45. *The Synthesis of Piperidine Derivatives. Part IV. 4-Phenylpiperidols.*

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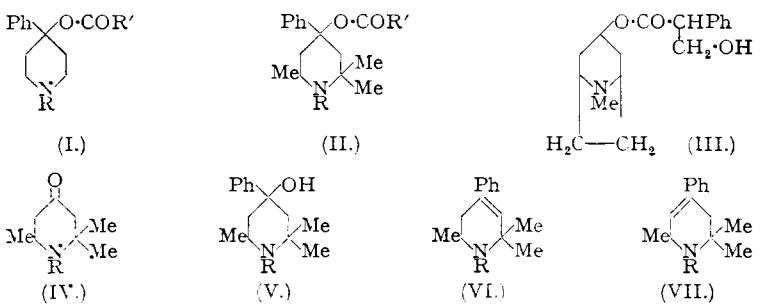
Attempts to prepare 4-acyloxy-4-phenyl-2 : 2 : 6-trimethyl-1-alkylpiperidines (II) are described. Phenylmagnesium bromide reacted with 2 : 2 : 6-trimethyl-4-piperidone to give 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine*, which readily gave the *N*-methyl derivative. Both compounds were dehydrated to the tetrahydropyridines with great facility, a circumstance which has frustrated the preparation of *O*-acyl and *O*-alkyl derivatives.

The introduction by Eisleb and Schaumann (*Deut. med. Wochenschr.*, 1939, **65**, 967) of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate ("Pethidine") as an analgesic of considerable potency has stimulated the examination of many new piperidine derivatives. The objective of such work is to prepare not only compounds of greater potency, but also those having no tendency to produce tolerance, drug addiction, and other undesirable side-effects which are characteristic of morphine and some of its derivatives. Although several highly active synthetic analgesics have been obtained it is evident, as a result of the wide clinical use of two of them ("Pethidine," "Amidone") that the problem of drug addiction has not been solved (see Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 349).

An interesting series of compounds (type I) has been described by Jensen and Lundquist (*Dansk. Tidsskr. Farm.*, 1943, **17**, 173) and by Ziering, Berger, Heineman, and Lee (*J. Org. Chem.*, 1947, **12**, 894). They were obtained by the action of arylmagnesium halides on 1-alkyl-4-piperidones to give carbinols which were esterified with a variety of acids. One of these



(I; R = Me, R′ = Et) was shown to have three times the analgesic activity of morphine in the experimental animal. The importance of configuration of the molecule was shown by examination of a further series of compounds similarly obtained from 1 : 3-dimethyl-4-piperidone (Ziering and Lee, *ibid.*, p. 911). The present communication is concerned with attempts to prepare related compounds (of type II) which are related to the natural antispasmodic atropine (III) in the same sort of way that the eucaines are related to cocaine.

2 : 2 : 6-Trimethyl-4-piperidone (vinyldiacetonamine) (IV; R = H) is readily obtained by condensation of diacetonamine (4-amino-4-methylpentan-2-one) and acetal (B.P. 101,738), and on treatment with phenylmagnesium bromide gave the desired 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* (V; R = H). This compound is dimorphic, and has m. p.s 91° and 96°. It was characterised as the *hydrochloride*, *hydrogen oxalate*, *picrate*, and *acetate*.

1 : 2 : 2 : 6-Tetramethyl-4-piperidone (*N*-methylvinyldiacetonamine) (IV; R = Me) is not

readily available, however, as it cannot be obtained by direct methylation of (IV; R = H) On the other hand, the carbinol corresponding to (IV), namely, 4-hydroxy-2 : 2 : 6-trimethylpiperidine, is easily *N*-methylated directly. As expected, therefore, *N*-methylation of the hydroxy-phenyltrimethylpiperidine (V; R = H) proceeded without difficulty, to give *4-hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine* (V; R = Me), characterised as the *hydrochloride* and *picrate*.

Both carbinols (V; R = H and Me) were readily dehydrated by warming them with alcoholic hydrogen chloride, to give *4-phenyl-2 : 2 : 6-trimethyl-* (VI or VII; R = H) and *4-phenyl-1 : 2 : 2 : 6-tetramethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine hydrochloride* (VI or VII; R = Me). Indeed, the dehydration was effected with such facility as to render the preparation of *O*-acyl and *O*-alkyl derivatives difficult or impossible, and for this reason attempts to obtain esters of type (II; R = Me) had to be abandoned.

When the magnesium complex from 2 : 2 : 6-trimethyl-4-piperidone and phenylmagnesium bromide was treated with acetic anhydride, the product consisted of a mixture of hydroxyphenyltrimethylpiperidine (V; R = H), phenyltrimethyltetrahydropyridine (VI or VII; R = H), and, curiously, *4-acetoxy-4-phenyl-2 : 2 : 6-trimethylpiperidine acetate* (acetate of II; R = H, R′ = Me), which was also characterised as the *hydrochloride*. The formation of this acetate is interesting, as it is evidently formed during distillation, by partial decomposition of acetoxyphenyltrimethylpiperidine with liberation of free acetic acid which then combines with another molecule of acetoxyphenyltrimethylpiperidine, to give the salt. Direct acetylation of hydroxyphenyltrimethylpiperidine (V; R = H), with acetic anhydride, gave *4-hydroxy-1-acetyl-4-phenyl-2 : 2 : 6-trimethylpiperidine*, together with unsaturated material (VI or VII). In the *N*-methyl series, the dehydration was found to be equally ready : under mild conditions, no reaction occurred, while under more vigorous conditions the base underwent almost complete dehydration. This resistance to acetylation is curious, as earlier workers experienced little difficulty in the preparation of compounds of type (I).

Experimental.

4-Hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (V; R = H).—To a Grignard solution (50% excess) prepared from bromobenzene (66·8 g.), magnesium (10·2 g.), and anhydrous ether (150 c.c.), 2 : 2 : 6-trimethyl-4-piperidone (20 g.; B.P. 101,738) in ether (25 c.c.) was added dropwise, with stirring. When the vigorous reaction had subsided, the solution was refluxed for a further hour, cooled, and then decomposed with ice and ammonium chloride. After being kept overnight the solid was collected, dried, extracted with ether to remove ether-soluble products, and recrystallised from ethanol–ether. Basification with sodium hydroxide, and extraction with ether, gave *4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine* (13 g.) as colourless needles, m. p. 91—92°, from light petroleum (Found : C, 76·7; H, 9·9; N, 6·6. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6; N, 6·4%). After distillation in a vacuum, it was obtained in the form of colourless prisms, m. p. 96—97°, which on repeated recrystallisation from light petroleum, reverted to the needle form, m. p. 91—92°. The *picrate*, prepared in ether and recrystallised from water, formed yellow prisms, m. p. 188—189° (decomp.) (Found : C, 53·6; H, 5·4; N, 12·8. $C_{20}H_{24}O_8N_4$ requires C, 53·6; H, 5·4; N, 12·5%). The *hydrogen oxalate*, prepared in ether and recrystallised from ethanol–ether, formed small colourless needles, m. p. 201—202° (decomp.) (Found : C, 62·2; H, 7·5; N, 4·8. $C_{16}H_{23}O_5N$ requires C, 62·1; H, 7·4; N, 4·5%). The *hydrochloride*, prepared in ether, and crystallised from ethanol–ether, formed colourless prisms, m. p. 247—248° (decomp.) (Found : C, 65·8; H, 8·5; N, 5·7. $C_{14}H_{22}ONCl$ requires C, 65·7; H, 8·6; N, 5·5%). In the preparation of this derivative a small quantity of the product of dehydration (see below) was also isolated. The *acetate* formed colourless prisms, m. p. 223—224° (decomp.), from acetone (Found : C, 69·2; H, 8·9; N, 5·2. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·0%).

4-Phenyl-2 : 2 : 6-trimethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine (VI or VII; R = H).—A solution of the above hydroxyphenyltrimethylpiperidine (1·75 g.) in ethanol (15 c.c.) was saturated with hydrogen chloride and then heated to 80°, for 6 hours, during which the solution was periodically re-saturated with hydrogen chloride. The solution was then cooled, basified with dilute sodium hydroxide solution, and extracted with ether. Evaporation gave a brown oil, b. p. 90—95°/0·5 mm. (1·5 g.); the pale yellow distillate darkened on storage. *4-Phenyl-2 : 2 : 6-trimethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine hydrochloride*, prepared from the base in ethereal solution, formed colourless prisms, m. p. 266—267° (decomp.), from ethanol–ether (Found : C, 70·6; H, 8·3; N, 6·1. $C_{14}H_{20}NCl$ requires C, 70·8; H, 8·4; N, 5·9%). The *hydrogen oxalate* recrystallised from ethanol–ether in small colourless needles, m. p. 207—208° (decomp.) (Found : C, 65·8; H, 6·9; N, 5·1. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2; N, 4·8%).

4-Acetoxy-4-phenyl-2 : 2 : 6-trimethylpiperidine.—2 : 2 : 6-Trimethyl-4-piperidone (5 g.) was treated with a 50% excess of phenylmagnesium bromide, as above, and the solution heated under reflux for 13 hours. Acetic anhydride (11 g.), in ether, was added to the cooled solution, which was then refluxed for a further 9 hours, cooled, and hydrolysed with ice and 6N-hydrochloric acid. The aqueous layer was separated, basified, and extracted with chloroform. Distillation of the residue gave 2 : 2 : 6-trimethyl-4-piperidone (0·7 g.) and a yellow oil (0·3 g.), b. p. 110—130°/2 mm. When the oil was set aside, a small amount of crystals separated and on recrystallisation from ethanol–ether gave *4-acetoxy-4-phenyl-2 : 2 : 6-trimethylpiperidine acetate* as colourless prisms, m. p. 176—177° (Found : C, 67·1; H, 8·1; N, 4·6. $C_{18}H_{27}O_4N$

requires C, 67·3; H, 8·4; N, 4·4%). 4-*Acetoxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine hydrochloride*, obtained in the usual way from the above acetate, formed colourless prisms, m. p. 238—239° (decomp.), from ethanol–ether (Found: C, 64·3; H, 7·9; N, 4·8. $C_{16}H_{24}O_2NCl$ requires C, 64·5; H, 8·1; N, 4·7%). The residual oil from the distillate was dissolved in ether and treated with hydrogen chloride. Crystallisation from ethanol–ether gave colourless prisms, m. p. 264—265° (decomp.), of 4-phenyl-2 : 2 : 6-trimethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine hydrochloride, identified by direct comparison with a specimen prepared as above, and also by analysis (Found: C, 70·9; H, 8·3; N, 5·4%).

Direct acetylation of 4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (1 g.) by refluxing it with acetic anhydride (5 g.) for 5 minutes, followed by basification and extraction with chloroform, gave a colourless solid. After being washed with dilute hydrochloric acid to remove basic material, and recrystallised from light petroleum, 4-*hydroxy*-1-*acetyl*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* was obtained as colourless needles, m. p. 112—113° (Found: C, 73·2; H, 8·8; N, 5·1. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

4-*Hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine* (V; R = Me).—A mixture of 4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (2 g.), and 40% aqueous formaldehyde (2 g.) was heated to 100°. After an hour, a vigorous reaction occurred, and the whole mass solidified. The solid was washed free from formaldehyde with water and recrystallised from light petroleum. 4-*Hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine* (2 g.) formed colourless needles, m. p. 133—134° (Found: C, 77·4; H, 9·7; N, 6·2. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9; N, 6·0%). The *hydrochloride*, prepared in ether and recrystallised from ethanol–ether, formed colourless prisms, m. p. 243—244° (decomp.) (Found: C, 66·8; H, 8·9; N, 5·4. $C_{15}H_{24}ONCl$ requires C, 66·8; H, 8·9; N, 5·2%).

Attempted Acetylation of 4-*Hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine*.—The esterification of carbinols of similar structure was reported by Jensen and Lundquist (*loc. cit.*), and by Ziering *et al.* (*loc. cit.* and *J. Org. Chem.*, 1947, **12**, 904). Their methods have been used and extended in attempts to acetylate 4-hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine, but without avail. Thus, treatment with acetyl chloride in the cold, with or without an inert solvent (ether, benzene) resulted in complete dehydration to (VI or VII; R = Me) within 48 hours. Acetic anhydride under similar conditions did not react, and heating at 100° or boiling under reflux with acetic anhydride and sodium acetate, pyridine, or a trace of concentrated sulphuric acid caused dehydration in varying degrees.

An unsuccessful attempt was also made to achieve acetylation by treatment with ethylmagnesium bromide, followed by reaction of the resulting magnesium complex with cold acetic anhydride (Houben, *Ber.*, 1906, **39**, 1736).

4-*Phenyl*-1 : 2 : 2 : 6-*tetramethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine* (VI or VII; R = Me).—A solution of the above hydroxyphenyltetramethylpiperidine (0·5 g.) in ethanol (10 c.c.) was saturated with hydrogen chloride and heated to 80° for 7 hours, during which the solution was periodically re-saturated with hydrogen chloride. Basification with sodium hydroxide, and extraction with ether, gave a brown oil. 4-*Phenyl*-1 : 2 : 2 : 6-*tetramethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine picrate* was prepared from this oil in ethanol and, after recrystallisation from ethanol formed yellow needles, m. p. 161—162° (decomp.) (Found: C, 57·5; H, 5·4; N, 12·6. $C_{21}H_{24}O_7N_4$ requires C, 57·6; H, 5·4; N, 12·6%).

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