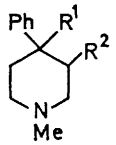
Enamines related to Pethidine

By J. W. Lewis and P. A. Mayor,* Reckitt and Sons Ltd., Pharmaceutical Research Laboratories, Hull

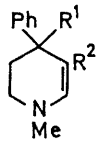
Dehydropethidine, prepared by the oxidation of pethidine with mercury(II) acetate, has been reduced with lithium aluminium hydride to 2-methyl-5-phenyl-2-aza-7-oxabicyclo[3,2,1]octane (7). The latter reacts with methyl vinyl ketone to give the corresponding 8-(2-acetylethyl)derivative (9), which is in equilibrium with its enamine form (10).

CYCLIC enamines may be conveniently prepared by the mercury(II) acetate oxidation of cyclic tertiary amines.[1] The oxidation of substituted piperidines in this way normally gives the corresponding substituted 1,2,3,4-tetrahydropyridines, although in some cases dimeric products are formed.[2] This reaction has now been applied to pethidine (1). The product was the expected dehydro-compound (2), the i.r. spectrum of which showed a band at 1640 cm.$^{-1}$ characteristic of an enamine double bond. The n.m.r. spectrum showed a pair of doublets centred at τ 3·86 and 5·26 (J 8 Hz) assigned to the two olefinic protons. Other features of the spectra were also as expected. The dehydro-compound gave an iminium perchlorate when treated with 70% perchloric acid in ethanol.

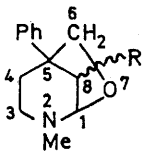
Dehydropethidine readily reacted with methyl vinyl ketone to give the addition product (3). The presence of the enamine double bond in the product was again confirmed by an i.r. band at 1660 cm.$^{-1}$; the n.m.r. spectrum in this case showed only one olefinic proton signal, at τ 4·03.



R¹	R²
(1) CO_2Et	H
(4) CO_2Et	$[CH_2]_2Ac$
(5) CO_2Et	$[CH_2]_2$·CH(Me)·OH
(6) CH_2·OH	H



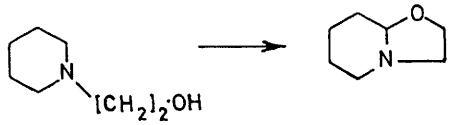
R¹	R²
(2) CO_2Et	H
(3) CO_2Et	$[CH_2]_2Ac$
(8) CH_2·OH	H
(10) CH_2·OH	$[CH_2]_2Ac$



R
(7) H
(9) $[CH_2]_2Ac$

The perchlorate salt of the adduct contains three reducible centres. Formic acid selectively reduced the iminium double bond to give the substituted pethidine (4), whereas sodium borohydride reduced both the iminium and the ketone groupings to give the saturated carbinol (5). Attempts to prepare 2-substituted derivatives of pethidine by treating the iminium perchlorates of the dehydro-compounds with Grignard reagents were unsuccessful. The products were inseparable mixtures.

Reduction of dehydropethidine with lithium aluminium hydride gave a low-melting solid together with a small amount of 'pethidine alcohol' (6), readily removed by extraction. The major reduction product was also obtained in a less pure state by dehydrogenation of pethidine alcohol with mercury(II) acetate. Lithium aluminium hydride would not normally be expected to reduce the double bond of an enamine base and yet the i.r. spectrum of the major product showed now band around 1650 cm.$^{-1}$. The compound was also transparent in the carbonyl and OH stretching regions. Any gross change in structure was excluded by the fact that hydrogenation in the presence of palladised charcoal gave (6) as the sole product. On this evidence the lithium aluminium hydride reduction product was assigned structure (7), in which the intermediate dehydrocarbinol (8) has cyclised *via* its iminium ion. An analogous cyclisation was observed [3] in the mercury(II) acetate dehydrogenation of 2-piperidinoethanols to give oxazolidines (Scheme).



SCHEME

The n.m.r. spectrum of the reduction product was generally in agreement with structure (7). The C-6 methylene protons are not equivalent and gave rise to a typical AB pattern with doublets centred at τ 5·84 and 6·16 (J 8 Hz). The coupling constant is small for a normal geminal coupling but it is not unreasonable for a geminal CH_2 attached to an electronegative group.[4] The signal for the C-1 proton appeared as a doublet centred at τ 5·20 (J 4 Hz). The chemical shift for this proton is reasonable, it being attached to a carbon atom bonded to both an oxygen and a nitrogen atom, but the splitting appears anomalous. However, in view of work described later it is apparent that the coupling between this proton and one of the C-8 methylene protons is zero. This would be expected [5] if the dihedral angle

[1] N. J. Leonard, A. S. Hay, R. W. Fulmer, and D. W. Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[2] N. J. Leonard and F. P. Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279.
[3] N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, 1960, **82**, 5148.
[4] H. J. Bernstein and N. Sheppard, *J. Chem. Phys.*, 1962, **37**, 3012.
[5] H. Conroy, *Adv. Org. Chem.*, 1960, **2**, 265.

between these protons is about 85°. A model suggests that this may well be the case.

The cyclised dehydropethidine alcohol (7) still showed some properties of an enamine; for example it condensed readily with methyl vinyl ketone. Since the adduct showed no evidence in the i.r. spectrum of bands due to hydroxy- or enamine functions, it must exist largely in the cyclised form (9). The n.m.r. spectrum of the adduct was basically similar to that of the starting material apart from signals due to the portion added. However, many of the principal bands were twinned, indicating that the product was a mixture. This supposition was supported by the t.l.c., which showed two spots. When the two spots were extracted separately and re-run, each extract gave the same mixture as the original. The adduct is thus an equilibrium mixture of C-8 isomers, equilibrium being achieved *via* the enamine form (10). The n.m.r. spectrum showed a complex two-proton signal near τ 6 assigned to the C-6 methylene protons. The overlap of the two spectra made assignment of individual lines difficult. However, since the proton at C-1 gave rise to a doublet centred at τ 5·35 (J 5 Hz) and a singlet at τ 5·47 the C-1 proton must couple with the C-8 proton in one isomer but not in the other.

EXPERIMENTAL

I.r. spectra were determined for liquid films or potassium bromide discs, for liquids and solids respectively. N.m.r. spectra were measured at 100 MHz (unless otherwise stated) for solutions in deuteriochloroform containing tetramethylsilane as internal reference, by use of a Varian T60 spectrometer. Other spectra (40 MHz) were obtained with a Perkin-Elmer spectrometer. Only the important bands are quoted.

Ethyl 1-*Methyl*-4-*phenyl*-1,2,3,4-*tetrahydropyridine*-4-*carboxylate* (2).—A solution of pethidine (10 g.) and yellow mercury(II) oxide (44 g.) in 40% aqueous acetic acid (200 ml.) was boiled for 10 hr. The precipitate of mercury(I) acetate was removed and the solution was saturated with hydrogen sulphide. The filtered solution was basified with potassium carbonate and extracted with ether. Distillation of the extract gave the *ester* as an oil (5 g.), b.p. 120—122°/0·5 mm. (Found: C, 72·8; H, 7·5; N, 5·7. $C_{15}H_{19}NO_2$ requires C, 73·4; H, 7·8; N, 5·7%), $\nu_{max.}$ 1730 (ester) and 1640 (enamine) cm.$^{-1}$, τ (40 MHz) 3·86 and 5 26 (each d, J 8 Hz, 6- and 5-protons).

A solution of the base in ether was treated with ethanol–70% perchloric acid (1 : 1) until distinctly acid. The precipitated *iminium perchlorate* gave prisms (5·2 g.), m.p. 139—141° (from ethanol) (Found: C, 52·0; H, 5·9; Cl, 10·45; N, 4·2. $C_{15}H_{19}NO_2,HClO_4$ requires C, 52·1; H, 5·8; Cl, 10·25; N, 4·2%).

5-(2-*Acetylethyl*)-4-*ethoxycarbonyl*-1-*methyl*-4-*phenyl*-2,3,4,5-*tetrahydropyridinium Perchlorate*.—A solution of the ester (2) (65 g.) and methyl vinyl ketone (100 ml.) in anhydrous dioxan (150 ml.) was kept at room temperature for 18 hr. and then distilled under reduced pressure. The fraction boiling at 160—164°/0·5 mm. was collected and dissolved in dilute acetic acid, and the solution was treated with an excess of aqueous sodium perchlorate. The precipitate gave the *iminium perchlorate*, m.p. 128—130° (from ethanol) (Found: C, 54·8; H, 6·4; Cl, 8·7; N, 3·4. $C_{19}H_{25}NO_3,HClO_4$ requires C, 54·9; H, 6·3; Cl, 8·5; N, 3·4%), $\nu_{max.}$ (for the base) 1730br (ester and ketone) and 1660 (enamine) cm.$^{-1}$, τ (40 MHz) 4·03 (s, 6-proton).

Ethyl 3-(2-*Acetylethyl*)-1-*methyl*-4-*phenylpiperidine*-4-*carboxylate* (4).—Formic acid (250 ml.) containing 5-(2-acetylethyl)-4-ethoxycarbonyl-1-methyl-4-phenyl-2,3,4,5-tetrahydropyridinium perchlorate (25 g.) was boiled under reflux for 18 hr. The solvent was evaporated off and the residue was basified with aqueous sodium hydroxide. The material extracted with ether from the aqueous mixture gave the *piperidine* (11 g.), m.p. 109—110° (from aqueous ethanol) (Found: C, 71·8; H, 8·1; N, 4·8. $C_{19}H_{27}NO_3$ requires C, 71·9; H, 8·6; N, 4·4%), $\nu_{max.}$ 1715 cm.$^{-1}$ (ester and ketone).

Ethyl 3-(3-*Hydroxybutyl*)-1-*methyl*-4-*phenylpiperidine*-4-*carboxylate* (5).—Sodium borohydride (1 g.) was added in portions to 5-(2-acetylethyl)-4-ethoxycarbonyl-1-methyl-4-phenyl-2,3,4,5-tetrahydropyridinium perchlorate (1 g.) in ice-cold methanol (20 ml.) with stirring during 10 min. The reaction was completed by heating the mixture on a steam-bath for 15 min. The solution was diluted with aqueous potassium hydroxide and extracted with ether. Evaporation of the extract and crystallisation of the residue from wet light petroleum (b.p. 60—80°) gave the *carbinol* as a hydrate, m.p. 55—58° (Found: C, 67·5; H, 9·4; N, 4·2. $C_{19}H_{29}NO_3,H_2O$ requires C, 67·6; H, 9·3; N, 4·2%), $\nu_{max.}$ 3400, 3220 (OH), and 1715 (ester) cm.$^{-1}$.

2-*Methyl*-5-*phenyl*-2-*aza*-7-*oxabicyclo*[3,2,1]*octane* (7).—Lithium aluminium hydride (0·7 g.) was added to ethyl 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-4-carboxylate (3·5 g.) in ether (50 ml.) and the mixture was refluxed for 30 min. Water (1·4 ml.) was added cautiously and the mixture was filtered. The filtrate was evaporated and the residual oil was treated with light petroleum (5 ml.; b.p. 60—80°); 4-hydroxymethyl-1-methyl-4-phenylpiperidine (0·25 g.) separated. The filtered solution was concentrated to give the *bicyclic product* (2·3 g.), m.p. 41—45°. T.l.c. indicated that it contained about 5% of the carbinol (6) which could not be removed by further extraction (Found: C, 76·8; H, 8·45; N, 6·6. $C_{13}H_{17}NO$ requires C, 76·8; H, 8·4; N, 6·9%). The i.r. spectrum of a solution in chloroform showed only a small band in the OH region due to the pethidine alcohol content. There were no absorption bands in the 1600—1800 cm.$^{-1}$ region. The n.m.r. spectrum showed τ 2·6—2·9 (5H, aromatic), 5·20 (d, J 4 Hz, 1-proton), 5·84 and 6·16 (each d, J 8 Hz, 6-protons), and 7·64 (s, NMe).

Hydrogenation of the Bicyclic Compound (7).—Compound (7) (0·5 g.) and palladised charcoal (0·1 g., 10%) in ethanol (25 ml.) were shaken in an atmosphere of hydrogen at room temperature and pressure for 30 min. during which time 1 equiv. of hydrogen was consumed. The solution was filtered and evaporated to give 4-hydroxymethyl-1-methyl-4-phenylpiperidine (0·5 g.), m.p. and mixed m.p. with an authentic specimen [6] 136°.

8-(2-*Acetylethyl*)-2-*methyl*-5-*phenyl*-2-*aza*-7-*oxabicyclo*-[3,2,1]*octane* (9).—A solution of the bicyclic compound (7) (20 g.) in methyl vinyl ketone (100 ml.) was boiled for 2 hr. Fractionation of the solution under reduced pressure gave the *adduct* (24·6 g.), b.p. 160—170°/1 mm. (Found: C, 74·2; H, 8·6; N, 4·6. $C_{17}H_{23}NO_2$ requires C, 74·7; H, 8·5; N, 5·1%), $\nu_{max.}$ ($CHCl_3$) 1714 cm.$^{-1}$ (ketone); no band could be

[6] S. Chiavarelli and G. B. Marini-Bettolo, *Rend. Ist. super. Sanita.*, 1955, **18**, 1014 (*Chem. Abs.*, 1958, **52**, 6340b).

assigned to an OH or an enamine group; τ 2·6—2·95 (5H, aromatic), 5·35 (d, J 5 Hz) and 5·47 (s) (total 1H, 1-proton), 5·75—6·13 (complex, 6-proton), 7·64 and 7·67 (NMe), and 7·95 and 8·00 (COMe). T.l.c. on silica [cyclohexane–acetone–methyl ethyl ketone–methanol–water (100 : 80 : 30 : 5 : 1)] showed two spots. The two components were separated by preparative t.l.c.; the bands were scraped off and extracted separately with chloroform. T.l.c. of the chloroform extracts still showed two spots that corresponded to the original mixture.

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