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ALKYL-OXYGEN HETEROLYSIS IN 4-ARYL AND 4-HETEROARYL-4-PIPERIDINOLS AND ESTERS

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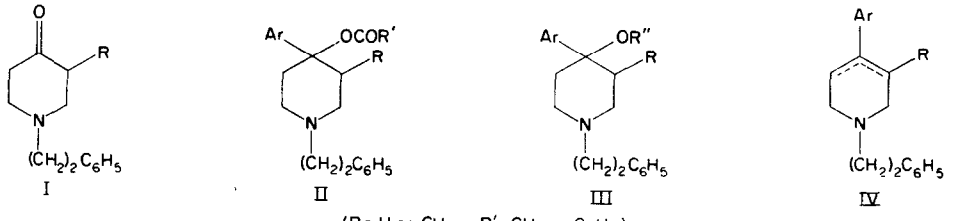
Abstract—Acetoxy and propionoxy esters of 1-phenethyl-4-(2′-furyl)-4-piperidinol hydrochlorides, upon treatment with one mole excess of hydrogen chloride in an alkanol, were converted into corresponding 4-alkoxy ethers and elimination products. These results are interpreted in terms of reactions of carbonium ions, produced from the esters by alkyl-oxygen heterolysis. Factors affecting carbonium ion generation and fate have been studied and include the electronic character of the 4-aryl substituent, nature and size of the nucleophile, degree of acidity and role of the piperidine nitrogen atom.

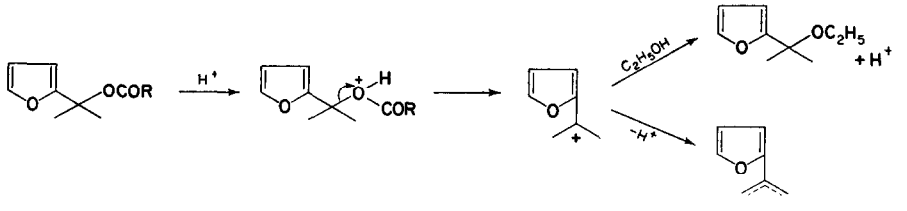
IN the course of work upon structure-action relationships in analgesics, 4-aryl and 4-heteroaryl isosteres of reversed esters of pethidine analogues were prepared by the reaction of acid anhydrides with the complex formed between a 4-piperidone (I) and a lithium aryl. Basic esters (II, Ar = 2-furyl) derived from lithium 2-furyl, upon careful



(R = H or CH_3 ; R′ = CH_3 or C_2H_5)

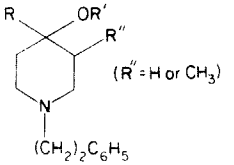
neutralization with hydrogen chloride, formed stable hydrochloride salts which had the normal ester carbonyl absorption band (peak at 1738 cm^{-1}). The latter salts in ethanol, upon treatment with one mole excess of hydrogen chloride, were converted in good yield into ethyl ethers (III, Ar = 2-furyl, R″ = C_2H_5) (ester carbonyl band absent, strong absorption band between 1094–1071 cm^{-1} ascribed to C—O stretching), while elimination products (IV, Ar = 2-furyl) were isolated from the mother liquors.

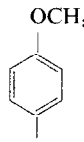
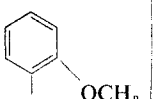
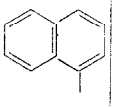
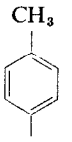
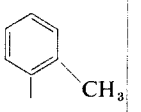
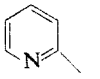
These transformations may be accounted for by alkyl-oxygen heterolysis of the esters,[1] analogous to that demonstrated by Duveen and Kenyon[2] for hydrogen phthalates of α-(2′-furyl) ethanol, to give carbonium ions that further react either with



[1] A. G. Davies and J. Kenyon, *Quart. Rev.* **9**, 203 (1955).
[2] D. I. Duveen and J. Kenyon, *J. Chem. Soc.* 621 (1936).

Table 1. Reactions of 4-piperidinols and esters

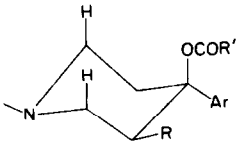


Compound No.	1	2	3	4	5	6	7	8	9
R									
Major product from Reaction A*	Olefin	Olefin	Ether	Ether	Ether	Ester	Ester	Ester	Ester
Major product from Reaction B†	Olefin	Olefin	Olefin	Olefin	Olefin	Ester	Ester	Ester	Ester
Reference	This work	This work	This work and 3	3	3	4	4	4	This work and 3

* *Reaction A* Ester (R′ = $COCH_3$) with excess of ethanolic hydrogen chloride.
† *Reaction B* Alcohol (R′ = H) refluxed with acetic anhydride–pyridine.

[3] A. H. Beckett, A. F. Casy and P. M. Phillips, *J. Med. Pharm. Chem.* **2**, 245 (1960).
[4] A. H. Beckett, A. F. Casy and G. Kirk, *J. Med. Pharm. Chem.* **1**, 37 (1959).

ethanol (serving as nucleophile) giving ethers, or by proton loss giving olefins. The reaction sequence illustrated below is acid catalysed, since the ester (II, Ar = 2′-furyl) salts are stable in ethanol. Such a mechanism is feasible in that the esters (II) are derived from t-alcohols and would thus be expected to form relatively stable carbonium ions. Furthermore, formation of the latter is additionally favoured since a trigonal configuration at C_4 relieves strain resulting from 1:3 diaxial interactions in the most probable conformation of the ester (V). A certain degree of electron release



V

in the alcohol moiety of the ester, a general requirement for alkyl-oxygen fission, must also be necessary in the present series, for not all the esters studied showed the same behaviour as the furyl compounds. It was desirable to obtain information relating the degree of electron release to both promotion of carbonium ion formation and to the fate of the ions once formed. This has been accomplished by comparing the results of the action of ethanolic hydrogen chloride upon a series of esters that bear 4-substituents of graded electron releasing character. (see Table 1, Reaction A).

Facile carbonium ion formation, made evident by the conversion of esters into olefins and ethers on treatment with one mole excess of cold ethanolic hydrogen chloride, is promoted by 4-substituents of high electron releasing power (compds. 1–5). A *p*-dimethylaminophenyl substituent is particularly effective in this respect since, while other alcohols formed unchanged hydrochloride salts under the above conditions, the alcohol (III, Ar = $C_6H_4pN(CH_3)_2$,R = R″ = H) gave the olefin(IV).[5] The corresponding acetoxyester appears to be highly labile even under near-neutral conditions since treatment of the 4-piperidone-lithium aryl complex with acetic anhydride, a process that led to acetoxy esters in all other cases, gave olefin in high yield. For both the *p*-dimethylaminophenyl and *p*-methoxyphenyl compounds conversion to highly conjugated systems (ε_{287} 21,630 and ε_{256} 17,460 respectively) of maximum linear extension must be an important factor in determining carbonium ion fate. Some opposition to attainment of planarity would be expected in olefins derived from compounds 3–5 since all bear aryl substituents that, in comparison with *p*-substituted phenyl, have increased steric requirements adjacent to the aryl carbon atom linked to the rest of the molecule. In these cases, this factor may be responsible, in part, for the observed isolation of ethers, rather than olefins, as major reaction products. The *o*-methoxyphenyl ester (compd. 2) gives olefin on treatment with one mole excess of cold ethanolic hydrogen chloride in spite of the low degree of conjugation in the olefin, made evident by comparison of its ultra-violet absorption spectrum with that of the *p*-methoxy counterpart (*o*-CH_3O, $\varepsilon_{277\cdot5}$ 2,470; *p*-CH_3O ε_{256} 17,460). The corresponding ether, however, would be expected to be a particularly crowded molecule, especially if allowance is made for solvation of the two oxygen atoms in the molecule; ether formation is thus not favoured. Esters substituted with groups of

[5] A. H. Beckett, R. G. Lingard and K. Hewitson, unpublished results.

TABLE 2. REACTIONS OF 4-ACETOXY-4-(2′-FURYL)-3-METHYL-1-PHENETHYLPIPERIDINE WITH ONE MOLE EXCESS OF HYDROGEN CHLORIDE* IN VARIOUS ALCOHOLS

Nucleophile	CH_3OH	CH_3CH_2OH	$CH_3(CH_2)_2OH$	$(CH_3)_2CHOH$	$CH_3(CH_2)_3OH$	$Cl(CH_2)_2OH$	$CH_2{=}CH{-}CH_2OH$
Major reaction product	Ether	Ether	Ether	Olefin	Ether	Ether	Olefin

* Generated from acetyl chloride and the appropriate alcohol.

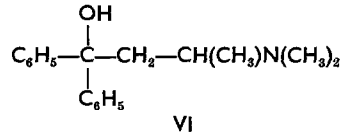
poorer electron releasing power (e.g. compds. 6–8) and of electron withdrawing character (e.g. 2-pyridyl, compd. 9) were stable in excess of cold ethanolic hydrogen chloride. The difference in reactions of the esters 1–5 and 6–9 is reflected in the behaviour of the corresponding alcohols on being heated with acetic anhydride and pyridine (see Table 1, Reaction B); alcohols 6–9 were esterified whereas alcohols 1–5 underwent elimination, a process which is assisted, irrespective of mechanism, by electron releasing groups.

Esters and alcohols (II and III, R = H or CH_3) behaved similarly indicating that the described reactions are not significantly influenced by methyl groups substituted on carbon adjacent to the reaction centre.

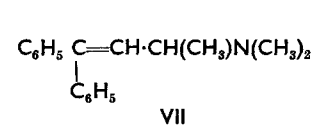
The influence of nature and size of the nucleophile upon carbonium ion fate has been studied in 2-furyl esters (II, R = R′ = CH_3) (see Table 2). Ethers were derived from unbranched alcohols (chain length 1–4 carbon atoms) while the α-branched alcohol, isopropanol, gave olefin (II, Ar = 2-furyl, R = CH_3); the corresponding isopropoxy ether would be a highly crowded molecule and thus its formation is unfavoured. Electronic factors, without effect upon reaction path when due to electronegative β-substituents (cf. results with ethanol and β-chloroethanol) are important in the case of allyl alcohol (which gave olefin) since n-propanol, of similar size, gave the n-propoxyether.

Some investigation has been made of acid conditions necessary to induce carbonium ion reactions in 4-piperidinols and esters that are unchanged by one mole excess of cold alcoholic hydrogen chloride. 4-Phenyl-4-piperidinols and esters were stable in cold methanol containing up to 6 per cent hydrogen chloride (equivalent to approx. 50 mole excess), but at the reflux temperature were converted, at the latter concentration, into methyl ethers. Under the same conditions, 16 per cent sulphuric acid (an equivalent molar proportion) was required to effect this result. A *p*-fluoro atom in the 4-phenyl group did not prevent methyl ether formation under these conditions. Replacement of methanol by ethanol or n-propanol containing 16 per cent sulphuric acid resulted in elimination products indicating that, at high acid concentrations, the small unfavourable steric factors introduced by the latter changes in nucleophile size are sufficient to make proton loss the predominant carbonium ion fate.

In acyclic basic alcohols, elimination is favoured by the presence of two phenyl groups at the carbinol carbon atom even using the smallest nucleophile, methanol, since the alcohol (VI) gives the 1-butene (VII), rather than the methyl ether, on



VI

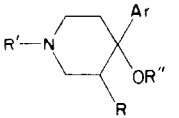


VII

treatment with methanol-sulphuric acid as above. 4-Piperidinols (III, R″ = H) bearing the electron withdrawing 2-pyridyl substituent are stable to strong acid conditions, e.g., a hot acetic-hydrochloric acid mixture which gave the olefin from corresponding 4-phenyl alcohols.[3] 2-Pyridyl acetoxy esters gave alcohols rather than methyl ethers on treatment with methanol-sulphuric acid as described.

1-(2′-Furyl)-cyclohexanol, prepared from cyclohexanone and lithium 2-furyl, contained the corresponding olefin as impurity (from ultra-violet absorption evidence.) It readily gave the olefin upon treatment with acetyl chloride in methylene dichloride.

TABLE 3. 4-ALKOXY-4-ARYL PIPERIDINE HYDROHALIDES



Ar	R	R′	R″	m.p.	Mol. formula	Found			Equiv. wt.	Required			Equiv. wt.	Strongest absorption peak in the 1150–1060cm^{-1} region
						C	H	N		C	H	N		
2-C_4H_3O	H	$(CH_2)_2C_6H_5$	CH_3	214°–216°	$C_{18}H_{24}ClNO_2$	67·4	7·5	4·7	315	67·2	7·5	4·35	322	1081 cm^{-1}
2-C_4H_3O	H	$(CH_2)_2C_6H_5$	C_2H_5	205°–206°	$C_{19}H_{26}ClNO_2$	67·8	7·6	4·4	332	68·0	7·75	4·2	336	1074 cm^{-1}
2-C_4H_3O	CH_3	$(CH_2)_2C_6H_5$	CH_3	168·5°	$C_{19}H_{26}ClNO_2$	67·8	7·6	4·3	332	68·0	7·75	4·2	336	1094 cm^{-1}
2-C_4H_3O	CH_3	$(CH_2)_2C_6H_5$	C_2H_5	181–182°	$C_{20}H_{28}ClNO_2$	68·7	8·25	4·0	349	68·6	8·0	4·0	350	1093 cm^{-1}
2-C_4H_3O	CH_3	$(CH_2)_2C_6H_5$	n-C_3H_7	170°	$C_{21}H_{30}ClNO_2$	68·4	8·25	—	368	69·3	8·25	—	364	1087 cm^{-1}
2-C_4H_3O	CH_3	$(CH_2)_2C_6H_5$	n-C_4H_9	165–166°	$C_{22}H_{32}ClNO_2$	68·8	8·55	3·7	372	69·9	8·5	3·7	378	1091 cm^{-1}
2-C_4H_3O	CH_3	$(CH_2)_2C_6H_5$	$(CH_2)_2Cl$	176–176·5°	$C_{20}H_{27}Cl_2NO_2$	62·8	7·4	3·7	386	62·5	7·0	3·6	384	1107 cm^{-1}
C_6H_5	H	$CH_2C_6H_5$	CH_3	217–217·5°	$C_{19}H_{24}ClNO$	72·0	7·3	4·6	313	71·8	7·6	4·4	318	1075 cm^{-1}
C_6H_5	CH_3	CH_3	CH_3	205–206°	$C_{14}H_{22}BrNO$	56·0	7·4	4·7	292	56·0	7·3	4·7	300	1088 cm^{-1}
C_6H_5	CH_3	$(CH_2)_2C_6H_5$	CH_3	208–210°	$C_{21}H_{28}BrNO$	65·2	7·1	3·5	—	64·6	7·2	3·6	—	1091 cm^{-1}
C_6H_5	H	$(CH_2)_2C_6H_5$	CH_3	219–220°	$C_{20}H_{26}ClNO$	73·0	7·7	—	325	72·4	7·75	—	332	1080 cm^{-1}
p-F-C_6H_4	H	$(CH_2)_2C_6H_5$	CH_3	232·5°	$C_{20}H_{25}BrFNO$	61·0	6·4	3·7	—	60·9	6·3	3·55	—	1073 cm^{-1}

An attempt to isolate the acetoxy ester from the product obtained by decomposing a cyclohexanone-lithium 2-furyl complex with acetic anhydride, resulted in impure olefin. These results demonstrate that 1-(2′-furyl)cyclohexanol and its acetoxy ester are less stable than piperidine counterparts and indicate that the ring nitrogen of the latter probably is an opposing influence to carbonium ion formation. This effect is to be expected since nitrogen, when protonated, has strong electron attracting properties which will influence the 4 position of the piperidine ring.

The ether hydrochlorides reported in this paper have strong absorption bands in the accepted C—O alkyl ether stretching frequency region (1150–1060 cm^{-1})[6] and peaks of highest intensity within this range extend from 1094 to 1071 cm^{-1} (see Table 3); corresponding alcohols absorb weakly in the same region. The thienyl ether (III, Ar = 2-thienyl, R = CH_3, R″ = C_2H_5) has a strong peak at 1092 cm^{-1} while the β-chloroethyl ether [III, Ar = 2-furyl, R = CH_3, R″ = $(CH_2)_2Cl$] has a peak absorption at 1107 cm^{-1}, somewhat outside the above range.

Certain of the ethers, notably III (Ar = 2-furyl, R = CH_3, R″ = C_2H_5), possess significant analgesic activity in mice; pharmacological results will be reported elsewhere.

EXPERIMENTAL*

4-Acetoxy-4-(2′-furyl)-3-methyl-1-(2′-phenethyl)piperidine. (II, Ar = 2-C_4H_3O, R = R′ = CH_3). A mixture of freshly distilled furan (1·7 g) and lithium phenyl in ether, prepared from lithium (0·43 g) and bromobenzene (4·75 g), was refluxed for 2 hr, cooled (ice-bath) and treated with the piperidone (I, R = CH_3, 5·4 g). The mixture was stirred at room temp for 10 min, the ice-bath replaced, acetic anhydride (3 ml) in ether added, and the product, after being stirred for a further 30 min at room temp, poured onto crushed ice and glacial acetic acid (3 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 and the crude ester (5·3 g) crystallized from n-propanol to give II (Ar = 2-C_4H_3O, R = R′ = CH_3), pale yellow plates, m.p. 88·5–89·5°. (Found: C, 72·9; H. 7·7; equiv. wt., 326. $C_{20}H_{25}NO_3$ requires: C, 73·4; H, 7·6%; equiv. wt., 327). The base, treated with acetyl chloride and ethanol (all in molar proportions) in acetone, gave the *hydrochloride*, m.p. 164° after recrystallization from ethanol–methyl ethyl ketone. (Found: C, 65·7; H, 7·2; N, 3·9. $C_{20}H_{26}ClNO_3$ requires: C, 66·0; H, 7·15; N, 3·85%). The latter base and salt both had a strong absorption peak at 1738 cm^{-1}, characteristic of an ester carbonyl group.

4-(2′-Furyl)-3-methyl-1-(2′-phenethyl)-4-propionoxypiperidine (II, Ar = 2-C_4H_3O, R = CH_3, R′ = C_2H_5) *hydrochloride.* m.p. 138–139° from acetone–methyl ethyl ketone, was similarly prepared. (Found: C, 67·1; H, 7·7; N, 4·1. $C_{21}H_{28}ClNO_3$ requires C, 66·8; H, 7·4; N, 4·0%). It had a strong absorption peak at 1736 cm^{-1}.

Reaction of 4-acetoxy-4-(2′-furyl)-3-methyl-1-(2′-phenethyl) piperidine (II, *Ar* = 2-C_4H_3O, *R* = *R′* = CH_3) *with hydrogen chloride* (2 *moles*) *in ethanol.* Acetyl chloride (24 g) in ethanol (100 ml) was added to a stirred, cooled solution of the crude ester (50 g) in ethanol (25 ml) and the product diluted with dry ether. After storage at 5° the corresponding *4-ethoxy ether* (III, Ar = 2-C_4H_3O, R = CH_3, R″ = C_2H_5) *hydrochloride*, m.p. 181°, separated in three crops (total 33·1 g). For analyses see Table 2. 4-(2′-Furyl)-3-methyl-1-(2′-phenethyl)tetrahydropyridine (IV, Ar = 2-C_4H_3O, R = CH_3) hydrochloride (1·2 g), m.p. and mixed m.p. 204°[3], λ max 263·5 mμ, ε 15,300 in H_2O, crystallized from the mother liquors after seeding. (Found: C, 71·2; H, 7·4. Calc. for $C_{18}H_{22}ClNO$: C, 71·15; H, 7·25%).

Reaction of the esters (II, Ar = 2-C_4H_3O, R = H or CH_3, R′ = CH_3) with acetyl chloride (2

* 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 0·02 N perchloric acid in glacial acetic acid using Oracet Blue B as indicator. Salts were crystallized from ethanol-ether or methanol-ether unless otherwise stated.

[6] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules.* Methuen, London (1954).

moles) in methanol, n-propanol, n-butanol and 2-chloroethanol gave the corresponding alkoxy ethers (III) (see Table 2). The ester (II, Ar = 2-C_4H_3O, R = R′ = CH_3, 1·5 g) in isopropanol (6 ml) gave the corresponding crude olefin (1·1 g, λ max 264 mμ, ε 12,900 in H_2O; I.R. spectrum showed trace O—H and C=O with no C—O) m.p. and mixed m.p. 204° after recrystallization from isopropanol–ether. A similar result was obtained using allyl alcohol.

4-(p-*dimethylaminophenyl*)-1-(2′-*phenethyl*)-1,2,3,6-*tetrahydropyridine.* 1-(2′-phenethyl)-4-piperidone (20 g) in benzene (100 ml) was added dropwise to ice-cooled lithium *p*-dimethylaminophenyl in ether, prepared from lithium (1·7 g) and *p*-dimethylaminophenyl bromide (24 g) and the mixture stirred for 10 min at room temp. The ice-bath was replaced, acetic anhydride (13 ml) in ether added and the product, after being stirred for a further 30 min at room temp, poured onto crushed ice and glacial acetic acid (13 ml). The purple solid which separated was washed, the free base liberated with aqueous ammonia, collected and crystallized from ethanol to give 4-(p-*dimethylaminophenyl*)-1-(2′-*phenethyl*)-1,2,3,6-*tetrahydropyridine* as a buff coloured solid m.p. 115–117°, λ max 287 mμ, ε 21,630 in ethanol. (Found: C, 82·3; H, 8·5; equiv. wt., 156. $C_{21}H_{26}N_2$ requires: C, 82·35; H, 8·5%; equiv. wt. 153).

4-(p-*Methoxyphenyl*)-1-(2′-*phenethyl*)-4-*piperidinol and related compounds.* The piperidone (I, R = H, 17·5 g) was added to *p*-methoxyphenyl magnesium bromide in ether, prepared from *p*-bromoanisole (32·3 g) and magnesium (4·3 g), and the product worked up as usual to give the *alcohol* (III, Ar = *p*-$CH_3OC_6H_4$, R = R″ = H), m.p. 134–135° after crystallization from benzene–petroleum ether b.p. 60–80°. (Found: C, 77·7; H, 7·8; equiv. wt. 317. $C_{20}H_{25}NO_2$ requires: C, 77·1; H, 8·1%; equiv. wt. 311). The latter alcohol (3 g) was refluxed for 3 hr with acetic anhydride (4·5 ml) and pyridine (4·5 ml) and the solvents removed under reduced press. The residue, on neutralization with ethanolic hydrogen chloride, gave the olefin (IV, Ar = *p*-$CH_3OC_6H_4$, R = H) *hydrochloride*, m.p. 218–220°, λ_{max} 256 mμ, ε 17,460 in H_2O. (Found: C, 72·7; H, 7·2; N, 4·2; equiv. wt. 331. $C_{20}H_{24}ClNO$ requires: C, 72·8; H, 7·3; N, 4·25%, equiv. wt. 330). The base obtained by treating the above Grignard reagent-piperidone complex with acetic anhydride prior to decomposition, gave, on neutralization with ethanolic hydrogen chloride, the *ester* (II, Ar = *p*-$CH_3OC_6H_4$, R = H, R′ = CH_3) *hydrochloride*, m.p. 198–200°. (Found: C, 67·4; H, 7·05; N, 3·9; equiv. wt. 396. $C_{22}H_{28}ClNO_3$ requires: C, 67·8; H, 7·2; N, 3·6; equiv. wt. 390). The latter, with excess of ethanolic hydrogen chloride gave the corresponding olefin hydrochloride, m.p. and mixed m.p. 217°.

4-(o-*Methoxyphenyl*)-1-(2′-*phenethyl*)-4-*piperidinol and related compounds.* Apart from the use of a lithium aryl (lithium *o*-methoxyphenyl), the alcohol (III, Ar = *o*-$CH_3OC_6H_4$, R = R″ = H) was prepared the same way as its *p*-methoxy counterpart. It gave a *hydrochloride*, m.p. 257°, λ_{max} 270·5 mμ, ε 2090 in H_2O. (Found: C, 69·3; H, 7·5; N, 4·1; equiv. wt. 348. $C_{20}H_{26}ClNO_2$ requires: C, 69·05; H, 7·5; N, 4·0%, equiv. wt., 348). The alcohol, on treatment with acetic anhydride and pyridine, as above, gave the *olefin* (IV, Ar = *o*-$CH_3OC_6H_4$, R = H) *hydrochloride*, m.p. 223°, λ_{max} 277·5 mμ, ε 2470 in H_2O. (Found: C, 72·55; H, 7·5; N, 4·2; equiv. wt., 331. $C_{20}H_{24}ClNO$ requires: C, 72·8; H, 7·3; N, 4·25%; equiv. wt. 330). The *acetoxy ester* (II, Ar = *o*-$CH_3OC_6H_4$, R = H, R′ = CH_3), obtained by treating lithium aryl–piperidone complex with acetic anhydride, gave a *hydrochloride*, m.p. 201°. (Found: C, 67·7; H, 7·2; N, 3·8; equiv. wt. 394. $C_{22}H_{28}ClNO_3$ requires: C, 67·8; H, 7·2; N, 3·6%; equiv. wt. 390). The latter, with excess of ethanolic hydrogen chloride, gave the corresponding olefin hydrochloride, m.p. and mixed m.p. 217°. (Found: equiv. wt., 328. Calc. for $C_{20}H_{24}ClNO$, equiv. wt., 330).

4-*Acetoxy*-1-(2′-*phenethyl*)-4-(2′-*pyridyl*)*piperidine* (II, Ar = 2-C_5H_4N, R = H, R′ = CH_3 *and related compounds.* The piperidone (I, R = H, 25·3 g) was added to lithium 2-pyridyl[7] in ether, prepared from lithium (2·25 g), butyl bromide (18 g) and 2-bromopyridine (18·8 g), the product decomposed with acetic anhydride (26 g) and worked up as usual to give the crude ester (36·5 g). It gave, with excess of ethanolic hydrogen chloride, the *ester* (II, Ar = 2-C_5H_4N, R = H, R′ = CH_3) *hydrochloride*, m.p. 234–235. (Found: C, 60·3; H, 6·9; N, 7·0; equiv. wt., 198. $C_{20}H_{26}Cl_2N_2O_2$ requires: C, 60·45; H, 6·85; N, 7·05%; equiv. wt. 199). A mixture of the latter ester (3 g) dry methanol (75 ml) and conc sulphuric acid (15 ml) was refluxed for 6 hr, cooled and made alkaline with strong aqueous ammonia (30 ml). The ammonium sulphate which separated was filtered and washed with methanol, the combined filtrate and washings concentrated, diluted with water and made alkaline again with aqueous ammonia. The base, isolated by ether extraction, with methanolic hydrogen chloride gave the 2′-*pyridyl alcohol* (III, Ar = 2′-C_5H_4N, R = R″ = H) *hydrochloride*,

[7] A. J. Nunn and K. Schofield, *J. Chem. Soc.* 589 (1952).

m.p. 225° (d). (Found: C, 59·9; H, 7·1; N, 7·65; equiv. wt. 177. $C_{18}H_{24}Cl_2N_2O$ requires: C, 60·6; H, 6·95; N, 7·7%; equiv. wt. 178). The latter alcohol (3 g) was refluxed for 3 hr with propionic anhydride (4·5 ml) and pyridine (4·5 ml) and the solvents removed under reduced press. The residue, with excess of ethanolic hydrogen chloride, gave 1-(2′-*phenethyl*)-4-*propionoxy*-4-(2′-*pyridyl*)*piperidine hydrochloride*, m.p. 217°(d). (Found: C, 61·0; H, 7·0; N, 6·9; equiv. wt., 206. $C_{21}H_{28}Cl_2N_2O_2$ requires: C, 61·3; H, 6·9; N, 6·8%; equiv. wt. 207).

1-*Benzyl*-4-*methoxy*-4-*phenylpiperidine hydrochloride*. A mixture of 1-benzyl-4-phenyl-4-piperidinol (1 g), dry methanol (25 ml) and conc sulphuric acid (5 ml) was refluxed for 6 hr, cooled and made alkaline with strong aqueous ammonia (10–12 ml). The ammonium sulphate which separated was filtered and washed with methanol, the combined filtrate and washings concentrated, diluted with water and made alkaline again with aqueous ammonia. The base, isolated by ether extraction, on treatment with methanolic hydrogen chloride gave 1-*benzyl*-4-*methoxy*-4-*phenylpiperidine hydrochloride*. For m.p. and analyses see Table 2.

The following methyl ether salts, derived from corresponding alcohols, acetoxy or propionoxy esters were prepared similarly: 1,3 *dimethyl*-4-*methoxy*-4-*phenylpiperidine hydrobromide*, 4-*methoxy*-3-*methyl*-1-(2′-*phenethyl*)-4-*phenylpiperidine hydrobromide*, 4-*methoxy*-1-(2′-*phenethyl*)-4-*phenylpiperidine hydrochloride*, and 4-(p′-*fluorophenyl*)-4-*methoxy*-1-(2′-*phenethyl*)*piperidine hydrobromide*. For analyses and m.ps. see Table 2.

1-Benzyl-4-phenyl-4-piperidinol (1 g), treated with conc sulphuric acid (5 ml) and ethanol (25 ml) as above, gave 1-*benzyl*-4-*phenyl*-1,2,3,6-*tetrahydropyridine hydrochloride* m.p. 203–203·5°, λ_{max} 243 mμ ε 14,010 in H_2O. (Found: C, 75·9; H, 6·9; equiv. wt. 284. $C_{18}H_{20}NCl$ requires: C, 75·7; H, 7·0%; equiv. wt., 286).

Similarly α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride gave 1,3-*dimethyl*-4-*phenyltetrahydropyridine hydrochloride* m.p. 187–188° from ethanol–ether, λ_{max} 236 mμ ε 11,440 in H_2O. (Found: C, 69·5; H, 8·1. $C_{13}H_{18}NCl$ requires: C, 69·8; H, 8·05%). α-3-Methyl-1-(2′-phenethyl)-4-phenyl-4-propionoxy hydrochloride (1 g), treated with conc sulphuric acid (5 ml) and n-propanol (25 ml) as above gave 3-*methyl*-1-(2′-*phenethyl*)-4-*phenyltetrahydropyridine hydrobromide* m.p. 224–225° from n-propanol–ether, λ_{max} 237 mμ, ε 9,230 in H_2O. (Found: C, 66·6; H, 6·9; equiv. wt. 363. $C_{20}H_{24}N$ Br requires: C, 67·0; H, 6·7%; equiv. wt. 358).

3-Dimethylamino-1,1-diphenylbutan-1-ol(VI; 1 g), treated with conc sulphuric acid (5 ml) and methanol (25 ml) as above, gave 3-dimethylamino-1,1-diphenylbut-1-ene hydrochloride m.p. 162–163° from methanol–ether, λmax 250 mμ, ε 13,850 in H_2O (Kjaer and Peterson[8] give m.p. 161°).

2′-*Furylcyclohexane derivatives*. Cyclohexanone (10·8 g) was added to lithium 2-furyl in ether, prepared from bromobenzene (18·8 g), lithium (1·9 g) and furan (8·2 g) and the product poured onto ice and extracted with ether. After drying (Na_2SO_4), the solvent was removed and the residue distilled to give crude 1-(2′-furyl)cyclohexanol (7·2 g) b.p. 83°/1·5 mm, λ_{max} 265·5 mμ ε 3,200 in ethanol; its I.R. spectrum showed bonded O—H near 3400 cm^{-1}. (Found: C, 73·3; H, 8·1. Calc. for $C_{10}H_{14}O_2$. C, 72·2; H, 8·5%). Acetyl chloride (6 g) was added to the crude alcohol (2·5 g) in methylene dichloride (15 ml) and the mixture refluxed. The solid which separated was recrystallized from benzene–petroleum ether b.p. 60–80° to give 1-(2′-*furyl*)*cyclohexene*, m.p. 268°, λ_{max} 227 mμ, ε 9360 in cyclohexane. (Found: C, 81·0; H, 8·2. $C_{10}H_{12}O$ requires: C, 81·0; H, 8·2%). Treatment of the cyclohexanone-lithium 2-furyl complex with acetic anhydride prior to decomposition gave crude 1-(2′-furyl)cyclohexene, b.p. 66°/1·6 mm, λ_{max} 265 mμ, ε 9320 in ethanol. (Found: C, 79·25; H, 8·4. Calc. for $C_{10}H_{12}O$: C, 81·2; H, 8·2%).

Infra-red absorption measurements. Spectra were measured on a Grubb Parsons' GS 2A spectrophotometer with a grating 1200 l.p.i. Determinations were carried out in Nujol and calibration was accurate to ±2 cm^{-1}.

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[8] A. C. Kjaer and P. V. Petersen, *Acta Chem. Scand.* **5**, 1145 (1951).