482. Found: C, 72.5; H, 7.6; N, 3.0; equiv. wt., 490.

2b (R′ = CH_3; R″ = *p*-$NO_2C_6H_4$) hydrochloride had m.p. 181° (an 11-hr. reflux period was employed in this case).

Anal. Calcd. for $C_{27}H_{29}ClN_2O_4$: C, 67.4; H, 6.1; N, 5.8; equiv. wt., 481. Found: C, 67.6; H, 6.1; N, 5.9; equiv. wt., 468.

Reaction of the Esters 2 (R″ = C_6H_5 or *p*-$NO_2C_6H_4$) with Ethanol–Sulfuric Acid. A.—A mixture of ester **2** (R′ = H; R″ = C_6H_5) hydrochloride (1.8 g.), dry ethanol (45 ml.), and concentrated H_2SO_4 (4.5 ml.) was heated under reflux for 6 hr., cooled, and made alkaline with strong aqueous ammonia. The precipitated ammonium sulfate was separated by filtration and washed with ethanol; the combined filtrate and washings were concentrated, diluted with water, and made alkaline again with aqueous ammonia. The recovered base (1.1 g.), with C_2H_5OH–HCl, gave the **ether 1b (R = C_2H_5; R′ = H) hydrochloride,** m.p. 240°. It had a strong absorption peak at 1070 cm.$^{-1}$ (Nujol mull), characteristic of ethers in this series.[2]

Anal. Calcd. for $C_{29}H_{28}ClNO$: C, 72.9; H, 8.1; N, 4.1; equiv. wt., 346. Found: C, 72.9; H, 8.1; N, 4.2; equiv. wt., 340.

The same ether resulted when the concentration of H_2SO_4 was reduced to 2.4% v./v.; ester was recovered when 1.4% acid was used.

B.—The ester **2b** (R′ = CH_3; R″ = C_6H_5) was recovered after treatment with 9 or 11% H_2SO_4 in ethanol as described above; use of 13% acid gave the alkene **3b** (R′ = CH_3) hydrobromide, m.p. 225°, undepressed by an authentic sample.[2]

C.—The ester **2b** (R′ = CH_3; R″ = *p*-$NO_2C_6H_4$) was recovered after treatment with 9% H_2SO_4 in ethanol as described above.

4-Benzoyloxy-1-benzyl-4-phenylpiperidine (4, R = $C_6H_5CH_2$; R′ = COC_6H_5).—1-Benzyl-4-piperidone (32.6 g.) in ether (40 ml.) was added to a stirred, cooled, solution of phenyllithium in ether prepared from bromobenzene (34.3 g.) and lithium (3.55 g.). After 1 hr., benzoyl chloride (56 ml.) was added, the product was stirred for a further hour and poured onto ice. The solid which separated was collected, washed with ether, and made alkaline with aqueous ammonia. The recovered base (40.2 g.) was crystallized from petroleum–ether (b.p. 60–80°) to give the ester **4** (R = $C_6H_5CH_2$; R′ = COC_6H_5), m.p. 91°.

Anal. Calcd. for $C_{32}H_{29}NO_2$: C, 80.8; H, 6.8; N, 3.8; equiv. wt., 372. Found: C, 80.9; H, 6.8; N, 3.7; equiv. wt., 369.

1-Benzyl-4-ethoxy-4-phenylpiperidine (4, R = $C_6HC_5H_2$; R′ = C_2H_5) hydrochloride, m.p. 175°, was prepared by treating the ester **4** (R = $C_6H_5CH_2$; R′ = COC_6H_5) with 9% H_2SO_4 in ethanol in the manner previously described.

Anal. Calcd. for $C_{26}H_{26}ClNO$: C, 72.4; H, 7.7; N, 4.2; equiv. wt., 332. Found: C, 72.4; H, 7.7; N, 4.5; equiv. wt., 324.

4-Ethoxy-4-phenylpiperidine (4, R = H; R′ = C_2H_5) and N-Substituted Derivatives.—A mixture of the ether **4** (R = $C_6H_5CH_2$; R′ = C_2H_5) hydrochloride (9.1 g.) in ethanol (100 ml.) and 10% palladium on carbon (1.2 g.) was shaken with hydrogen at room temperature and pressure. When the theoretical volume of hydrogen had been absorbed, the mixture was filtered, and the filtrate was evaporated. The residual solid (6.1 g.) was crystallized from acetone to give the **secondary amine 4 (R = H; R′ = C_2H_5) hydrochloride,** m.p. 191°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.7; H, 8.4; N, 5.8; equiv. wt., 242. Found: C, 64.2; H, 8.3; N, 5.8; equiv. wt., 250.

A mixture of the secondary base **4** (R = H; R′ = C_2H_5) hydrochloride (1.8 g.), 10% palladium on carbon (0.6 g.), 40% aqueous formaldehyde (2.25 g.), and water (25 ml.) was shaken with hydrogen until gas absorption ceased and processed as above. The recovered base, with C_2H_5OH–HCl, gave the **N-methyl base 4 (R = CH_3; R′ = C_2H_5) hydrochloride,** m.p. 199°.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.7; H, 8.7; N, 5.5; equiv. wt., 256. Found: C, 65.4; H, 8.7; N, 5.7; equiv. wt., 253.

2-Dimethylaminoethyl phenyl ketone methiodide (2.55 g.) and sodium carbonate (1.7 g.) were added to a solution of the secondary base **4** (R = H; R′ = C_2H_5) (1.5 g.) in dimethylformamide (35 ml.), and dry nitrogen was bubbled through the mixture for 7 hr. Water (60 ml.) was added and the solvent was evaporated. The residue (1.5 g.), with C_2H_5OH–HCl, gave the **1-(2-benzoylethyl)piperidine 4 [R = $(CH_2)_2COC_6H_5$; R′ = C_2H_5] hydrochloride,** m.p. 156° from acetone.

Anal. Calcd. for $C_{22}H_{28}ClNO_2$: C, 70.7; H, 7.5; N, 3.7; equiv. wt., 374. Found: C, 70.5; H, 7.5; N, 3.9; equiv. wt., 392.

A mixture of the secondary base **4** (R = H; R′ = C_2H_5) (1.1 g.), 4-chloro-*p*-fluorobutyrophenone (1.2 g.), sodium bicarbonate (0.84 g.), a trace of powdered potassium iodide, and toluene (80 ml.) was heated under reflux for 72 hr. The product was filtered, washed with water, and the organic phase was dried and evaporated. The residue (2.2 g.), with C_2H_5OH–HCl, gave the **1-(3-*p*-fluorobenzoylpropyl)piperidine 4 (R = $(CH_2)_3$-**

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COC_6H_4-*p*-F; R′ = C_2H_5) **hydrochloride**, m.p. 229–230° (from ethanol).

Anal. Calcd. for $C_{23}H_{29}ClFNO_2$: C, 68.0; H, 7.2; N, 3.5; equiv. wt., 406. Found: C, 68.1; H, 7.0; N, 3.2; equiv. wt., 400.

Preparation and Reactions of Benzoyl Esters of 4-Tolyl-4-piperidinols (2c and d, R′ = H; R″ = C_6H_5). The salt from 1-phenethyl-4-piperidone (8.1 g.) and *o*-tolyllithium [derived from *o*-bromotoluene (8.55 g.) and lithium (0.79 g.)] was decomposed with benzoyl chloride (12 g.) in a manner described above as in the synthesis of ester **4** (R = $C_6H_5CH_2$; R′ = CO-C_6H_5). The recovered base (13.6 g.), crystallized from petroleum ether (b.p. 60–80°), gave **4-benzoyloxy-4-*o*-tolyl piperidine 2c** (**R′ = H; R″ = C_6H_5**), m.p. 101°.

Anal. Calcd. for $C_{27}H_{29}NO_2$: C, 81.1; H, 7.3; N, 3.5; equiv. wt., 400. Found: C, 80.8; H, 7.1; N, 3.7; equiv. wt., 407.

This ester gave a hydrochloride, m.p. 208° (Calcd. for $C_{27}H_{30}ClNO_2$: equiv. wt., 436. Found: equiv. wt., 441), when neutralized with C_2H_5OH-HCl; with 2 *M* proportions of HBr in ethanol it gave the **alkene 3c** (**R′ = H**) **hydrobromide**, m.p. 274° (from acetone-ether).

Anal. Calcd. for $C_{20}H_{24}BrN$: C, 67.1; H, 6.7; equiv. wt., 358. Found: C, 67.2; H, 6.5; equiv. wt., 366.

4-Benzoyloxy-4-*p*-tolylpiperidine (2d, R′ = H; R″ = C_6H_5), m.p. 71° from petroleum ether (b.p. 60–80°), was prepared in the same manner as the *ortho* isomer.

Anal. Calcd. for $C_{27}H_{29}NO_2$: C, 81.1; H, 7.3; N, 3.5; equiv. wt., 400. Found: C, 80.8; H, 7.6; N, 3.5; equiv. wt., 403.

This ester gave a hydrochloride, m.p. 202° (Calcd. for $C_{27}H_{30}ClNO_2$: equiv. wt., 436. Found: equiv. wt., 440), when neutralized with C_2H_5OH-HCl; with 2 *M* proportions of HCl in ethanol it gave the alkene **3d** (R′ = H) hydrochloride, m.p. 233° from ethanol (lit.[9] m.p. 235°), λ_{max} 249.5 mμ (ε 16,950) in H_2O.

Anal. Calcd. for $C_{20}H_{24}ClN$: C, 76.5; H, 7.7; N, 4.4; equiv. wt., 314. Found: C, 76.9; H, 7.9; N, 4.1; equiv. wt., 318.

4-Benzoyloxy-4-*m*-tolylpiperidine 2e (R′ = H; R″ = C_6H_5) hydrochloride, m.p. 191°, was prepared in the same manner as the *ortho* isomer.

Anal. Calcd. for $C_{27}H_{30}ClNO_2$: C, 74.3; H, 7.0; N, 3.2; equiv. wt., 436. Found: C, 73.9; H, 7.0; N, 3.1; equiv. wt., 438.

This ester was recovered after treatment with excess of C_2H_5OH-HCl; when treated with 9% H_2SO_4 in ethanol in the manner described for the preparation of the ether **1b** (R = C_2H_5; R′ = H), it gave the ether **1e** (**R = C_2H_5; R′ = H**) **hydrochloride**, m.p. 227° from ethanol. In Nujol it had a strong absorption peak at 1070 cm.$^{-1}$ (C-O-C).

Anal. Calcd. for $C_{22}H_{30}ClNO$: C, 73.4; H, 8.4; N, 3.9; equiv. wt., 360. Found: C, 73.3; H, 8.3; N, 3.8; equiv. wt., 364.

When the ester was heated with 9% H_2SO_4 in 1-propanol or 2-propanol, the alkene **3e** (R′ = H), m.p. 225–226° (lit.[9] 236°) was isolated.

Anal. Calcd. for $C_{20}H_{28}ClN$: C, 76.6; H, 7.7; equiv. wt., 314. Found: C, 76.8; H, 8.0; equiv. wt., 315.

4-Acetoxy-4-*m*-methoxyphenyl-1-phenethylpiperidine (2f, R′ = H; R″ = CH_3).—The salt from 1-phenethyl-4-piperidone (5.1 g.) and *m*-methoxyphenylmagnesium bromide [derived from *m*-bromoanisole[18] (9.3 g.) and magnesium (1.3 g.)] was decomposed with acetic anhydride (6 g.) in a manner analogous to the synthesis of the ester **4** (R = $C_6H_5CH_2$; R′ = COC_6H_5). The recovered base (3.1 g.), after being neutralized with C_2H_5OH-HCl, gave the **ester 2f** (**R′ = H; R″ = CH_3**) **hydrochloride**, m.p. 200° (from ethanol).

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.8; H, 7.2; N, 3.6; equiv. wt., 390. Found: C, 67.6; H, 6.9; N, 3.6; equiv. wt., 400.

This ester was recovered after treatment with excess of C_2H_5OH-HCl; when the ester (2.5 g.) was heated under reflux for 1 hr. with a mixture of glacial acetic acid (21 ml.) and concentrated HCl (8.5 ml.), the **alkene 3f** (**R′ = H**) was recovered, characterized as a **hydrochloride**, m.p. 202°, λ_{max} 245 mμ (ε 8320), 286 mμ (ε 1970) in H_2O.

Anal. Calcd. for $C_{20}H_{24}ClNO$: C, 72.8; H, 7.3; N, 4.2; equiv. wt., 330. Found: C, 72.4; H, 7.6; N, 4.3; equiv. wt., 328.

4-Acetoxy-4-[2-(5-methylfuryl)]-1-phenethylpiperidine (2h, R′ = H; R″ = CH_3).—2-Methylfuran (9.1 g.) in ether (30 ml.) was added to phenyllithium in ether [prepared from lithium (1.6 g.) and bromobenzene (17.3 g.)], the mixture was heated under reflux for 19 hr., cooled, and treated with 1-phenethyl-4-piperidone (19 g.) in benzene (30 ml.). The mixture was stirred at room temperature for 2 hr., acetic anhydride (20 ml.) was added, and the product (after being stirred for a further 30 min. at room temperature) was poured onto crushed ice and glacial acetic acid. The solid which separated on storage at 5° was washed with ether and made alkaline with aqueous ammonia. The recovered base (9.1 g.) was neutralized with C_2H_5OH-HCl to give the **ester 2h** (**R′ = H; R″ = CH_3**) **hydrochloride**, m.p. 202° (from ethanol).

Anal. Calcd. for $C_{20}H_{26}ClNO_3$: C, 66.0; H, 7.2; N, 3.9; equiv. wt., 364. Found: C, 65.9; H, 7.5; N, 3.9; equiv. wt., 366.

The ester, with 2 *M* proportions of HCl in ethanol, gave the alkene **3h** (**R′ = H**) **hydrochloride**, m.p. 208-209°, λ_{max} 273 mμ (ε 17,200) in H_2O.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.1; H, 7.2; N, 4.6; equiv. wt., 304. Found: C, 71.0; H, 6.9; N, 4.7; equiv. wt., 307.

α-1,3-Dimethyl-4-(*p*-nitrophenyl)-4-propionoxypiperidine.—α-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride[19] (3.8 g.) in glacial acetic acid (7 ml.) was added dropwise to a cold mixture of fuming nitric acid (16 ml.) and glacial acetic acid (10 ml.). The mixture was stirred overnight at room temperature, the solvent was evaporated under reduced pressure, and the base was recovered. The product (2.0 g.), with HBr in C_2H_5OH, gave **α-1,3-dimethyl-4-(*p*-nitrophenyl)-4-propionoxypiperidine hydrobromide**, m.p. 238° from ethanol. In Nujol it had strong absorption peaks at 1740 (ester C = O), 1515, and 1350 cm.$^{-1}$ (aromatic NO_2).

Anal. Calcd. for $C_{16}H_{23}BrN_2O_4$: C, 49.4; H, 6.0; N, 7.2; equiv. wt., 387. Found: C, 49.4; H, 6.0; N, 7.1; equiv. wt., 391.

4-Ethoxy-4-(*p*-fluorophenyl)-1-phenethylpiperidine (1j, R = C_2H_5; R′ = H).—A solution of 4-acetoxy-4-(*p*-fluorophenyl)-1-phenethylpiperidine[20] (1 g.) in ethanol (25 ml.) and concentrated H_2SO_4 (2.5 ml.) was heated under reflux for 6 hr. and processed as previously described. The recovered base (0.7 g.), with a slight excess of C_2H_5OH-HCl, gave the **ether 1j** (**R = C_2H_5; R′ = H**) **hydrochloride**, m.p. 224° (from ethanol). It had a strong absorption peak at 1070 cm.$^{-1}$ (C-O-C). The n.m.r. spectra were obtained on a 60 Mc. Varian (A-60) instrument (deuteriochloroform, carbon tetrachloride, or deuterium oxide solutions with tetramethylsilane as an internal standard).

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