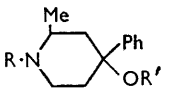
540. *Some Isomeric Hydroxypiperidines.*

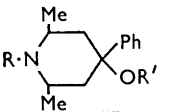
By N. J. Harper, A. H. Beckett, and A. D. J. Balon.

The isomers of 2-methyl- and 2,6-dimethyl-4-hydroxy-1-phenethylphenylpiperidine and of 4-hydroxy-2,6-dimethyl-4-phenylpiperidine have been separated. Configurational assignments for them have been based on chemical reactions and physical properties. Difficulties in the preparation of certain tertiary amines from phenethylamine and unsaturated esters are explained on steric and electronic grounds. Attempts to alkylate some piperidones are described.

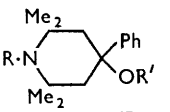
Compounds related to the " reversed " esters of pethidine, namely, hydroxypiperidines and their esters, (I—III where R = H, or $CH_2 \cdot CH_2Ph$, and R′ = H, Ac, or Et·CO), have been prepared as potential analgesics by treatment of the appropriate 4-piperidone with phenyl-lithium and esterification of the resultant alcohols.



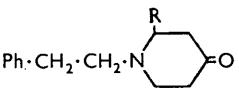
(I)



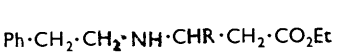
(II)



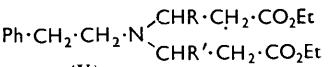
(III)



(VI)



(IV)

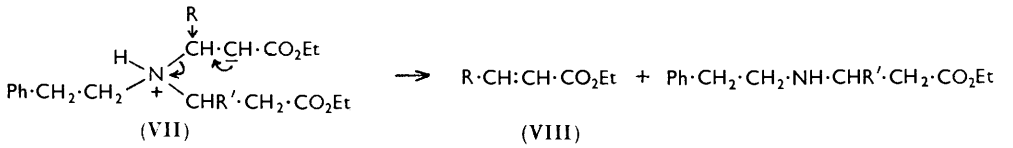


(V)

Synthesis of 2-methyl-1-phenethyl-4-piperidone (VI; R = Me) was attempted by addition of ethyl acrylate to (IV; R = Me), followed by ring closure and decarboxylation. Condensation of ethyl crotonate with phenethylamine gave the secondary amine (IV; R = Me) in good yield, which in a small-scale reaction with ethyl acrylate gave the tertiary amine (V; R = Me, R′ = H) but in low yield; increase in reaction time led to the formation of the more symmetrical diester (V; R = R′ = H) by thermal decomposition of the secondary (IV; R = Me) and the tertiary (V; R = Me, R′ = H) amine formed during the condensation. Distillation of the product obtained by the reaction of the base (IV; R = Me) with ethyl acrylate gave ethyl crotonate as one fraction, in amount which increased with the bath-temperature. Condensations of amines with unsaturated esters are known to be reversible.[1,2] If it is assumed that the initial step in elimination is loss

[1] McElvain and Stork, *J. Amer. Chem. Soc.*, 1946, **68**, 1049.
[2] Morosawa, *Bull. Chim. Soc. Japan*, 1958, **31**, 418.

of a proton from the α-carbon atom of an ester moiety, the proton combining with the amino-nitrogen atom to give a charged complex (cf. VII; R = Me, R′ = H or *vice versa*), then



(VII) (VIII)

the electron-flow from the crotonate moiety is greater than from the acrylate moiety, so that preferential elimination of the crotonate group (VIII; R = Me) results. Steric factors also favour elimination in this direction since increased " crowding " of the amino-nitrogen atom in this type of compound favours elimination.[3]

The mixture of secondary and tertiary amines obtained from the base (IV; R = Me) and ethyl acrylate was therefore treated with nitrous acid and the resultant mixed tertiary amines were cyclised and decarboxylated to give a mixture of 1-phenethyl-4-piperidone (VI; R = H) and its 2-methyl derivative. The latter ketone crystallised; the former was isolated from the mother-liquors as the diethyl ketal hydrochloride.

2,6-Dimethyl-1-phenethyl-4-piperidone was prepared by decarboxylating the product of a Mannich reaction between phenethylamine, acetaldehyde, and diethyl acetonedicarboxylate. Attempts to separate *cis*- and *trans*-isomers of this ketone were unsuccessful. A projected route to 2,6-dimethyl-1-phenethyl-4-piperidone by cyclisation of the diester (V; R = R′ = Me) was precluded since attempts to prepare the latter from ethyl crotonate and phenethylamine gave *N*-phenethylcrotonamide. This amide was also formed by the reaction of ethyl crotonate with the monoester (IV; R = Me).

2,2,6,6-Tetramethyl-4-piperidone was prepared by Hall's method,[4] and *cis*-2,6-dimethyl-4-piperidone was obtained in 46% yield from ammonia, acetaldehyde, and diethyl acetonedicarboxylate by a modification of Hall's method.[4]

All the ketones except the tetramethyl derivative were characterised as diethyl ketal hydrohalides obtained during attempts to prepare the hydrohalide salts in ethanol (cf. Brooks and Walker [5] and Beckett *et al.*[6]).

The 4-piperidones were converted into the corresponding 4-hydroxy-4-phenylpiperidines by phenyl-lithium. When position 1 was unsubstituted, " inverse " addition of phenyl-lithium to the piperidone gave higher yields than the normal procedure.

2-Methyl-1-phenethyl-4-piperidone (IX; R = CH_2·CH_2Ph) gave two isomeric alcohols (A and B in the ratio 2 : 1) which were separated by fractional crystallisation of their hydrochlorides. *cis*-2,6-Dimethyl-4-piperidone (XX) also gave two alcohols (A and B in the ratio 12 : 13), these being separated by chromatography. The mixture of isomeric 2,6-dimethyl-1-phenethyl-4-piperidones gave the three theoretically possible alcohols (designated A, B, and C) in the ratio of 9 : 2 : 1; these were separated by fractional crystallisation of the free bases.

Difficulties were experienced in the esterification of the hydroxy-piperidines. Treatment of the *N*-substituted alcohols with an acid anhydride in pyridine under conditions which gave esters of related hydroxypiperidines [6] eliminated water to give the 2,3,5,6-tetrahydropyridine derivative. However, the lithium complex of the alcohol with an acid anhydride gave the normal ester in some cases, the product being isolated as the hydrohalide salt under mild conditions (Badger *et al.*[7] have shown that compounds of this type undergo acid-catalysed elimination). Keten was used when the above methods

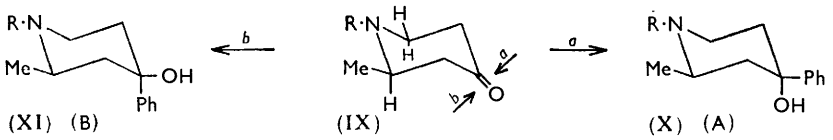
[3] Erickson, *J. Amer. Chem. Soc.*, 1952, **74**, 6281.
[4] Hall, *J. Amer. Chem. Soc.*, 1957, **79**, 5444.
[5] Brookes and Walker, *J.*, 1957, 3173.
[6] Beckett, Casy, and Kirk, *J. Med. Pharm. Chem.*, 1959, **1**, 37.
[7] Badger, Cook, and Donald, *J.*, 1950, 197.

failed. When the ketone had a free NH group the possibility of *N*-acylation or *O* ⟶ *N*-acyl migration was a complicating factor.[8,9] The A isomer of 4-hydroxy-*cis*-2,6-dimethyl-4-phenylpiperidine was esterified by the " lithium complex " method; the B isomer was not esterified under these conditions and refluxing its hydrobromide with magnesum in acetyl bromide gave the 1,2,3,6-tetrahydropyridine compound.

Attempts to *N*-alkylate *cis*-2,6-dimethyl-4-piperidone, its diethyl ketal, or the *N*-lithium complex of the ketal with 3-bromopropylbenzene were unsuccessful; the ketone was, however, alkylated in low yield by ethylene oxide under pressure. Steric hindrance by the 2,6-methyl groups is probably responsible for these difficulties; *e.g.*, this ketone was *N*-benzylated in less than 20% yield under conditions which gave a 60% yield from 2,5-dimethyl-4-piperidone.[10] Badger *et al.*[7] found that while it was difficult to alkylate 2,2,6-trimethyl-4-piperidone, the corresponding 4-hydroxy-4-phenylpiperidine was methylated with ease by formaldehyde; in the present investigation, all the methylations were successful when refluxing aqueous formaldehyde was used. The A isomer of 4-hydroxy-*cis*-2,6-dimethyl-4-phenylpiperidine gave a tetrahydro-oxazine, which yielded the 4-hydroxy-1-methylpiperidine on treatment with alcoholic hydrobromic acid.

Configurational Assignments.—The configurational consignments now to be made for the isomers (I and II; R = $CH_2 \cdot CH_2Ph$, R′ = H and III; R = R′ = H) are based on addition to piperidones of organometallic derivatives, elimination and esterification, and dissociation constants and infrared spectra of the alcohols.

The structures (X; isomer A, *cis*-Me/Ph) and (XI; isomer B, *trans*-Me/Ph) are assigned on the following evidence: (*a*) During the addition of phenyl-lithium to the ketone (IX), steric hindrance of attack from side " b " results in preferential introduction of the equatorial phenyl group (cf. X). The ratio A : B = 2 : 1 is lower than that (3 : 1) obtained on similar addition to 1,3-dimethyl-4-piperidone in which the 3-methyl group increases this hindrance.[6]



(XI) (B) (IX) (X) (A)

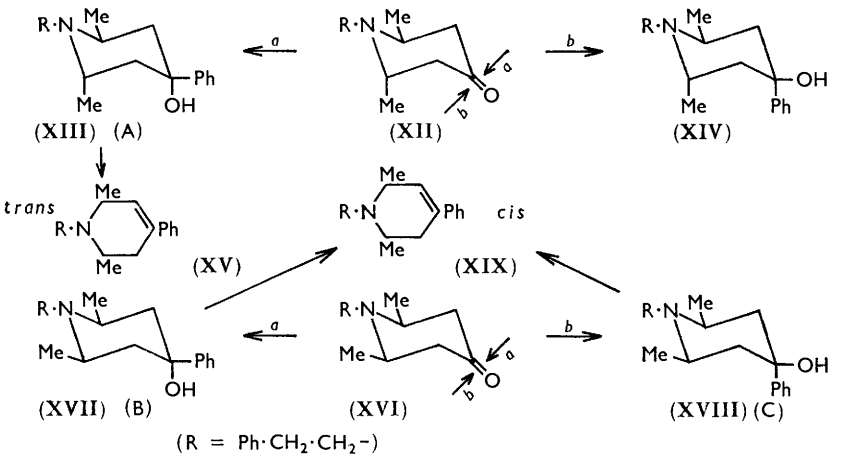
R = Ph·CH_2·CH_2

(*b*) The infrared absorption spectrum of isomer A (X) resembled those of compounds of α-prodine type (*eq*-Ph), and that of the isomer B resembled those of the β-prodine type (*ax*-Ph). Further, in compounds of α-prodine type, the strongest absorption peak between 1000—1250 cm.$^{-1}$ is at ~1150 cm.$^{-1}$, but it is at ~1030 cm.$^{-1}$ for the β-prodine type.[6,11] A similar pattern is found in the A and B isomers, the former absorbing at 1114 and 1060 cm.$^{-1}$. (*c*) On treatment with keten, isomer B gave the ester, whereas isomer A was not esterified, indicating that the hydroxy-group in isomer B is the less hindered.

The isomers formed from the mixed 2,6-dimethyl-1-phenethyl-4-piperidones are assigned the following configurations; A, *trans*-Me,Me (XIII); B, *cis*-Me,Me, *cis*-Me,Ph (XVII); C, *cis*-Me,Me, *trans*-Me,Ph (XVIII), the evidence being as follows: (*a*) Elimination from isomers B (XVII) and C (XVIII) gave identical products (XIX) which indicated their derivation from the *cis*-Me,Me ketone, while isomer A (XIII) gave a different product (XV), indicating its formation from the *trans*-Me,Me ketone. (*b*) The infrared spectra of isomers A and B (XIII and XVII), but not of isomer C (XVIII), showed intermolecular hydrogen-bonding indicating a similar spatial arrangement of the hydroxy-groups in A and B. Elimination studies established that isomer A has a *trans*-Me,Me relation and would therefore have an equatorial phenyl and an axial hydroxyl group (largest group

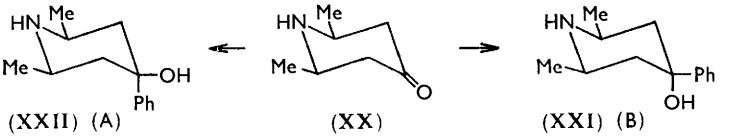
[8] Fodor and Nador, *Nature*, 1952, **169**, 462.
[9] Nickon and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5566.
[10] Nazarov and Rudenko, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1948, 610.
[11] Beckett, Casy, and Harper, *Chem. and Ind.*, 1959, 19.

equatorial); isomer B therefore has a similar equatorial phenyl group (cf. XVII). (*c*) These conclusions were substantiated by consideration of the dissociation constants of the alcohols (p. 2711). Isomers B and C had similar pK'_a values (8·40 and 8·57 respectively):

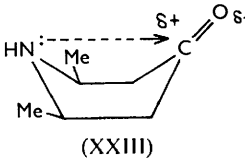


isomer A had pK'_a 9·06, indicating a similar geometry of the methyl groups in isomers B and C. (*d*) Although only a 30% yield of alcohols was obtained by reaction of the mixture (XII and XVI) with phenyl-lithium, and definite conclusions cannot be drawn, the 2 : 1 ratio of isomers B and C derived from the ketone (XVI) is in agreement with predictions based on the stereochemistry of addition to ketones.

The alcohols (A) and (B) obtained from *cis*-2,6-dimethyl-4-piperidone (XX) are assigned the configuration *trans*- (XXII) and the *cis*-Me,Ph (XXI) respectively on the following evidence: (*a*) While isomer A gave a hydrobromide, isomer B under similar



conditions lost water and gave a tetrahydropyridine; the axial and equatorial hydroxyl-group respectively in B and A is indicated. In support of this, esterification of isomer A, but not of isomer B, by the " lithium-complex " method proceeded smoothly. (*b*) Isomer A had its strongest absorption peak in the 1000—1200 cm.$^{-1}$ region at 1141 cm.$^{-1}$, in close agreement with that (1143 cm.$^{-1}$) for isomer C of 4-hydroxy-2,6-dimethyl-4-phenyl-1-phenethylpiperidine (XVIII) which has an equatorial hydroxyl group. Similarly isomer B of the alcohol (XXI) has its strongest peak in this region at 1013 cm.$^{-1}$, in agreement with that (1018 cm.$^{-1}$) for isomer B of its phenethyl derivative (XVII) which has been shown to have an axial hydroxyl group.



The ketone (XX) gave the isomeric alcohols in approximately a 1 : 1 ratio although a 2 : 1 ratio would have been expected. A possible explanation is that the boat form of this ketone plays a significant rôle in the reaction, the electronic attraction from N to C=O, as indicated in formula (XXIII), altering the normal boat–chair equilibrium.

Experimental

Preparation of 4-Piperidones.—Ethyl β-phenethylaminobutyrate (IV; R = Me). Ethyl crotonate (513 g.) and phenethylamine (363 g.) in 96% ethanol (200 c.c.) were left at room temperature for 42 days. Fractional distillation under reduced pressure then gave the amino-ester (645 g.), b. p. 122—125°/0·1 mm., n_D^{19} 1·4978 (Found: equiv., 234. Calc. for $C_{14}H_{21}O_2N$:

equiv., 235). [*Picrate*, yellow needles (from ethanol), m. p. 109° (Found: C, 51·5; H, 5·2; N, 12·4%; equiv., 460. $C_{20}H_{24}O_9N_4$ requires C, 51·7; H, 5·2; N, 12·1%; equiv., 464).]

Ethyl β-(N-2-*ethoxycarbonyl*-N-*phenethylamino*)*butyrate* (V; R = Me, R′ = H). (*a*) The preceding ester (69 g.) was refluxed with ethyl acrylate (51 g.) for 48 hr. Distillation then gave the tertiary amino-ester (43·5 g.), b. p. 162—168°/0·2 mm., n_D^{21} 1·4938 (Found: equiv., 338. Calc. for $C_{19}H_{29}O_4N$: equiv., 335). (*b*) The ester (IV; R = Me) (235 g.) and ethyl acrylate (150 g.) were refluxed for 120 hr. and then distilled, to give (i) mainly ethyl acrylate (94 g.), b. p. <120°/16 mm., (ii) unchanged amino-ester (82 g.), b. p. 125—138°/0·4 mm. (Found: equiv., 240) (picrate, m. p. and mixed m. p. 109°), and (iii) a basic oil (95 g.), b. p. 164—168°/0·4 mm. (Found: equiv., 315), which gave an oily hydrochloride, hydrobromide, and picrate. A final distillation fraction (52 g.), b. p. 138—142°, contained mainly ethyl crotonate. Fraction (iii) was cyclised and decarboxylated, to give 1-phenethyl-4-piperidone, m. p. 61—63°, with the correct infrared spectrum. With ethanolic hydrochloric acid it gave the diethyl ketal hydrochloride, m. p. 185° (decomp.), undepressed on admixture with 1-phenethyl-4-piperidone diethyl ketal hydrochloride, m. p. 179—183° (decomp.).

2-*Methyl*-1-*phenethyl*-4-*piperidone* (VI; R = Me). The ester (IV; R = Me) (235 g.) and ethyl acrylate (150 g.) were heated at 80—85° for 8 days. The excess of ethyl acrylate was removed under reduced pressure. The residue was cooled, treated with 24% w/v hydrochloric acid (750 c.c.), and cooled to −5°. Sodium nitrite (135 g.) was added during 1 hr., and the solution shaken for 1 hr., allowed to warm to room temperature, extracted with ether (2 × 1 l.), made alkaline with sodium carbonate, and treated with an excess of ammonia solution. Extraction with ether, and drying and evaporation of the extract, gave a light yellow oil (238·5 g.) (Found: equiv., 341. Calc. for $C_{19}H_{29}O_4N$: equiv., 335). This oil (25 g.) was added to a stirred suspension of sodium (8·3 g.) in xylene (300 c.c.) and warmed at 60° to start reaction. A further quantity of the oil (90 g.) was added dropwise at a rate sufficient to maintain gentle reaction, the mixture was then refluxed for 1 hr., and after it had cooled water (300 c.c.) was added. The aqueous phase was separated, extracted with ether, acidified with concentrated hydrochloric acid, and treated with a further 300 c.c. of this acid. The whole was heated on a steam-bath for 2 hr. to effect decarboxylation, evaporated to small bulk, treated with 50% w/v sodium hydroxide solution (80 c.c.), and extracted with ether. The combined ethereal extracts were evaporated to give a solid (52 g.) which, recrystallised from light petroleum, yielded 2-methyl-1-phenethyl-4-piperidone (25 g.), m. p. 74—78° (Found: equiv., 222. Calc. for $C_{14}H_{19}ON$: equiv., 217); dissolution in ethanolic hydrochloric acid gave the *diethyl ketal hydrochloride*, m. p. 148·5—149°, forming needles from ethanol–ether (Found: C, 66·3; H, 9·4; N, 4·4%; equiv., 330. $C_{18}H_{30}O_2NCl$ requires C, 66·0; H, 9·2; N, 4·3%; equiv., 328). The mother-liquor from the crystallisation of the above piperidone was evaporated; it gave a solid which on crystallisation from ethanolic hydrochloric acid gave 1-phenethyl-4-piperidone diethyl ketal hydrochloride, m. p. 185° (decomp.), undepressed on admixture with an authentic sample, m. p. 179—183° (decomp.).[12]

2,6-*Dimethyl*-1-*phenethyl*-4-*piperidone*. Phenethylamine hydrochloride (86 g.) in water (160 c.c.) was added dropwise to a stirred, cooled solution of acetaldehyde (50 g.) in diethyl acetonedicarboxylate (101 g.). The mixture was left for 24 hr., and the excess of aldehyde removed under reduced pressure. The residue was stored overnight at 0°, mixed isomers of diethyl 2,6-dimethyl-4-oxopiperidine-3,5-dicarboxylate hydrochloride (133 g.) crystallising. A portion (60 g.) of these crystals was heated in 20% w/v hydrochloric acid (300 c.c.) for 24 hr., then evaporated to small bulk, made alkaline with concentrated aqueous ammonia, and extracted with chloroform to yield a viscous red oil (30 g.) (Found: equiv., 217. Calc. for $C_{15}H_{21}ON$: 231); dissolution in ethanolic hydrobromic acid gave 2,6-*dimethyl*-1-*phenethyl*-4-*piperidone diethyl ketal hydrobromide*, m. p. 134·5—135° (decomp.), as needles (Found: C, 59·0; H, 8·3; Br, 20·3%; equiv., 390. $C_{19}H_{32}O_2NBr$ requires C, 59·0; H, 8·4; Br, 20·7%; equiv., 386).

Attempts to prepare the Ester (V; R = R′ = Me.—(a) *From phenethylamine*. Ethyl crotonate (285 g.) was refluxed with phenethylamine (121 g.) for 7 days. Distillation of the product gave N-*phenethylcrotonamide* (182 g.), b. p. 140—144°/0·2 mm., which solidified and recrystallised from light petroleum (b. p. 80—100°) as needles, m. p. 78·5—79° (Found: C, 75·6; H, 7·8; N, 7·3. $C_{12}H_{15}ON$ requires C, 76·1; H, 8·0; N, 7·4%).

(b) *From the ester* (IV; R = Me). This ester (34 g.) and ethyl crotonate (35 g.) were refluxed

[12] Kirk, Ph.D. Thesis, London, 1958.

for 7 days. Distillation of the product under reduced pressure gave *N*-phenethylcrotonamide (28 g.), b. p. 146—150°/0·8 mm., m. p. and mixed m. p. 78·5—79°.

cis-2,6-*Dimethyl*-4-*piperidone*.[4]—Dry ammonia was passed into a solution of diethyl acetonedicarboxylate (202 g.) and acetaldehyde (88 g.) in ether (200 c.c.) at $-25° \pm 5°$. The mixture, treated as described by Hall,[4] gave *cis*-2,6-dimethyl-4-piperidone (53 g.), b. p. 58—59°/1 mm., n_D^{19} 1·4687 (Hall [4] gives b. p. 99—105°/22 mm., n_D^{19} 1·4648). Dissolution in ethanolic hydrochloric acid gave the *diethyl ketal hydrochloride*, m. p. 196° (decomp.) (from acetone–ether) (Found: C, 55·3; H, 10·0; N, 6·1; Cl, 15·2%; equiv., 236. $C_{11}H_{24}O_2NCl$ requires C, 55·5; H, 10·2; N, 5·9; Cl, 14·9%; equiv., 238).

2,2,6,6-*Tetramethyl*-4-*piperidone*.—Prepared by Hall's method,[4] this had b. p. 89—92°/11 mm., m. p. 35° (lit.,[4] b. p. 102—105°/18 mm., m. p. 34—36°).

4-*Hydroxy*-2-*methyl*-1-*phenethyl*-4-*phenylpiperidine* (I; R = $CH_2 \cdot CH_2Ph$, R′ = H).—2-Methyl-1-phenethyl-4-piperidone (10·0 g.) in benzene (20 c.c.) was added dropwise to stirred, cooled ethereal phenyl-lithium (prepared from lithium, 1·26 g., and bromobenzene, 14·2 g.). The mixture was refluxed for 1 hr., poured on ice, and made acidic with hydrochloric acid. The aqueous phase was extracted with ether and made alkaline with concentrated ammonia solution. Extraction with benzene then gave a light yellow solid (13·5 g.). The hydrochloride of this was fractionally crystallised from ethanol–ether, to give (i) 4-*hydroxy*-2-*methyl*-1-*phenethyl*-4-*phenylpiperidine* (*isomer A*) *hydrochloride* (8·5 g.) as plates, m. p. 214·5—215° (Found: C, 72·7; H, 8·1; N, 4·3%; equiv., 335. $C_{20}H_{26}ONCl$ requires C, 72·4; H, 7·9; N, 4·2%; equiv., 332) [the *base* (from light petroleum) had m. p. 79° (Found: C, 81·9; H, 8·3; N, 4·8%; equiv., 293. $C_{20}H_{25}ON$ requires C, 81·3; H, 8·5; N, 4·7%; equiv., 295)], and (ii) *isomer B hydrochloride*, m. p. 174—175° (softens at 96°) (Found: C, 66·7; H, 7·7%; equiv., 355. $C_{20}H_{26}ONCl,1\frac{1}{2}H_2O$ requires C, 67·0; H, 8·1%; equiv., 359) [*base* (from light petroleum), m. p. 98° (Found: C, 81·5; H, 8·3; N, 5·0%; equiv., 294)].

4-*Hydroxy*-2,6-*dimethyl*-1-*phenethyl*-4-*phenylpiperidine* (II; R = $CH_2 \cdot CH_2Ph$, R′ = H).—The mixed isomers (21·3 g.) of 2,6-dimethyl-1-phenethyl-4-piperidone in ether (50 c.c.) were added dropwise to stirred, cooled ethereal phenyl-lithium (from lithium, 1·68 g., and bromobenzene, 19·0 g.). Treatment as above gave a light brown oil (20·7 g.) which on fractional crystallisation from light petroleum gave three alcohols: *isomer A* (6·91 g.), m. p. 122·5° (Found: C, 81·0; H, 8·5; N, 4·7%; equiv., 311. $C_{21}H_{27}ON$ requires C, 81·5; H, 8·8; N, 4·5%; equiv., 309); *isomer B* (1·48 g.), m. p. 142·5—143° (Found: C, 81·5; H, 8·8; N, 4·5%; equiv., 309); and *isomer C* (0·74 g.), m. p. 134° (Found: C, 81·9; H, 8·7; N, 4·4%; equiv., 310).

4-*Hydroxy*-cis-2,6-*dimethyl*-4-*phenylpiperidine* (II; R = R′ = H).—An ethereal solution of phenyl-lithium (from lithium, 4·82 g., and bromobenzene, 54·2 g.) was added to a stirred cooled solution of *cis*-2,6-dimethyl-4-piperidone (40·0 g.) in ether (50 c.c.), and the solution was stirred overnight, then treated in the usual manner, giving a pale yellow oil (44·2 g.). Distillation under reduced pressure removed unchanged ketone (12·1 g.). The residue (32·0 g.) was chromatographed in 19 : 1 light petroleum–benzene (100 c.c.) on alumina. Elution with the same mixture afforded 4-*hydroxy*-cis-2,6-*dimethyl*-4-*phenylpiperidine*, *isomer B* (11·92 g.), m. p. 147—147·5° (Found: C, 76·3; H, 9·3; N, 6·9%; equiv., 205. $C_{13}H_{19}ON$ requires C, 76·0; H, 9·3; N, 6·8%; equiv., 205); elution with ethanol gave *isomer A* (13·76 g.), m. p. 91·5° (Found: C, 75·9; H, 9·4; N, 6·9%; equiv., 206). Isomer A gave a *hydrobromide* (from ethanol–ether), m. p. 244·5° (decomp.) (Found: C, 54·9; H, 7·0; N, 5·1; Br, 27·6%; equiv., 286. $C_{13}H_{20}ONBr$ requires C, 54·6; H, 7·1; N, 4·9; Br, 27·9%; equiv., 286), and a *hydrochloride* (from ethanol–ether), m. p. 239—240° (decomp.) (Found: C, 64·6; H, 8·4; N, 6·0; Cl, 14·8%; equiv., 243. $C_{13}H_{20}ONCl$ requires C, 64·6; H, 8·3; N, 5·8; Cl, 14·7%; equiv., 242). Isomer B gave a *hydrobromide*, m. p. 216° (decomp.) (from ethanol–ether) (Found: C, 54·6; H, 7·0; N, 5·1; Br, 27·9%; equiv., 286), during the preparation of which there was obtained also 1,2,3,6-*tetrahydro*-cis-2,6-*dimethyl*-4-*phenylpyridine hydrobromide*, m. p. 262—264° (decomp.) (from ethanol–ether) (Found: C, 58·3; H, 6·8; N, 5·3; Br, 30·1%; equiv., 266. $C_{13}H_{18}NBr$ requires C, 58·2; H, 6·8; N, 5·2; Br, 29·8%; equiv., 268), $\lambda_{max.}$ 244 mμ (ε 12,480).

4-*Hydroxy*-2,2,6,6-*tetramethyl*-4-*phenylpiperidine* (III; R = R′ = H).—An ethereal solution of phenyl-lithium (from lithium, 2·48 g., and bromobenzene, 28·0) was added dropwise to a stirred, cooled solution of 2,2,6,6-tetramethyl-4-piperidone (25·0 g.) in ether (100 c.c.). Treatment in the usual manner gave the *alcohol* (16·2 g.) which, crystallised from light petroleum, had m. p. 131·5° (Found: C, 77·3; H, 9·9; N 6·1%; equiv., 236. $C_{15}H_{23}ON$ requires C, 77·2; H, 9·9; N, 6·0%; equiv., 233).

Alkylation with Aqueous Formaldehyde.—The hydroxy-piperidines were refluxed for 1 hr. with an excess of 40% w/v aqueous formaldehyde, and water was then removed under reduced pressure. 4-Hydroxy-2,6-dimethyl-4-phenylpiperidine (3·3 g.) gave its 1,2,6-*trimethyl derivative*, m. p. 127—127·5° (from light petroleum) (2·7 g.) (Found: C, 76·8; H, 9·6; N, 6·4%; equiv., 218. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·7; N, 6·4%; equiv., 219). Isomer B of this dimethyl alcohol gave 6,7-dimethyl-4-phenyl-3-oxo-1-azabicyclo[2,2,2]octane as a yellow oil, whose infrared spectrum showed a strong absorption characteristic of a cyclic ether but no NMe or OH band. This product, on treatment with ethanolic hydrobromic acid, gave the *isomer B* of the 1,2,6-*trimethyl derivative hydrobromide*, m. p. 207·5—208° (decomp.) (from ethanol–ether) (Found: C, 55·6; H, 7·4; N, 4·8%; equiv., 294. $C_{14}H_{22}ONBr$ requires C, 56·0; H, 7·4; N, 4·7%; equiv., 300). 4-Hydroxy-2,2,6,6-tetramethyl-4-phenylpiperidine gave an oil which on treatment with ethanolic hydrochloric acid gave 4-hydroxy-1,2,2,6,6-pentamethyl-4-phenylpiperidine hydrochloride as needles (from ethanol–ether), m. p. 241—242° (decomp.) (Lyle [13] cites m. p. 235—236° and 242—244°) (Found: C, 63·7; H, 9·6; N, 4·6%; equiv., 304. Calc. for $C_{16}H_{26}ONCl,H_2O$: C, 63·7; H, 9·4; N, 4·6%; equiv., 302).

Esterification of the Hydroxypiperidines.—Four general methods were used; the products were isolated as the hydrohalide salts from ethanol–ether.

Method A. The alcohol was refluxed for 3 hr. with the acid anhydride and pyridine; the solvents were removed under reduced pressure.

Method B. The alcohol in benzene was added to stirred ethereal phenyl-lithium. The mixture was refluxed for 1 hr., then cooled, and the acid anhydride in ether was added. The resultant suspension was left overnight, then poured on ice, and excess of hydrochloric acid was added.

Method C. The hydroxypiperidine hydrochloride in chloroform was cooled to 0° and 2 drops of ethanolic hydrochloric acid (10% w/v) were added. Keten [14] was passed through the solution for 1 hr., after which the solvent was removed under reduced pressure.

Method D. The hydroxypiperidine hydrobromide was refluxed with acetyl bromide and magnesium for 2 hr., and the excess of acetyl bromide removed under reduced pressure.[15]

(*a*) 4-Hydroxy-2-methyl-1-phenethyl-4-phenylpiperidine, isomer A. Methods A, B, and C gave only unchanged alcohol.

Isomer B. Method C gave 4-*acetoxy*-2-*methyl*-1-*phenethyl*-4-*phenylpiperidine hydrobromide* as needles, m. p. 199·5° (Found: C, 63·5; H, 6·8; N, 3·5%; equiv., 418. $C_{22}H_{28}O_2NBr$ requires C, 63·1; H, 6·7; N, 3·4%; equiv., 418).

(*b*) 4-Hydroxy-2,6-dimethyl-1-phenethyl-4-phenylpiperidine, isomer A. By method A, this isomer (1·0 g.) and acetic anhydride (1·5 c.c.) gave 1,2,3,6-*tetrahydro*-2,6-*dimethyl*-1-*phenethyl*-4-*phenylpyridine hydrobromide* (0·97 g.), m. p. 186° (decomp.) (Found: C, 68·4; H, 7·4; N, 3·8; Br, 21·5%; equiv., 375. $C_{21}H_{26}NBr$ requires C, 67·7; H, 7·1; N, 3·8; Br, 21·5%; equiv., 372), $\lambda_{max.}$ 244·5 mμ (ε 13,960). Method B afforded 4-*acetoxy*-2,6-*dimethyl*-1-*phenethyl*-4-*phenylpiperidine hydrobromide*, m. p. 203° (Found: C, 64·0; H, 6·8; N, 3·3; Br, 18·4%; equiv., 430. $C_{23}H_{30}O_2NBr$ requires C, 63·9; H, 7·0; N, 3·2; Br, 18·5%; equiv., 432).

By methods A and B, isomer B gave only 1,2,3,6-*tetrahydro*-2,6-*dimethyl*-1-*phenethyl*-4-*phenylpyridine hydrobromide*, m. p. 227—228° (decomp.) (Found: C, 68·7; H, 7·2; N, 3·7; Br, 21·2%; equiv., 376), $\lambda_{max.}$ 241·5 mμ (ε 14,200).

By methods A and B, isomer C gave only 1,2,3,6-tetrahydro-2,6-dimethyl-1-phenethyl-4-phenylpyridine hydrobromide, m. p. and mixed m. p. 227—228°.

(*c*) 4-Hydroxy-*cis*-2,6-dimethyl-4-phenylpiperidine, isomer A. Method D gave only 1,2,3,6-tetrahydro-*cis*-2,6-dimethyl-4-phenylpyridine hydrobromide, m. p. and mixed m. p. 262—264° (decomp.). Method B gave 4-*acetoxy*-cis-2,6-*dimethyl*-4-*phenylpiperidine hydrobromide*, m. p. 196° (decomp.) (Found: C, 55·2; H, 6·8; N, 4·4%; equiv., 332. $C_{15}H_{22}O_2NBr$ requires C, 54·9; H, 6·8; N, 4·3%; equiv., 328).

Isomer B, by methods B and D, gave only unchanged alcohol, or 1,2,3,6-tetrahydro-*cis*-2,6-dimethyl-4-phenylpyridine hydrobromide, m. p. 262—264°.

(*d*) 4-Hydroxy-1,2,6-trimethyl-4-phenylpiperidine. Neither isomer was changed on use of method B or C.

(*e*) 4-Hydroxy-2,2,6,6-tetramethyl-4-phenylpiperidine. Method B gave 4-*acetoxy*-2,2,6,6-*tetramethyl*-4-*phenylpiperidine hydrochloride* as needles, m. p. 202—203° (decomp.) (Found:

[13] Lyle, *J. Org. Chem.*, 1957, **22**, 1280.
[14] Williams and Hurd, *J. Org. Chem.*, 1940, **5**, 122.
[15] Spassow, "Organic Syntheses," Wiley and Sons, New York, 1955, Coll. Vol. III, p. 144.

C, 65·2; H, 8·2; N, 4·4; Cl. 11·5%; equiv., 318. $C_{17}H_{26}O_2NCl$ requires C, 65·5; H, 8·4; N, 4·5; Cl, 11·4%; equiv., 312). When method D was used, the only product isolated was 1,2,3,6-*tetrahydro*-2,2,6,6-*tetramethyl*-4-*phenylpyridine hydrochloride*, m. p. 270—271·5° (Found: C, 71·9; H, 8·8; N, 5·4%; equiv., 252. $C_{15}H_{22}NCl$ requires C, 71·5; H, 8·8; N, 5·6; equiv., 252), $\lambda_{max.}$ 244·5 mμ (ε 13,00).

(*f*) 4-Hydroxy-1,2,2,6,6-pentamethyl-4-phenylpiperidine was unaffected by method B or C.

1-*Benzyl*-2,6-*dimethyl*-4-*piperidone*.—A solution of *cis*-2,6-dimethyl-4-piperidone (9·5 g.) and benzyl chloride (14·3 g.) in dioxan (10 c.c.) was heated at 100° for 16 hr. The solvent was removed under reduced pressure, the residue suspended in water, made acid with concentrated hydrochloric acid, extracted with ether, and made alkaline with sodium hydroxide solution, and the free base was then extracted with chloroform. The combined chloroform extracts, when dried and evaporated, gave a dark brown oil (9·9 g.) which was distilled, to give 1-benzyl-2,6-dimethyl-4-piperidone (3·2 g.), b. p. 137—140°/0·2 mm. (Found: equiv., 210. Calc. for $C_{14}H_{19}ON$: equiv., 217); dissolution in ethanolic hydrochloric acid gave the *diethyl ketal hydrochloride*, m. p. 217° (decomp.) (Found: N, 4·25%; equiv., 319. $C_{18}H_{30}O_2NCl$ requires N, 4·27%; equiv., 328).

Dissociation Constants.—Dissociation constants were determined by the method of Beckett *et al.*[16] pK_a' of 4-hydroxy-1-phenethyl-4-phenylpiperidine was 8·30. Other pK_a''s were: (X) 8·57, (XI) 8·55; (XIII) 9·06, (XVII) 8·40, (XVIII) 8·57. We thank Dr. P. Demoen, of Research Laboratorium Dr. C. Janssen, Beerse, Belgium, for these determinations.

Infrared Absorption.—Infrared spectra were determined by using a Hilger H.800 double-beam automatic recording spectrophometer fitted with sodium chloride optics. Calibration was accurate within ±3 cm.$^{-1}$ over the region 650—2000 cm.$^{-1}$ and ±5 cm.$^{-1}$ over the region 2000—5000 cm.$^{-1}$. We thank Mr. T. H. E. Watts and Mr. G. H. Battershaw of Smith, Kline and French Analytical Laboratory, London, for these determinations.

School of Pharmacy, Chelsea College of Science and Technology,
Manresa Road, London, S.W.3. [*Received, November 18th*, 1959.]

[16] Beckett, Casy, Harper, and Phillips, *J. Pharm. Pharmacol.*, 1956, **8**, 860.