Alkyl–Oxygen Heterolyses in 4-Arylpiperidin-4-ols and Related Esters. Part III.[1] Some 4-Alkoxy-4-arylpiperidines

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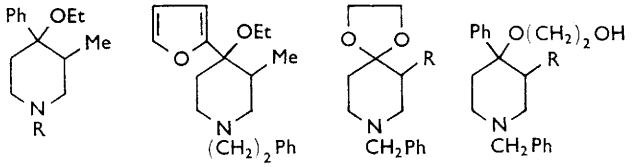
The acid-catalysed etherification of some 4-arylpiperidin-4-ols (and esters) is reported and the greater reactivity of *cis*, compared with *trans* (3-Me,4-Ph) 3-methyl analogues demonstrated. 4-Alkoxypiperidine syntheses of the Williamson type and by the ring opening of 4-piperidone ethylene ketals with phenylmagnesium bromide are also described.

THE reactions described in this Paper were directed towards the synthesis of 4-ethoxy-3-methyl-4-phenylpiperidines (I), compounds of pharmacological interest in view of the marked analgesic potency of 4-ethoxy-4-(2-furyl)-3-methyl-1-(2-phenethyl)piperidine (II). Analogues of the alkoxypiperidine (I) lacking a 3-methyl substituent have previously been obtained from 4-arylpiperidin-4-ols (and esters) but the methods used were inapplicable to the corresponding 3-methyl derivatives.[1b] It was important to obtain the particular ethers (I) because the potent analgesic (II) loses most of its activity when the 3-methyl group is absent.[2]



(I) (II) (III) (IV)

Williamson-type syntheses fail when applied to basic 4-phenylpiperidin-4-ols,[1b] but give ethers when the sodium salt of 4-phenyl-1-toluene-*p*-sulphonylpiperidin-4-ol is alkylated[3] (1-phenylacetyl-4-phenylpiperidin-4-ol, another non-basic derivative studied in this respect, was recovered after treatment with sodamide followed by ethyl iodide). The sodio-derivative of 3-methyl-4-phenyl-1-toluene-*p*-suphonylpiperidin-4-ol also gave an ether when treated with methyl iodide but would not react with ethyl iodide or allyl bromide. Another route, based upon the ring opening of cyclohexanone ethylene ketal with Grignard reagents,[4] involved treating a 1-benzyl-4-piperidone ethylene ketal (III) with phenylmagnesium bromide to give a 4-(2-hydroxyethoxy)-derivative (IV), followed by removal of the latter's terminal hydroxyl group. The ethylene ketal (III; R = H) hydrochloride formed in good yield when a mixture of 1-benzyl-4-piperidone and ethylene glycol was acidified; the corresponding 3-methylketal (III; R = Me) did not form under these mild conditions (a 3-methyl group is known to impede ketal formation in 4-piperidones[5]) but was obtained by heating a benzene solution of the reactants in the presence of a slight excess of toluene-*p*-sulphonic acid. The ketal (III; R = H), heated with an excess of phenylmagnesium bromide in benzene for 16 hr., gave the 4-(2-hydroxyethoxy)-derivative (IV; R = H) in 50% yield † but the 3-methylketal (III; R = Me) failed to react with either phenylmagnesium bromide or phenyl-lithium under similar conditions.

Analogues of compound (I) lacking a 3-methyl substituent can be obtained by heating 4-arylpiperidin-4-ols and their corresponding esters with ethanolic or methanolic sulphuric acid.[1b] This method also yields 4-methoxy-3-methyl derivatives when 3-methyl-4-phenyl-4-propionyloxypiperidines are heated with methanol–sulphuric acid; the same esters, however, eliminate to give tetrahydropyridine derivatives when heated with ethanol–sulphuric acid [1b] (these reactions are considered to proceed *via* carbonium ions generated by acid-catalysed alkyl-oxygen fission [1a]).

All attempts to prepare the 4-ethoxy-3-methylpiperidines (I), so far described, have involved the use of the α-(*trans*-3-Me,4-Ph) diastereoisomers of 4-phenyl-3-methylpiperidin-4-ols and esters [(V) favoured conformation [6]] and the failure of methods successful in

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† The open chain analogue (the diethyl ketal) was unaffected by the same reagent.

[1] (*a*) Part I, A. F. Casy, A. H. Beckett, and N. A. Armstrong, *Tetrahedron*, 1961, **16**, 85; (*b*) Part II, A. F. Casy and N. A. Armstrong, *J. Med. Chem.*, 1965, **8**, 57.

[2] A. F. Casy, A. H. Beckett, G. H. Hall, and D. K. Vallance, *J. Med. Pharm. Chem.*, 1961, **4**, 535.

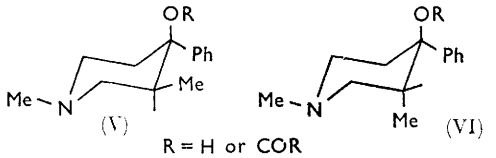
[3] P. A. J. Janssen, D.P. 97,424/1961.

[4] R. A. Mallory, S. Rovinski, and I. Scheer, *Proc. Chem. Soc.*, 1964, 416.

[5] A. F. Casy, *Experientia*, 1964, **20**, 437.

[6] A. F. Casy, *Tetrahedron*, 1966, **22**, 2711.

the case of piperidinols without 3-substituents, shows that an equatorial 3-methyl group opposes ether formation whether this occurs by a displacement reaction

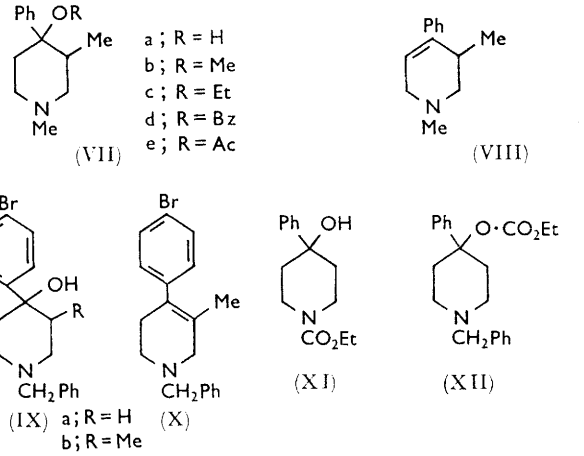


R = H or COR

or *via* alkyl–oxygen heterolysis. In the α-isomers, opposition is probably a result of the gauche interaction between the 3-methyl (equatorial) group and the C-4 non-aromatic substituent (axial). This steric factor may affect the acid-catalysed reactions both by retarding carbonium ion formation (assuming this to proceed *via* a complex of increased bulk) and by influencing the fate of a carbonium ion once it is formed (proton loss, leading to alkenes, should be favoured at the expense of nucleophilic attack, leading to ethers, since the latter course may regenerate the gauche interaction). In corresponding β-(*cis*-3-Me,4-Ph) diastereoisomers, interaction between the 3-methyl group and the C-4 oxygen function is greatly reduced in the favoured conformation (VI) [6] and the more ready etherification of β-isomers, anticipated from this fact, has been confirmed in the present work by a comparative study of the reactivity of *cis*–*trans* pairs towards alcohol–sulphuric acid mixtures. Total product compositions were estimated from proton magnetic resonance (p.m.r.) spectral evidence (in mixtures, signals characteristic of individual components were well separated) and major components isolated as hydrochloride salts. The α-piperidinol (VIIa) was recovered after being heated for 6 hr. with 16% sulphuric acid in either methanol or ethanol, whereas the β-isomer, under the same conditions, gave the 4-methoxypiperidine (VIIb) and the alkene (VIII) (minor product) with methanol; the alkene was the exclusive product when ethanol was used. At a lower acid concentration (8%), the β-piperidinol (VIIa) in ethanol gave the 4-ethoxy-derivative (VIIc) in moderate yield with a trace of alkene. The α-4-benzoyloxy-ester (VIId) was unaffected by a 6 hr. reflux period with 8% sulphuric acid in ethanol (elimination occurred when the acid concentration was 13%), whereas the β-ester (VIId) gave a mixture consisting chiefly of equal parts of the 4-ethoxy-derivative (VIIc) and the alkene (VIII) together with traces of the original ester. The β-acetoxy-ester (VIIe) was converted to the ethyl ether (VIIc) almost exclusively after a 6 hr. reflux period with 8% sulphuric acid in ethanol, this method proving the best route to 4-ethoxy-3-methyl derivatives.* β-1-Benzyl-3-methyl 4-phenyl-4-propionyloxypiperidine also gave the corresponding 4-ethoxy-derivative, together with some elimination product, in the same reaction.

* Evidence that ethers derived from β-piperidinols and esters (VII) retain the *cis*-3-Me,4-Ph configuration will be given elsewhere.

Because of evidence that a *p*-halogen substituent in the 4-phenyl group of a 4-acetoxypiperidine facilitates acid-catalysed etherification,[1b] use of 4-*p*-bromophenylpiperidines as substrates was investigated. The 4-piperidinols (IX) were obtained by treating *p*-bromophenyl-lithium with a 1-benzyl-4-piperidone. The 4-*p*-bromophenylpiperidinol (IXa), unaffected by 8% sulphuric acid in ethanol, gave 4-alkoxy-derivatives when heated with 16% sulphuric acid in ethanol or methanol. These results indicate that an aromatic *p*-bromo-substituent in 4-phenylpiperidin-4-ols favours ether, rather than alkene formation since the corresponding non-halogen derivative (IXa, Br replaced by H)



is dehydrated by hot 16% sulphuric acid in ethanol.[1b] The 4-*p*-bromophenyl-3-methylpiperidinol (IXb) was stable in hot methanol containing 20% sulphuric acid, but gave the alkene (X) when the acid concentration was raised to 25%.

Ether exchange was also investigated as a route to 4-ethoxypiperidines. In trial experiments, 1-benzyl-4-methoxy-4-phenylpiperidine was heated with 8% sulphuric acid in ethanol; the product (isolated as a hydrochloride) was a mixture of the corresponding 4-ethoxy-derivative (40%), the elimination product (20—30%), and starting material. When the experiment was repeated using 12% sulphuric acid, 1-benzyl-4-phenyl-1,2,5,6-tetrahydropyridine was the exclusive product.

Wright and Brabander [8] report that 1-benzylpiperidine is readily debenzylated by ethyl chloroformate, and the action of the same reagent upon 1-benzyl-4-phenylpiperidin-4-ol was studied in this work as a possible route to a non-basic 4-phenylpiperidinol and, after hydrolysis of the intermediate carbamate, to 4-phenylpiperidin-4-ol. This route was not pursued, however, since the 1-benzyl-4-ethylcarbonate (XII) was formed in addition to the desired carbamate (XI).

EXPERIMENTAL †

3-Methyl-4-phenyl-1-toluene-p-sulphonylpiperidin-4-ol and its Reactions.—Toluene-*p*-sulphonyl chloride (13 g.) in

† Sulphuric acid refers to the concentrated acid and i.r. data to Nujol mulls; see Table, footnote *a*, for p.m.r. details.

isobutyl methyl ketone (50 ml.) was added to a stirred suspension of 3-methyl-4-phenylpiperidin-4-ol [9] (10 g.) and anhydrous sodium carbonate (17 g.) in the same solvent (150 ml.). The mixture was heated under reflux for 16 hr. then cooled and stirred with water (100 ml.) to dissolve inorganic salts. The remaining solid was collected and recrystallised from chloroform to give the 1-*toluene*-p-*sulphonylpiperidinol* (8 g.), m. p. 182—184° (Found: C, 65·4; H, 6·9; N, 4·1. $C_{19}H_{23}NO_3S$ requires C, 66·1; H, 6·7; N, 4·1%). Methyl iodide (5·1 g.) was added to a cooled mixture of sodamide (0·41 g.), the 1-toluene-*p*-sulphonylpiperidinol (3 g.), and toluene (20 ml.) which had previously been heated under reflux until evolution of ammonia ceased (2 hr.). After a further reflux period of 16 hr. the product was stirred with water (10 ml.) and the insoluble residue collected and recrystallised from acetone–chloroform to give 4-*methoxy*-3-*methyl*-4-*phenyl*-1-*toluene*-p-*sulphonylpiperidine* (3·6 g.), m. p. 200—203° (Found: C, 66·7; H, 6·7; N, 3·7. $C_{20}H_{25}NO_3S$ requires C, 66·85; H, 6·95; N, 3·9%) $\nu_{max.}$ 1070 cm.$^{-1}$ (C–O–C).

4-*Phenyl*-1-*phenylacetylpiperidin*-4-*ol*.— Phenylacetyl chloride (14·9 g.) was added to a solution of 4-phenylpiperidin-4-ol (26·9 g.), potassium carbonate (12·8 g.) in methanol (110 ml.), and water (25 ml.). The product was stirred for 3 hr. at room temperature, and then diluted with water (300 ml.). An ethereal extract of the mixture was washed with dilute hydrochloric acid, dried (Na_2SO_4), and evaporated to give the 1-*phenylacetylpiperidinol* (8 g.), m. p. 90—93° (from acetone) (Found: C, 77·2; H, 7·4; N, 4·9. $C_{19}H_{21}NO_2$ requires C, 77·3; H, 7·1; N, 4·75%); $\nu_{max.}$ 3350 (OH) and 1600 cm.$^{-1}$ (C=O).

1-*Benzyl*-4-*piperidone Ethylene Ketals* (III) *and Their Reactions*.—Acetyl chloride (8 ml., 0·08 mole) was added dropwise to a cooled solution of 1-benzyl-4-piperidone (7 g., 0·04 mole) in ethylene glycol (25 ml.). After storage at 5°, the *ethylene ketal* (III; R = H) *hydrochloride* (5 g.), m. p. 248° (from ethanol) separated (Found: C, 62·0; H, 7·4; N, 5·0. $C_{14}H_{20}ClNO_2$ requires C, 62·3; H, 7·4; N, 5·2%). 1-Benzyl-3-methyl-4-piperidone was recovered when treated in this way. A mixture of toluene-*p*-sulphonic acid (10·3 g.), ethylene glycol (12·2 g.), and benzene (120 ml.) was heated under reflux for 2 hr. in a flask fitted with a Dean–Stark adaptor, to remove water. 1-Benzyl-3-methyl-4-piperidone (10 g.) in benzene (25 ml.) was then added and the product heated under reflux for a further 6 hr. when the calculated amount of water (0·9 ml.) had separated. The cooled product was made alkaline with aqueous sodium hydroxide, extracted with benzene, and the dried (Na_2SO_4) extract evaporated. The residue (11 g.), with ethanolic hydrogen chloride, gave the *ethylene ketal* (III; R = Me) *hydrochloride* (11 g.), m. p. 172—173° (from ethanol) (Found: C, 63·4; H, 7·5; N, 4·95. $C_{15}H_{22}ClNO_2$ requires C, 63·5; H, 7·75; N, 4·9%). The ethylene ketal (III; R = H) (23 g.) in benzene (80 ml.) was added to a stirred solution of phenylmagnesium bromide prepared from bromobenzene (31 g.), magnesium (6 g.), and ether (100 ml.). The ether was then evaporated and the remaining benzene solution heated under reflux for 16 hr., cooled, and poured onto an ice–ammonium chloride mixture. The free base (31·5 g.), isolated as usual, with ethanolic hydrogen chloride gave the 4-(2-*hydroxyethoxy*)*piperidine* (IV; R = H) *hydrochloride* (18 g.), m. p. 200° from ethanol–

P.m.r. characteristics of reaction products obtained by treating 1,3-dimethyl-4-phenylpiperidinols and related compounds with alcoholic sulphuric acid (6 hr. reflux period)

No.	Substrate	Reactants	Sample	P.m.r. characteristics [a] Ether	Alkene [b]	Substrate
1	β-(VIIa)	16% H_2SO_4–MeOH	Total base	173 [c] (OMe) 136 [c] (NMe) 44 [d] (sec.-Me) (major) [f]	352 [e] (vinylic H) 142 [c] (NMe) 60 [d] (sec.-Me) (minor)	
2			Pure HCl	175 [c] } O- and 173 [c] } N-Me 61 [d] (sec.-Me)		
3	β-(VIIa)	8% H_2SO_4–ethanol	Total base	65 [e] (OCH_2Me) 42 [d] (sec.-Me) (major)	350 [e] (vinylic H) (trace)	46 [d] (sec.-Me) [g] (minor)
4	β-(VIId)	8% H_2SO_4–ethanol	Total base [i]	136 [c] (NMe) 65 [c] (OCH_2Me) 42·5 [d] (sec.-Me) (major)	352 [h] (vinylic H) 141 [c] (NMe) 60 [d] (sec.-Me) (minor)	482 [h] (aryl H) [j] 46 [d] (sec.-Me) (minor)
5			Pure HCl	176 [c] (NMe) 67 [e] (OCH_2Me) 60 [c] (sec.-Me)		
6	β(VIIc)	8% H_2SO_4–ethanol	Total base	136 [b] (NMe) 65 [e] (OCH_2Me) 43 [d] (sec.-Me) (major)	351 [h] (vinylic H) 60 [d] (sec.-Me) (trace)	45 [d] (sec.-Me) (trace)
7	β-1-Benzyl-3-methyl-4-phenyl-4-propionoxypiperidine hydrochloride	8% H_2SO_4–ethanol	Total base	65 [e] (OCH_2Me) 43·5 [d] (sec.-Me) (major)	354 [h] (vinylic H)	47 [d] (sec.-Me) [k]
8	1-Benzyl-4-methoxy-4-phenylpiperidine hydrochloride	8% H_2SO_4–ethanol	HCl (m. p. 175—205°)	68 [e] (OCH_2Me) (40%)	357 [h] (vinylic H) (trace)	179 [c] (OMe) (60%)

[a] Chemical shifts in c./sec. from tetramethylsilane (60 Mc./sec.), coupling constants in c./sec., solvent deuteriochloroform. Ref. 9. [c] Singlet. [d] Doublet $J = 7$ approx. [e] Triplet $J = 7$ approx. [f] Proportions assessed from integral data. [g] Ref. 6. [h] Centre of multiplet. [i] ν_{max} 1710 cm.$^{-1}$ (C:O). [j] Aryl protons *ortho* to CO of ester (VIId) COPh group. [k] Ref. 7.

[7] A. F. Casey, M. A. Iorio, and P. Pocha, *J. Chem. Soc.* (*C*), 1967, 942.

[8] W. B. Wright, jun., and H. J. Brabander, *J. Org. Chem.*, 1961, **26**, 4057.

[9] A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef, *Tetrahedron*, 1965, **21**, 3387.

ether (Found: C, 68·7; H, 7·4%; Equiv., 344. $C_{20}H_{26}ClNO_2$ requires C, 69·1; H, 7·5%; Equiv., 347); $\nu_{max.}$ 3350 (OH) and 1080 cm.$^{-1}$ (C–O–C).

Reactions of α- and β-1,3-Dimethyl-4-phenylpiperidin-4-ols and Related Compounds with Alcoholic Sulphuric Acid.—New compounds used in this work were the β-*4-acetoxypiperidine* (VIIe) *hydrochloride*, m. p. 210—212° (from ethanol) (Found: C, 63·3; H, 8·0; N, 4·5. $C_{15}H_{22}ClNO_2$ requires C, 63·5; H, 7·8; N, 4·9%), the α-*4-benzoyloxypiperidine* (VIId) *hydrochloride*, m. p. 194—195° (Found: C, 67·4; H, 7·3; N, 4·1. $C_{20}H_{24}ClNO_2,0{\cdot}5H_2O$ requires C, 67·7; H, 7·05; N, 3·95%), $\nu_{max.}$ 3400 cm.$^{-1}$ (H_2O), and the β-*isomer* (VIId) *hydrochloride*, m. p. 214—215° (from ethanol–ether) (Found: C, 69·3; H, 7·15; N, 4·6. $C_{20}H_{24}ClNO_2$ requires C, 69·5; H, 6·95; N, 4·1%), obtained by treating the piperidinol (VIIa) (5 g.) in benzene (80 ml.) with a 2 mole excess of the appropriate acyl chloride and heating the product under reflux for 5 hr. when the ester hydrochloride separated. A solution of the β-piperidinol (VIIa) (4 g.) in methanol (50 ml.) and sulphuric acid (10 ml.) was heated under reflux for 6 hr., cooled and neutralised with aqueous ammonia. The precipitated ammonium sulphate was collected, washed, and the combined filtrate and washings concentrated. The residue was shaken with chloroform and aqueous ammonia and the organic phase dried (Na_2SO_4) and evaporated. The residue (Table, No. 1) with ethanolic hydrogen chloride, gave the *4-methoxypiperidine* (VIIb) *hydrochloride* (2·5 g.), m. p. 223—226° (decomp.) (from ethanol–ether) (Found: C, 65·5; H, 8·3; N, 5·5. $C_{14}H_{22}ClNO$ requires C, 65·75; H, 8·6; N, 5·5%), $\nu_{max.}$ 1085 cm.$^{-1}$ (C–O–C) (p.m.r., Table, No. 2). The β-piperidinol, treated with ethanol–sulphuric acid (16% v/v) as above gave the tetrahydropyridine (VIII) hydrochloride, m. p. and mixed m.p. 196°.[9] See Table, No. 3, for p.m.r. characteristics of the total base derived from β-(VIIa) after a 6 hr. reflux period in ethanol–sulphuric acid (8%). The total base (Table, No. 4) derived from the β-4-benzoyloxypiperidine (VIId) hydrochloride (9 g.) after a 6 hr. reflux period with sulphuric acid (10 ml.) and ethanol (100 ml.), was acidified with ethanolic hydrogen chloride and fractionally crystallised to give the alkene (VIII) hydrochloride (0·7 g.), m. p. and mixed m. p. 193°, and the *4-ethoxypiperidine* (VIIc) *hydrochloride* (3 g.), m. p. 216—217° (decomp.) (from ethanol–ether) (Found: C, 66·7; H, 8·9; N, 5·6. $C_{15}H_{24}ClNO$ requires C, 66·8; H, 8·9; N, 5·2%), $\nu_{max.}$ 1080 cm.$^{-1}$ (C–O–C) (p.m.r. Table, No. 5). Mixtures of similar compositions were obtained from β-form of compound (VIId) after reflux periods of 41 hr. (5% sulphuric acid) and 67 hr. (8% sulphuric acid) (no ester in latter case). The α-ester (VIId) was recovered after 6 hr. in refluxing ethanol–sulphuric acid (8%) and gave the alkene (VIII) hydrochloride, m. p. and mixed m. p. 193°, with 13% sulphuric acid. The β-4-acetoxypiperidine (VIIe) hydrochloride (1 g.) with ethanol (25 ml.) and sulphuric acid (2·5 ml.), gave the 4-ethoxypiperidine (VIIc) hydrochloride (0·7 g.), m. p. and mixed m. p. 218° (decomp.), after a 6 hr. reflux period (total base, Table, No. 6). β-1-Benzyl-3-methyl-4-phenyl-4-propionoxypiperidine hydrochloride[7] (1 g.), treated as above, gave a total base (Table, No. 7) from which was isolated 1-benzyl-3-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (0·2 g.), m. p. 244° (lit.,[9] 246—247°) and *1-benzyl-4-ethoxy-3-methyl-4-phenylpiperidine hydrochloride* (0·5 g.), m. p. 203—205° (decomp.) (from ethanol–ether) Found: C, 72·5; H, 7·9; N, 3·8. $C_{21}H_{28}ClNO$ requires C, 72·95; H, 8·1; N, 4·05%), $\nu_{max.}$ 1080 cm.$^{-1}$ (C–O–C). 1-Benzyl-4-methoxy-4-phenylpiperidine hydrochloride[1a] (1 g.), treated as above gave a hydrochloride, m. p. 175—205° (decomp.) which was a mixture of the starting material and the corresponding 4-ethoxy-derivative and elimination product (Table, No. 8); when sulphuric acid (4 ml.) in ethanol (28 ml.) was used, 1-benzyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (0·7 g.), m. p. 203° (lit.,[1a] m. p. 203—203·5°) was isolated.

1-Benzyl-4-p-bromophenylpiperidin-4-ols (IX) *and Their Reactions.*—*p*-Dibromobenzene (52·4 g.) in ether (250 ml.) was added to a stirred solution of butyl-lithium in ether (100 ml.) prepared from 1-bromobutane (30·4 g.) and lithium (3·1 g.) at −40° (bath temp.). After the mixture had been stirred for a further 2 hr. at this temperature, 1-benzyl-4-piperidone (21 g.) in ether (25 ml.) was added (−40° maintained during addition) and the product stirred for 2 hr. at room temperature and then poured onto crushed ice and acetic acid (40 ml.). The aqueous phase was separated and made alkaline with aqueous ammonia when the piperidinol (IXa) (20 g.), m. p. 85—88°, precipitated. It gave a *hydrochloride*, m. p. 227° (from ethanol) (Found: C, 56·4; H, 5·4%; Equiv., 382. $C_{18}H_{21}BrClNO$ requires C, 56·5; H, 5·5%; Equiv., 383); $\nu_{max.}$ 3400 cm.$^{-1}$ (OH). Impure piperidinol (19 g.) from the mother-liquors gave a further quantity of the hydrochloride (19·5 g.), m. p. and mixed m. p. 227°. The same reaction using 1-benzyl-3-methyl-4-piperidone (22·5 g.) (reaction mixture stirred for 15 hr. at room temperature), gave the impure piperidinol (IXb) (20 g.) as an oil which formed a *hydrochloride* (18 g.), m. p. 213—219° (from ethanol) (Found: C, 57·6; H, 5·9; N, 3·5. $C_{19}H_{23}BrClNO$ requires C, 57·5; H, 5·8; N, 3·5%), $\nu_{max.}$ 3400 cm.$^{-1}$ (OH). The piperidinol (IXa) (1 g.) treated with methanol (25 ml.) and sulphuric acid (5 ml.) in the manner described, gave *1-benzyl-4-p-bromophenyl-4-methoxypiperidine hydrochloride* (0·5 g.), m. p. 228° (from methanol) (Found: C, 57·95; H, 5·8; N, 3·8. $C_{19}H_{23}BrClNO$ requires C, 57·5; H, 5·8; N, 3·5%), $\nu_{max.}$ 1080 cm.$^{-1}$ (C–O–C); OMe p.m.r. signal, 170 (singlet) c./sec. When ethanol was used in the same reaction, 1-benzyl-4-*p*-bromophenyl-4-ethoxypiperidine was obtained. It gave a *hydrochloride*, m. p. 228—232° (from ethanol) (Found: C, 58·2; H, 5·7; N, 3·65. $C_{20}H_{25}BrClNO$ requires C, 58·5; H, 6·1; N, 3·4%), $\nu_{max.}$ 1080 cm.$^{-1}$ (C–O–C); $OCH_2\mathit{Me}$ p.m.r. signal 68 c./sec. (triplet $J = 7$). The piperidinol (IXb) was unaffected by methanol containing 20% sulphuric acid and gave a product chiefly composed of the alkene (X) when the acid concentration was 25%; p.m.r. signals (c./sec.) of total base 439 main peak of multiplet (aryl protons), 217 singlet (CH_2Ph), 92 broad singlet (t-Me).

Reaction of 1-Benzyl-4-phenylpiperidin-4-ol with Ethyl Chloroformate.—Ethyl chloroformate (8 g.) was added to 1-benzyl-4-phenylpiperidin-4-ol (10 g.) in benzene (40 ml.) and the mixture heated under reflux for 18 hr. Ether (80 ml.) and 2N-sodium hydroxide (40 ml.) was added to redissolve the solid which separated on cooling, and the organic phase separated, washed with dilute hydrochloric acid, dried (Na_2SO_4) and evaporated. The residual solid (8·5 g.) was recrystallised from ethanol to give *1-ethoxycarbonyl-4-phenylpiperidin-4-ol*, m. p. 154° (Found: C, 67·5; H, 7·5. $C_{14}H_{19}NO_3$ requires C, 67·8; H, 7·6%), $\nu_{max.}$ 3400 (OH) and 1670 cm.$^{-1}$ (amide C:O); p.m.r. signals (c./sec.) 446, 439 main peaks of multiplet (5 aryl protons), 250, quartet $J = 7$ (CO_2CH_2Me), 76 triplet $J = 7$ ($CO_2CH_2\mathit{Me}$). The acid washings deposited a solid (2·5 g.) which was recrystallised from ethanol to give the *1-benzyl-*

4-*ethylcarbonate* (XII) ***hydrochloride***, m. p. 180—181° (Found: C, 64·0; H, 7·45; N, 3·6. $C_{21}H_{26}ClNO_3,H_2O$ requires C, 64·0; H, 7·1; N, 3·6%), $\nu_{max.}$ 3300 (H_2O) and 1720 cm.$^{-1}$ (CO); p.m.r. signals (c./sec.): 442 main peak of multiplet (10 aryl protons), 255 singlet (CH_2Ph), 244 quartet $J = 7$ (OCO_2CH_2Me), 73 triplet $J = 7$ (OCO_2CH_2Me).

The p.m.r. spectra were recorded on a Varian A-60 instrument with tetramethylsilane as internal standard; we thank Miss J. Lovenack, School of Pharmacy, University of London, for carrying out these measurements.

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