226. *Derivatives of 4-Ethoxycarbonyl- and 4-Hydroxy-4-phenylpiperidine.*

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By condensation of 3-aryloxy-1 : 2-epoxypropanes with the bases (I; R = H) and (I*a*; R = H), the corresponding 3-aryloxy-2-hydroxypropyl derivatives were readily prepared. 4-Hydroxy-4-phenylpiperidine (I*b*; R = R″ = H) likewise yielded the *N*-(2-hydroxy-3-phenoxypropyl) derivative, but all attempts to convert this compound into the 4-monopropionate proved unsuccessful.

During studies of aryloxyhydroxypropyl amines we found that attachment of the 3-aryloxy-2-hydroxypropyl residue (II) on to the nitrogen atom of cyclic amines such as 1 : 2 : 3 : 6-tetrahydropyridine leads to compounds with significant analgesic activity.[1] In seeking to obtain more potent analgesics, we have condensed a series of 3-alkoxy- and 3-aryloxy-propane 1 : 2-epoxides with 4-ethoxycarbonyl-4-phenylpiperidine [2] (I; R = H), obtaining the compounds listed in the Table. Their biological study, for which we are indebted to Dr. A. David and Dr. C. Bianchi (B.D.H. Biological Department, Godalming, Surrey) revealed that many of them were highly potent analgesics in the tail-pinch technique in mice. Similar types (I) in which the nitrogen substituent (R) is phenethyl,[3] α-hydroxyphenethyl,[3] *p*-aminophenethyl,[4,5] 2-morpholinoethyl and 2-(1 : 2 : 3 : 6-tetrahydropyridino)ethyl [6] were reported by other groups of workers while the present work was in progress. In addition 4-phenyl-4-propionylpiperidine (I*a*; R = H), readily prepared by reaction between 4-cyano-4-phenyl-1-toluene-*p*-sulphonylpiperidine [2] and ethylmagnesium bromide, was condensed with 1 : 2-epoxy-3-phenoxypropane to give the related 1-(2-hydroxy-3-phenoxypropyl)-4-phenyl-4-propionylpiperidine [I*a*; R = $Ph{\cdot}O{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2$]. Reaction between 1 : 5-dichloro-3-cyano-3-phenylpentane and 2-hydroxy-3-*o*-tolyloxypropylamine furnished the related 4-cyano-1-(2-hydroxy-3-*o*-tolyloxypropyl)-4-phenylpiperidine (hydrochloride).

Attention was next directed to the preparation of analogous derivatives of 4-hydroxy-4-phenylpiperidine [7-10] (I*b*; R = R″ = H), which were required as their 4-propionates. The parent base (I*b*; R = R″ = H), was initially obtained by a variation of the method originally described by Hartough *et al.*,[11] and more fully investigated by Schmidle and Mansfield,[12] in which α-methylstyrene is condensed with aqueous formaldehyde and ammonium chloride to yield tetrahydro-6-methyl-6-phenyl-1 : 3-oxazine (III; R = H), which passes on acid hydrolysis into the required piperidinol. For larger-scale work its preparation by direct aqueous hydrolysis of 4-bromo-4-phenylpiperidine [13] proved more convenient. Condensation of 4-hydroxy-4-phenylpiperidine (I*b*; R = R″ = H) with 1 : 2-epoxy-3-phenoxy- and 1 : 2-epoxy-3-*o*-tolyloxy-propane furnished the corresponding 4-hydroxy-1-(2-hydroxy-3-aryloxypropyl)-4-phenylpiperidine [I*b*; R″ = H, R = $Ph{\cdot}O{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2$ or $Me{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2$]. The phenoxy-diol [I*b*; R″ = H, R = $Ph{\cdot}O{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2$] was also prepared in low overall yield by condensation of 2-hydroxy-3-phenoxypropylamine hydrochloride with α-methylstyrene and formaldehyde

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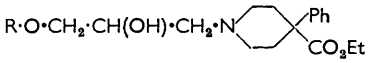
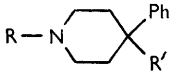


R	Base or salt *	M. p.	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
H	B	77—79° †	$C_{17}H_{25}O_4N$	66·8	8·2	4·6		66·4	8·2	4·6	
	B,HCl	151—152	$C_{17}H_{26}O_4NCl$			4·2	10·5			4·1	10·3
	B,P *	145—146	$C_{23}H_{28}O_{11}N_4$			10·2				10·4	
Et	B,HCl	141—143	$C_{19}H_{30}O_4NCl$	61·2	7·6	3·8	9·9	61·3	8·1	3·8	9·6
Bu^n	B,HCl	154	$C_{21}H_{34}O_4NCl$	63·2	8·6	3·8		63·0	8·6	3·5	
	B,P	89—91	$C_{27}H_{37}O_{11}N_4$	54·3	5·9	9·1		54·6	6·3	9·4	
Ph	B	111	$C_{23}H_{29}O_4N$	72·2	7·7	3·8		72·0	7·6	3·7	
	B,HCl	178—179 / 146—148	$C_{23}H_{30}O_4NCl$	65·6 / 65·7	7·3 / 7·3	3·2 / 3·4	8·4 / 8·5	65·8	7·2	3·3	8·5
	B,HBr	163—164	$C_{23}H_{30}O_4NBr$	59·3	6·2	2·9	17·4 (Br)	59·5	6·5	3·0	17·2 (Br)
	B,P	152	$C_{29}H_{32}O_{11}N_4$	56·7	5·4	9·4		56·8	5·3	9·2	
	B,H_2SO_4	181 / 264	$C_{23}H_{31}O_8NS$	57·7 / 57·6	6·5 / 6·6	3·1 / 3·2		57·4	6·5	2·9	
	B,H_3PO_4	174—175	$C_{23}H_{32}O_8NP$	57·3	6·8	3·0		57·4	6·7	2·9	
	B,I	131—133	$C_{25}H_{35}O_8NS$	58·7	7·0	2·9		58·9	6·9	2·8	
	B,S	166	$C_{23}H_{32}O_7N_2S$	57·7	7·1	6·0	6·8 (S)	57·5	6·7	5·8	6·7 (S)
	B,L	131—133	$C_{26}H_{35}O_7N$	66·0	7·4	2·8		65·9	7·5	3·0	
	B,G	153—154	$C_{26}H_{38}O_{10}NP$	56·3	7·1	2·4		56·2	6·9	2·5	
	B,T	137—138	$C_{60}H_{64}O_{14}N_2$	65·4	7·0	2·7		65·5	7·0	3·1	
	B,M	150—151	$C_{24}H_{33}O_7N_5$	60·5	6·9	3·0		60·1	7·0	2·9	
	B,H_3PO_2	116—118	$C_{23}H_{32}O_6NP,\frac{1}{2}H_2O$	60·5	6·8	3·1		60·2	7·2	3·1	
o-Tolyl	B	81—83	$C_{24}H_{31}O_4N$	72·3	7·7	3·4		72·5	7·9	3·5	
	B,HCl	188—189	$C_{24}H_{32}O_4NCl$	66·2	7·7	3·3	8·4	66·4	7·4	3·2	8·2
	B,P	164—166	$C_{30}H_{34}O_{11}N_4$	57·4	5·2	8·7		57·5	5·5	8·9	
m-Tolyl	B	80—81	$C_{24}H_{31}O_4N$	72·1	8·0	3·5		72·5	7·9	3·5	
	B,HCl	157—159	$C_{24}H_{32}O_4NCl$	66·1	7·1	3·0	8·4	66·4	7·4	3·2	8·2
	B,P	151—152	$C_{30}H_{34}O_{11}N_4$	57·5	5·4	9·0		57·5	5·5	8·9	
	B,G	139—145	$C_{27}H_{40}O_{10}NP$	56·7	6·9	2·5		56·9	7·1	2·5	
p-Tolyl	B	111—113	$C_{24}H_{31}O_4N$	73·1	7·9	3·4		72·5	7·9	3·5	
	B,HCl	152—154	$C_{24}H_{32}O_4NCl$	65·8	7·3	3·0	8·4	66·4	7·4	3·2	8·2
	B,P	168—169	$C_{30}H_{34}O_{11}N_4$	57·2	5·2	8·8		57·5	5·5	8·9	
o-C_6H_4·OMe	B	89—90	$C_{24}H_{31}O_5N$	70·2	7·8	3·7		69·7	7·6	3·4	
	B,HCl	147—148	$C_{24}H_{32}O_5NCl$	63·6	7·1	3·3	7·7	64·0	7·2	3·1	7·9
	B,P	159—160	$C_{30}H_{34}O_{12}N_4$			8·4				8·7	
o-C_6H_4F	B	80—81	$C_{23}H_{28}O_4NF$	68·5	7·1			68·8	7·0		
	B,HCl	158—159	$C_{23}H_{29}O_4NClF$	63·2	7·0	3·4	8·5	63·1	6·7	3·2	8·1
	B,P	132—134	$C_{29}H_{31}O_{11}N_4F$			9·1				8·9	
o-C_6H_4Cl	B	81—83	$C_{23}H_{28}O_4NCl$	66·6	6·8	3·5	8·4	66·1	6·8	3·4	8·5
	B,HCl	171—172	$C_{23}H_{29}O_4NCl_2$	61·3	6·5	3·1		60·8	6·4	3·1	
	B,P	153—155	$C_{29}H_{31}O_{11}N_4Cl$	53·9	4·7	8·7	5·2	53·8	4·8	8·7	5·5
m-C_6H_4Cl	B	89—90	$C_{23}H_{28}O_4NCl$	66·2	6·7	3·4	8·6	66·1	6·8	3·4	8·5
	B,HCl	162—163	$C_{23}H_{29}O_4NCl_2$	60·6	6·4	3·1	15·5	60·8	6·4	3·1	15·6
	B,P	139—140	$C_{29}H_{31}O_{11}N_4Cl$	53·6	4·8	8·6	5·4	53·8	4·8	8·7	5·5
	B,G	129—133	$C_{26}H_{37}O_{10}NClP$	53·0	6·4	2·2	6·3	52·9	6·3	2·4	6·0
p-C_6H_4Cl	B	103—104	$C_{23}H_{28}O_4NCl$	66·1	6·5	3·7	8·7	66·1	6·8	3·4	8·5
	B,HCl	165—166	$C_{23}H_{29}O_4NCl_2$	60·6	6·3	3·3	15·8	60·8	6·4	3·1	15·6
	B,P	148	$C_{29}H_{31}O_{11}N_4Cl$			8·7	5·5			8·7	5·5
	B,G	135—138	$C_{26}H_{37}O_{10}NClP$	52·1	6·2	2·6	6·2	52·9	6·3	2·4	6·0
o-C_6H_4·C_3H_5	B,HCl	204—206(d)	$C_{26}H_{34}O_4NCl$	67·9	7·4	3·1	7·6	67·9	7·5	3·0	7·7
	B,P	139—140	$C_{32}H_{36}O_{11}N_4$	58·8	5·4			58·9	5·6		
	B,G	125—127	$C_{29}H_{42}O_{10}NP$	58·6	7·1	2·3		58·5	7·1	2·4	
p-C_6H_4·NHAc	B	144—145	$C_{25}H_{32}O_5N_2$	68·6	7·6	6·2		68·1	7·3	6·4	
p-C_6H_4·NH_2	B,HCl	*ca.* 230(d)	$C_{23}H_{32}O_4N_2Cl_2,\frac{1}{2}H_2O$	57·4	6·8	5·7		57·5	6·9	5·8	
p-C_6H_4·CO_2Et	B	86—88	$C_{26}H_{33}O_6N$	68·7	7·0	2·7		68·5	7·3	3·1	
	B,HCl	176—178	$C_{26}H_{34}O_6NCl$	63·2	7·1	2·9	7·3	63·4	7·0	2·8	7·2
	B,P	160—161	$C_{32}H_{36}O_{13}N_4$	56·3	5·3	7·9		56·1	5·3	8·2	
$CHPh_2$	B,HCl	171—172	$C_{30}H_{36}O_4NCl$	70·6	7·0	2·9	7·1	70·1	7·1	2·7	7·0
	B,P	128—130	$C_{36}H_{38}O_{11}N_4$	61·6	5·6	8·4		61·5	5·5	8·0	
*cyclo*Hexyl	B,HCl	164—166	$C_{23}H_{36}O_4NCl$	64·9	8·7	3·3	8·2	64·8	8·5	3·3	8·3
RO: Δ³-Piperidino	B,HCl	181—185(d)	$C_{22}H_{34}O_3N_2Cl_2,H_2O$	57·1	7·3	6·0	15·6	57·0	7·8	6·0	15·3
RO: Δ³-Piperidino	B,P	182—183	$C_{34}H_{38}O_{17}N_8,H_2O$	48·1	4·4	13·1		48·1	4·7	13·2	
RO: Morpholino	B	70—72	$C_{21}H_{32}O_4N_2$	67·1	8·5	7·7		67·0	8·6	7·4	
RO: Morpholino	B,HCl	206	$C_{21}H_{34}O_4NCl_2,\frac{1}{2}H_2O$	55·0	7·8	6·0		55·0	7·7	6·1	
RO: Morpholino	B,P	181—182	$C_{33}H_{38}O_{18}N_8$	47·3	4·5	13·2		47·5	4·6	13·4	

* B = Base; B,P = Picrate; B,G = α-Glycerophosphate; B,I = Isethionate; B,S = Sulphamate; B,L = Lactate; B,T = Tartrate; B,M = Methanesulphonate. † B. p. 194°/0·3 mm.

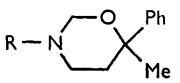
to yield tetrahydro-3-(2-hydroxy-3-phenoxypropyl)-6-methyl-6-phenyl-1 : 3-oxazine [III; R = Ph·O·CH_2·CH(OH)·CH_2], followed by hot acid hydrolysis.

Acylation of the foregoing diols with propionic anhydride–concentrated sulphuric acid furnished the dipropionates. Their selective hydrolysis to the 4-monopropionates, however, could not be achieved; *e.g.*, treatment with 1 equiv. of ethanolic sodium hydroxide



(I ; R′ = CO_2Et)
(I*a* ; R′ = COEt)
(I*b* ; R′ = OR″)

Ar·O·CH_2·CH(OH)·CH_2· (II)



(III)

at room temperature or with 1 equiv. of anhydrous sodium carbonate in methanol under reflux furnished only the respective diols.

In view of these discouraging results we turned to the preparation of 4-phenyl-4-propionoxypiperidine (I*b*; R = H, R″ = COEt), intending to condense this intermediate with the appropriate 3-aryloxy-1 : 2-epoxypropane.

Treatment of the hydrochloride (from I*b*; R = R″ = H) with acetic or propionic anhydride at 100° led to recovery of unchanged material. Enforced acylation in the presence of a trace of concentrated sulphuric acid resulted in the formation of 1-acetyl- and 1-propionyl-1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine, respectively.

Debenzylation of 1-benzyl-4-phenyl-4-propionoxypiperidine (I*b*; R = CH_2Ph, R″ = COEt) was next examined. Catalytic hydrogenation with 1 mol. of hydrogen furnished unchanged material (32%), 4-phenylpiperidine (38%), and smaller amounts of 1-benzyl-4-phenylpiperidine, 4-hydroxy-4-phenyl-1-propionylpiperidine, and the propionic acid salt of 4-hydroxy-4-phenylpiperidine. The facile loss of the propionate group during catalytic hydrogenation was unexpected, but probably arises from the relation between the 4-hydroxyl and 4-phenyl groups of (I*b*; R″ = H) which constituted a substituted benzyl alcohol. In support thereof we find that catalytic hydrogenation of 1-benzyl-4-hydroxy-4-phenylpiperidine (I*b*; R = CH_2Ph, R″ = H) gives the expected 4-hydroxy-4-phenylpiperidine as sole identifiable product. In the expectation that the diphenylmethyl group would be removed more readily than benzyl, the condensation of 4-hydroxy-4-phenylpiperidine with diphenylmethyl bromide was examined, but only 1-diphenylmethyl-1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine was obtained. No better results attended attempts to convert 4-bromo-4-phenylpiperidine into the 4-propionoxy-derivative with sodium propionate, dehydrohalogenation with concomitant *N*-acylation taking place with formation of 4-hydroxy-4-phenyl-1-propionylpiperidine. Production of the last compound presumably involves the formation of a 4-propionoxy-intermediate followed by $O \longrightarrow N$ migration of the acyl residue.

In a further approach to the required 4-monopropionates, 2-diphenylmethoxy-3-phenoxypropyl chloride and bromide were prepared by reaction of the 2-hydroxy-3-phenoxypropyl halides with diphenylmethanol in the presence of toluene-*p*-sulphonic acid as catalyst.[14] Their condensation with 4-hydroxy-4-phenylpiperidine yielded the required intermediate [I*b*; R = Ph·O·CH_2·CH(O·CHPh_2)·CH_2, R″ = H] which resisted propionylation, however, presumably through steric hindrance introduced by the diphenylmethyl residue. The tetrahydropyranyl ether of 2-hydroxy-3-phenoxypropyl chloride was cleaved during condensation with the piperidinol. Reaction of 3-phenoxy-2-propionoxypropyl chloride with 2 mols. of the piperidinol in 2-ethoxyethanol gave the propionyl derivative (I*b*; R = COEt, R″ = H) and the base [I*b*; R = Ph·O·CH_2·CH(OH)·CH_2, R″ = H].

[14] Petrow, Stephenson, and Thomas, *J. Pharm. Pharmacol.*, 1956, **8**, 666.

Experimental

M. p.s are uncorrected.

The methods employed for the preparation of the compounds listed in the Table are illustrated by the following four examples.

1-(2 : 3-*Epoxypropyl*)-1 : 2 : 3 : 6-*tetrahydropyridine*.—2 : 3-Epoxypropyl chloride (92·5 g.) was added slowly with stirring at $<30°$ to 1 : 2 : 3 : 6-tetrahydropyridine (83 g.) in water (400 ml.). After being stirred at 25—30° for 4 hr. the mixture was cooled to 0° and treated slowly with sodium hydroxide (42 g.) in water (60 ml.); it was then saturated with salt and extracted with chloroform. After removal of the chloroform the residual oil was distilled under reduced pressure to yield the *product*, b. p. 34°/0·3 mm. (Found: C, 68·8; H, 9·5; N, 9·7. $C_8H_{13}ON$ requires C, 69·0; H, 9·4; N, 10·1%).

4-*Ethoxycarbonyl*-1-[2-*hydroxy*-3-(1 : 2 : 3 : 6-*tetrahydropyridino*)*propyl*]-4-*phenylpiperidine Dihydrochloride Hydrate*.—The foregoing epoxide (5·8 g.) and 4-ethoxycarbonyl-4-phenylpiperidine (9·35 g.) in light petroleum (20 ml., b. p. 60—80°) were heated under reflux for 2 hr. After removal of the solvent the residual base was converted in ethanol–ether into the *dihydrochloride* which crystallised from the same solvent in needles.

4-*Ethoxycarbonyl*-4-*phenyl*-1-(3-cyclo*hexyloxy*-2-*hydroxypropyl*)*piperidine Hydrochloride*.—A solution of 3-*cyclo*hexyloxy-2-hydroxypropyl chloride (9·65 g.) and 4-ethoxycarbonyl-4-phenylpiperidine (11·7 g.) in ethanol (25 ml.) was treated with anhydrous sodium carbonate (3 g.), and the mixture heated under reflux for 10 hr. The base, isolated by dilution with water and extraction with chloroform, was converted directly into the *hydrochloride* which separated from ethanol–ether in prisms.

4-*Ethoxycarbonyl*-1-(2-*hydroxy*-3-m-*tolyloxypropyl*)-4-*phenylpiperidine*.—A solution of 1 : 2-epoxy-3-*m*-tolyloxypropane (8·2 g.) and 4-ethoxycarbonyl-4-phenylpiperidine (11·7 g.) in light petroleum (15 ml., b. p. 60—80°) was heated under reflux for 1 hr. The *product* separated in fluffy needles on cooling and was crystallised from aqueous ethanol. The *hydrochloride* separated from ethanol–ether in minute needles.

1-(2-*Acetoxy*-3-*phenoxypropyl*)-4-*ethoxycarbonyl*-4-*phenylpiperidine hydrochloride*, m. p. 143° after crystallisation from benzene (Found: C, 65·6; H, 6·9; N, 2·9; Cl, 8·0. $C_{25}H_{32}O_5NCl$ requires C, 65·0; H, 7·0; N, 3·0; Cl, 7·7%), was obtained by reaction of 4-ethoxycarbonyl-1-(2-hydroxy-3-phenoxypropyl)-4-phenylpiperidine (8 g.) with acetyl chloride (1·8 g.) in benzene (40 ml.) under reflux for 1½ hr.

1-(2-*Benzoyloxy*-3-*phenoxypropyl*)-4-*ethoxycarbonyl*-4-*phenylpiperidine hydrochloride* had m. p. 172—176° (Found: C, 68·3; H, 7·0; N, 2·7; Cl, 6·6. $C_{30}H_{34}O_5NCl$ requires C, 68·7; H, 6·6; N, 2·7; Cl, 6·8%) after crystallisation from ethanol–ether. The *base*, m. p. 86—88° (Found: N, 3·1. $C_{30}H_{33}O_5N$ requires N, 2·9%), crystallised from light petroleum (b. p. 60—80°).

4-*Ethoxycarbonyl*-1-(2-*hydroxy*-3-*phenoxypropyl*)-4-*phenylpiperidine* N-*oxide hydrochloride*, m. p. 170° (decomp.) (Found: C, 63·4; H, 6·9; N, 3·5. $C_{23}H_{30}O_5NCl$ requires C, 63·3; H, 7·0; N, 3·2%) after crystallisation from ethanol–ether, was prepared by the action of peracetic acid solution on the base at 80° for 1 hr.

4-*Ethoxycarbonyl*-1-(2-*hydroxy*-2-*methyl*-3-*phenoxypropyl*)-4-*phenylpiperidine hydrochloride*, needles, m. p. 171—172° (Found: C, 66·7; H, 7·3; N, 3·4; Cl, 8·3. $C_{24}H_{32}O_4NCl$ requires C, 66·4; H, 7·4; N, 3·2; Cl, 8·2%) after crystallisation from ethanol, was prepared by condensation of 1 : 2-epoxy-2-methyl-3-phenoxypropane (8·2 g.) with 4-ethoxycarbonyl-4-phenylpiperidine (11·65 g.) in light petroleum (25 ml., b. p. 60—80°) under reflux for 2 hr., followed by treatment of the product with hydrogen chloride. The *picrate* had m. p. 109—111° (Found: C, 57·4; H, 5·7; N, 8·6. $C_{30}H_{34}O_{11}N_4$ requires C, 57·5; H, 5·5; N, 8·9%) after crystallisation from ethyl acetate–light petroleum (b. p. 60—80°).

4-*Ethoxycarbonyl*-1-(2-*hydroxy*-2-*methyl*-3-o-*tolyloxypropyl*)-4-*phenylpiperidine hydrochloride* separated from ethyl acetate in needles, m. p. 177° (Found: C, 66·8; H, 8·0; N, 3·2; Cl, 7·9. $C_{25}H_{34}O_4NCl$ requires C, 67·0; H, 7·7; N, 3·1; Cl, 7·9%). The *picrate* had m. p. 130—131° (Found: C, 58·0; H, 5·6; N, 9·2. $C_{31}H_{36}O_{11}N_4$ requires C, 58·1; H, 5·7; N, 8·8%) after crystallisation from ethyl acetate–light petroleum (b. p. 40—60°).

4-*Phenyl*-4-*propionyl*-1-*toluene*-p-*sulphonylpiperidine*.—To a stirred solution of ethylmagnesium bromide [prepared from magnesium (3 g.) and ethyl bromide (15 g.) in ether (20 ml.) and anisole (20 ml.)] a solution of 4-cyano-4-phenyl-1-toluene-*p*-sulphonylpiperidine (16 g.) in

anisole (90 ml.) was added slowly, and reaction completed by heating on the steam-bath for 2 hr. After cooling in ice, water was added, the mixture was acidified with hydrochloric acid, and the solvents were removed by steam distillation. The residual product, after drying at 60°, had m. p. 84—89° (yield 86%). Its purification proved difficult and the material was directly hydrolysed as indicated below.

4-*Phenyl*-4-*propionylpiperidine Hydrochloride.*—The foregoing compound (44 g.) was heated under reflux for 2 hr. with concentrated sulphuric acid (70 ml.) and water (40 ml.). The mixture was diluted with water and extracted with benzene to remove non-basic material. The aqueous phase was made alkaline with aqueous sodium hydroxide, and the product isolated with benzene, and converted into the *hydrochloride* (32 g.), m. p. 210° (Found: C, 66·4; H, 7·8; N, 5·5; Cl, 14·0. $C_{14}H_{20}ONCl$ requires C, 66·2; H, 7·9; N, 5·5; Cl, 14·0%) after crystallisation from ethanol–ether.

1-(2-*Hydroxy*-3-*phenoxypropyl*)-4-*phenyl*-4-*propionylpiperidine Hydrochloride.*—The foregoing hydrochloride (10 g.) was converted into the base, which was treated in benzene (20 ml.) with 1 : 2-epoxy-3-phenoxypropane (8 g.). The mixture was heated on the steam-bath for 3 hr., cooled, and treated with a slight excess of hydrogen chloride. The *hydrochloride* had m. p. 187° (Found: C, 68·3; H, 7·1; N, 3·5; Cl, 8·8. $C_{23}H_{30}O_3NCl$ requires C, 68·4; H, 7·5; N, 3·5; Cl, 8·8%) after crystallisation from ethanol–ether.

4-*Cyano*-1-(2-*hydroxy*-3-o-*tolyloxypropyl*)-4-*phenylpiperidine Hydrochloride.*—A mixture of 1 : 5-dichloro-3-cyano-3-phenylpentane (5 g.) and 2-hydroxy-3-*o*-tolyloxypropylamine (10 g.) in hexanol (100 ml.) was heated under reflux for 2 hr., the solvent removed by steam-distillation, and the residue acidified with concentrated hydrochloric acid. The *product* which separated had m. p. 226° (Found: C, 68·2; H, 7·3; N, 7·1; Cl, 9·1. $C_{22}H_{27}O_2N_2Cl$ requires C, 68·3; H, 7·0; N, 7·2; Cl, 9·2%) after crystallisation from ethanol–ether.

4-*Hydroxy*-4-*phenylpiperidine.*[12]—(*a*) The following improved procedure was adopted: A solution of tetrahydro-6-methyl-6-phenyl-1 : 3-oxazine (147 g.) in 18·5% hydrochloric acid (177 g.) was heated on the steam-bath for 30 min. and set aside overnight. Heating was continued for 2½ hr., and the mixture again left overnight. It was then poured into water (580 ml.) and made alkaline with excess of 50% sodium hydroxide solution, and the separated oil isolated with toluene. After concentration of the toluene extract, the product (37 g.) separated on cooling and was collected. Concentration of the filtrate followed by distillation of the residue at 0·2 mm. yielded 62 g. of unchanged material (b. p. 120°) and a higher-boiling fraction which yielded a further 6·3 g. of the piperidinol. Crystallisation of the combined crops from toluene yielded the product (37·35 g.), m. p. 158—160°.

(*b*) 1 : 2 : 3 : 6-Tetrahydro-4-phenylpyridine (50 g.) was added dropwise with stirring to 50% w/v hydrobromic acid in acetic acid (150 ml.), below 25°. The paste was diluted with acetic acid (100 ml.), and stirring continued for 30 min. The solid 4-*bromo*-4-*phenylpiperidine* hydrobromide (84 g.) was collected, washed with a little acetic acid and with ether and crystallised from ethanol–ether, forming fawn needles, m. p. 209—211° (Found: C, 40·9; H, 4·8; N, 4·4; Br, 49·5. $C_{11}H_{15}NBr_2$ requires C, 41·1; H, 4·7; N, 4·4; Br, 49·8%).

The foregoing hydrobromide (3·21 g.) in water (40 ml.) was heated on the steam-bath for 1 hr., and the solution made alkaline with 50% sodium hydroxide solution to yield 4-hydroxy-4-phenylpiperidine (90%), m. p. 158—160°. The hydrochloride crystallised from ethanol–ether in needles, m. p. 223—224° (decomp.). The *oxalate* separated from ethanol in cubes, m. p. 202—203° (decomp.) (Found: C, 58·7; H, 6·5. $C_{13}H_{17}O_5N$ requires C, 58·5; H, 6·4%).

4-*Hydroxy*-1-(2-*hydroxy*-3-*phenoxypropyl*)-4-*phenylpiperidine.*—(*a*) A solution of 4-hydroxy-4-phenylpiperidine (10·62 g.) in acetone (100 ml.) was treated with 1 : 2-epoxy-3-phenoxypropane (9·0 g.), and the solution heated on the steam-bath for 2 hr. After removal of solvent, the residual solid was crystallised from ethanol to yield the *product* (18·5 g.) in prisms, m. p. 120—122°, b. p. 232°/0·5 mm. (Found: C, 73·6; H, 7·6; N, 4·1. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·7; N, 4·3%). The *hydrochloride* had m. p. 138—140° (Found: C, 66·2; H, 7·4; N, 3·4; Cl, 10·2. $C_{20}H_{26}O_3NCl$ requires C, 66·0; H, 7·2; N, 3·4; Cl, 9·8%) after crystallisation from ethanol–ether.

(*b*) A mixture of 2-hydroxy-3-phenoxypropylamine hydrochloride (38·0 g., 0·187 mole) and α-methylstyrene (22 g., 0·187 mole) was heated to 60° with vigorous stirring, 37% formaldehyde solution (63·6 g., 0·783 mole) added, and the mixture heated at 85° for 5 hr. It was then cooled, made alkaline with excess of 50% aqueous sodium hydroxide, and the oil isolated with toluene, and distilled at 0·2 mm. to yield a fraction (24 g.), b. p. 196—230°. This was dissolved in dry

ether and slowly deposited 4-hydroxy-1-(2-hydroxy-3-phenoxypropyl)-4-phenylpiperidine (3·2 g.), m. p. 120—121°, which was removed. The fraction soluble in ether was distilled at 0·5 mm. to yield tetrahydro-3-(2-hydroxy-3-phenoxypropyl)-6-methyl-6-phenyl-1 : 3-oxazine, b. p. 210—220°. It formed a *hydrochloride*, m. p. 156—157° (Found: C, 65·9; H, 7·2. $C_{21}H_{28}O_3NCl$ requires C, 66·0; H, 7·2%) strongly depressed on admixture with the hydrochloride of the foregoing piperidinol (m. p. 138—140°).

The oxazine base (5·5 g., 0·0168 mole) was dissolved in 18·5% hydrochloric acid (3·6 g., 0·0168 mole), and the solution heated on the steam-bath for 7 hr. It was stored at room temperature for 3 days, reheated for 3 hr., then cooled and made alkaline with excess of 50% aqueous sodium hydroxide. The oil which separated was isolated with ether and distilled at 0·25 mm. Unchanged oxazine (2·8 g., 51%) was obtained, b. p. 204—212°, together with 4-hydroxy-1-(2-hydroxy-3-phenoxypropyl)-4-phenylpiperidine (1·5 g., 27%), b. p. 227—231°, m. p. 118—120° after crystallisation from ethanol.

1-(3-*Phenoxy*-2-*propionoxypropyl*)-4-*phenyl*-4-*propionoxypiperidine*.—The foregoing *diol* (10 g.), dissolved in propionic anhydride (100 ml.), was treated with concentrated sulphuric acid (4 drops), and the mixture heated on the steam-bath for 3 hr. After removal of propionic anhydride at reduced pressure, the residue was partitioned between ether and aqueous sodium carbonate. The dried ethereal extract was treated with a slight excess of hydrogen chloride. The resultant *hydrochloride* separated from acetone in shining plates, m. p. 129—131° (Found: C, 65·4; H, 7·2; N, 3·3. $C_{26}H_{34}O_5NCl$ requires C, 65·6; H, 7·2; N, 2·9%).

4-*Hydroxy*-1-(2-*hydroxy*-3-*o*-*tolyloxypropyl*)-4-*phenylpiperidine* separated from aqueous ethanol in prisms, m. p. 131° (Found: C, 73·6; H, 7·8; N, 4·2. $C_{21}H_{27}O_3N$ requires C, 73·9; H, 7·9; N, 4·1%). The *hydrochloride* crystallised from ethanol–ether in small plates, m. p. 175—177° (Found: N, 3·8; Cl, 9·4. $C_{21}H_{28}O_3NCl$ requires N, 3·7; Cl, 9·4%).

The *dipropionate hydrochloride* formed small plates, m. p. 175—176° (Found: C, 65·7; H, 7·6; N, 2·8; Cl, 7·0. $C_{27}H_{36}O_5NCl$ requires C, 66·2; H, 7·4; N, 2·9; Cl, 7·2%), from acetone. It (2 g., 0·004 mole) was converted into the base, which was dissolved in methanol (10 ml.), anhydrous sodium carbonate (0·2 g., 0·002 mole) added, and the mixture heated under reflux for 3 hr. and filtered, the filtrate evaporated to dryness, and the residue crystallised from ethanol to yield the original diol (0·5 g.), m. p. 130—132°.

1-*Benzyl*-4-*hydroxy*-4-*phenylpiperidine* (cf. [10,12]).—To a solution of 4-hydroxy-4-phenylpiperidine (17·7 g.) in *tert.*-butyl alcohol (100 ml.) was added a solution of sodium *tert.*-butoxide [from sodium (2·3 g.) in *tert.*-butyl alcohol (100 ml.)], followed by benzyl chloride (12·95 g.), and the mixture heated under reflux for 1 hr. It was diluted with methanol and filtered, the filtrate evaporated to dryness under reduced pressure, and the residue crystallised from light petroleum (b. p. 60—80°). The product (22·5 g., 82%) had m. p. 107—109°, b. p. 176°/0·1 mm. Its hydrochloride formed needles, m. p. 224—225° (Found: C, 71·2; H, 7·4; N, 4·6; Cl, 11·6. Calc. for $C_{18}H_{22}ONCl$: C, 71·2; H, 7·3; N, 4·6; Cl, 11·7%), from ethanol–ether.

1-Benzyl-4-phenyl-4-propionoxypiperidine hydrochloride,[10] m. p. 189—190° (Found: C, 70·3; H, 7·2; N, 4·1; Cl, 10·1. Calc. for $C_{21}H_{26}O_2NCl$: C, 70·1; H, 7·2; N, 3·9; Cl, 9·8%) after crystallisation from ethanol–ether, was prepared by treatment of the foregoing base (9 g.) with propionic anhydride (90 ml.) containing concentrated sulphuric acid (7 drops) on the steam-bath for 6 hr. The *base* had b. p. 174—177°/0·4 mm.

Hydrogenation of 1-*Benzyl*-4-*phenyl*-4-*propionoxypiperidine*.—(*a*) A solution of the base (22 g.) in ethanol (200 ml.) was hydrogenated at room temperature by using 5% palladium–charcoal catalyst (5 g.), and the reaction stopped when 1 mol. of hydrogen had been absorbed. The product was distilled at 0·5 mm. A small quantity (*ca.* 0·4 g.) of propionic acid was collected, followed by fractions: (i) 4·2 g., b. p. 94—102°; (ii) 2·3 g., b. p. 120—150°; (iii) 4·2 g., b. p. 150—170°; and (iv) 7·15 g., b. p. 170—182°. Fraction (i) solidified on cooling and proved to be 4-phenylpiperidine.[15] It formed a *picrate*, m. p. 162—163° (Found: N, 14·6. $C_{17}H_{18}O_7N_4$ requires N, 14·4%) from ethanol. An authentic specimen of 4-phenylpiperidine, prepared by hydrogenation of 1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine in ethanol with palladised charcoal at room temperature, had b. p. 133—135°/11 mm., m. p. 57—58°, and formed a picrate, m. p. 161—163°, identical with that described above. Fractions (ii) and (iii) were combined and on trituration with ether yielded 4-*hydroxy*-4-*phenylpiperidine propionate* (1·5 g.), m. p. 163—165° (Found: C, 66·9; H, 8·5; N, 5·5. $C_{14}H_{21}O_3N$ requires C, 66·9; H, 8·4; N, 5·6%) after crystallisation from ethyl acetate, identical with synthetic material. After removal of this salt

[15] Adkins, Kuick, Farlow, and Wojcik, *J. Amer. Chem. Soc.*, 1934, **56**, 2427.

the residual oil was distilled at 0·4 mm. to yield 1-benzyl-4-phenylpiperidine [16] (1·9 g.), b. p. 151°, n_D^{22} 1·5692, which formed a *picrate*, m. p. 151—152° (Found: C, 60·1; H, 5·0; N, 11·7. $C_{24}H_{24}O_7N_4$ requires C, 60·0; H, 5·0; N, 11·7%). The m. p. was not depressed on admixture with an authentic sample. Fraction (iv), on treatment with ether, yielded 4-*hydroxy*-4-*phenyl*-1-*propionylpiperidine* (1·6 g.), which separated from ethyl acetate in prisms, m. p. 173—174° (Found: C, 71·6; H, 7·7; N, 6·2. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·0%). An authentic sample was prepared for comparison by heating the propionate of 4-hydroxy-4-phenylpiperidine for 20 min. at 240—250° and crystallising the residue from ethyl acetate.

(*b*) The foregoing hydrogenation was repeated, but after removal of the catalyst and the alcohol, the residue was extracted with ether and the extract washed with aqueous sodium carbonate to remove free propionic acid. The dried ethereal extract deposited 4-hydroxy-4-phenylpiperidine (50·5%), m. p. 158—160°, on cooling. Concentration of the filtrate followed by distillation of the residual oil at 1·2 mm. yielded 4-phenylpiperidine (9%), b. p. 98—100°, together with starting material (29%), b. p. 188—192°.

Hydrogenation of 1-*Benzyl*-4-*hydroxy*-4-*phenylpiperidine.*—A solution of this piperidine (16 g.) in ethanol (150 ml.) was hydrogenated at 60° by using 5% palladium–charcoal (5 g.). The slow reaction was stopped when 0·95 mol. of hydrogen had been absorbed. After removal of catalyst and solvent, the residue crystallised from toluene to yield prisms of 4-hydroxy-4-phenylpiperidine (8 g.), m. p. 158—160°.

1 : 2 : 3 : 6-*Tetrahydro*-4-*phenyl*-1-*propionylpyridine.*—To a solution of 4-hydroxy-4-phenylpiperidine hydrochloride (10·65 g.) in propionic anhydride (200 ml.) was added concentrated sulphuric acid (10 drops), and the mixture heated on the steam-bath for 1 hr. After removal of the anhydride under reduced pressure the residue was made alkaline with aqueous sodium carbonate, and the oil isolated with ether and purified by distillation at 0·3 mm. to yield the *product*, b. p. 158—160° (Found: C, 77·7; H, 8·0; N, 6·7. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%). A corresponding reaction with acetic anhydride gave a 93% yield of the acetyl analogue, b. p. 163—165°/0·5 mm., m. p. 67—69°, not depressed on admixture with an authentic specimen.

1-*Diphenylmethyl*-1 : 2 : 3 : 6-*tetrahydro*-4-*phenylpyridine.*—A mixture of 4-hydroxy-4-phenylpiperidine (26·4 g., 2 mol.) and diphenylmethyl chloride (15·15 g.) was heated at 145° for 15 min. The cooled melt was extracted with boiling ethyl acetate to remove insoluble 4-hydroxy-4-phenylpiperidine hydrochloride (15·1 g.). The filtrate was evaporated to dryness, and the solid residue crystallised from ethanol to yield the *product* (17·8 g.) in needles, m. p. 128—131° (Found: C, 89·0; H, 7·2; N, 3·8. $C_{24}H_{23}N$ requires C, 88·6; H, 7·1; N, 4·3%).

Reaction of 4-*Bromo*-4-*phenylpiperidine Hydrobromide with Sodium Propionate in Propionic Acid.*—The foregoing hydrobromide (32·1 g.) was added to a solution of sodium propionate (19·2 g., 2 mol.) in propionic acid (200 ml.), and the mixture heated on the steam-bath with stirring for 1 hr. After removal of sodium bromide the filtrate was evaporated to dryness under reduced pressure, the residue made alkaline with dilute sodium hydroxide, and the oil isolated with ether. Distillation under reduced pressure yielded 1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine (12·2 g., 77%), b. p. 100°/0·7 mm., and 4-hydroxy-4-phenyl-1-propionylpiperidine (2 g.), b. p. 194—196°/0·3 mm., m. p. 173—174° (see above).

1 : 2 : 3 : 6-*Tetrahydro*-1-(2-*hydroxy*-3-*o*-*tolyloxypropyl*)-4-*phenylpyridine.*—(*a*) A solution of 1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine (6·36 g.) in benzene (15 ml.) was treated with 1 : 2-epoxy-3-*o*-tolyloxypropane (6·56 g.), and the mixture heated under reflux for 2 hr. Removal of the solvent followed by distillation at 0·2 mm. yielded the *product* (11·05 g.), b. p. 216—222°, m. p. 82—84° (Found: C, 77·6; H, 7·8; N, 4·6. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%) after crystallisation from light petroleum (b. p. 80—100°). The *hydrochloride* formed needles, m. p. 148—151° (Found: N, 3·9; Cl, 9·9. $C_{21}H_{26}O_2NCl$ requires N, 4·3; Cl, 10·2%) after crystallisation from methanol–ethyl acetate.

(*b*) A mixture of 2-hydroxy-3-*o*-tolyloxypropylamine hydrochloride (87·9 g., 0·4 mole) and 40% formaldehyde solution (66·8 g., 0·83 mole) was treated at 65° with stirring with α-methylstyrene (23·6 g., 0·2 mole) added during 10 min. The temperature was allowed to fall slowly to 30°, and methanol (50 ml.) was then added, and the mixture set aside at room temperature for 2 days. After removal of solvent under reduced pressure, concentrated hydrochloric acid (56 ml.) was added, and the mixture heated with stirring on the steam-bath for 3 hr. It was cooled, diluted with water (80 ml.), and extracted with toluene to remove non-basic material.

[16] Paden and Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2487.

The aqueous fraction was made alkaline with excess of 50% aqueous sodium hydroxide, and the oil isolated with three portions of toluene, and distilled at 0·25 mm. to yield the product (21·7 g.), b. p. 212—218°. The hydrochloride had m. p. 148—151° (after crystallisation from methanol–ethyl acetate), not depressed on admixture with the compound prepared as in (*a*).

The foregoing base (3·23 g.) in acetic acid (3 ml.) was treated with 50% w/v hydrobromic acid in acetic acid (3·24 ml., 2 mol.) at room temperature for 2 days. The product which separated, m. p. 176—178° (after crystallisation from ethanol–ether), proved to be the hydrobromide of the starting material.

2-Diphenylmethoxy-3-phenoxypropyl Chloride.—To a solution of diphenylmethanol (20 g., 0·108 mole) and 2-hydroxy-3-phenoxypropyl chloride (25 g., 0·134 mole) in toluene (100 ml.) was added toluene-*p*-sulphonic acid (200 mg.), and the mixture was heated in a Dean–Stark apparatus for 15 min., the calculated amount of water (1·94 ml.) then having collected. The cooled solution was washed with sodium carbonate solution and with water, the solvent removed under reduced pressure, and the residual oil distilled at 0·05 mm. to yield the *product* as a viscous oil, b. p. 178° (Found: C, 75·2; H, 6·4; Cl, 9·8. $C_{22}H_{21}O_2Cl$ requires C, 74·9; H, 6·0; Cl, 10·1%). 2-Diphenylmethoxy-3-phenoxypropyl bromide, similarly prepared, had b. p. 190°/0·05 mm.

1-(2-Diphenylmethoxy-3-phenoxypropyl)-1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine.—(*a*) A mixture of 2-diphenylmethoxy-3-phenoxypropyl chloride (35·25 g., 0·1 mole) and 4-hydroxy-4-phenylpiperidine (35·4 g., 0·2 mole) was heated at 160° for 1 hr. then cooled and boiled with ethyl acetate to remove 4-hydroxy-4-phenylpiperidinium chloride (18·5 g.). The ethyl acetate extract was washed with water and dried (K_2CO_3), and the solvent removed. The residual oil was fractionated at 0·1 mm. to yield the product (65%) as an oil, b. p. 280°. The *hydrochloride* separated from ethanol–ether in needles, m. p. 186—187° (Found: C, 74·9; H, 6·8; N, 2·6; Cl, 6·8. $C_{33}H_{36}O_3NCl$ requires C, 74·8; H, 6·8; N, 2·6; Cl, 6·7%).

(*b*) A mixture of 2-diphenylmethoxy-3-phenoxypropyl chloride (14·1 g., 0·04 mole), 4-hydroxy-4-phenylpiperidine (7·08 g., 0·04 mole), and sodium *tert.*-butoxide (0·04 mole) in *tert.*-butyl alcohol (60 ml.) was heated on the steam-bath for 30 hr. Sodium chloride (0·75 g.) was removed (theory, 2·35 g.). The filtrate was concentrated, and the residue triturated with ether to yield unchanged piperidinol (3·9 g., m. p. 159—160°). Treatment of the filtrate with hydrogen chloride yielded 4-hydroxy-4-phenylpiperidine hydrochloride together with a hydrochloride (3 g.), m. p. 182—183°, identical with that described in (*a*).

Attempted propionation of 1-(2-diphenylmethoxy-3-phenoxypropyl)-1 : 2 : 3 : 6-tetrahydro-4-phenylpyridine with propionic anhydride (containing a few drops of concentrated sulphuric acid), at 100° for several hours or under reflux for a short period, yielded unchanged material as the only identifiable product. Similarly, attempted esterification with propionic acid–pyridine–benzenesulphonyl chloride [17] proved unsuccessful.

3-Phenoxy-2-propionoxypropyl chloride had b. p. 149—152°/3·5 mm. (Found: C, 59·4; H, 6·4; Cl, 14·7. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·2; Cl, 14·6%).

Reaction of 3-Phenoxy-2-propionoxypropyl Chloride with 4-Hydroxy-4-phenylpiperidine.—A mixture of 4-hydroxy-4-phenylpiperidine (17·7 g., 0·1 mole) and 3-phenoxy-2-propionoxypropyl chloride (12·15 g., 0·05 mole) was heated with stirring until homogeneous, then at 100° for 48 hr. The melt was boiled with ethyl acetate to remove insoluble 4-hydroxy-4-phenylpiperidinium chloride (9·3 g.). Concentration of the extract followed by distillation of the residue at 0·5 mm. yielded fractions: (i) unchanged 3-phenoxy-2-propionoxypropyl chloride (5·6 g., b. p. 122—140°); (ii) 3·2 g., b. p. 150—195°; (iii) 5 g., b. p. 224—228°, and (iv) 5 g., b. p. 230—236°. Fraction (ii) on treatment with ether yielded 4-hydroxy-4-phenyl-1-propionylpiperidine (1·5 g., m. p. 173—174°, after crystallisation from aqueous ethanol, not depressed in admixture with authentic material). Fractions (iii) and (iv) on treatment with ether followed by fractionation of the resultant solids from aqueous ethanol yielded 4-hydroxy-1-(2-hydroxy-3-phenoxypropyl)-4-phenylpiperidine (3·4 g.), m. p. 119—120° not depressed on admixture with an authentic specimen), and a further quantity (1·0 g.) of 4-hydroxy-4-phenyl-1-propionylpiperidine.

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[17] Brewster and Ciotti, *ibid.*, 1955, **77**, 6214.