Synthesis and Mass Spectra of Some 3-Acylamino-2-piperidones

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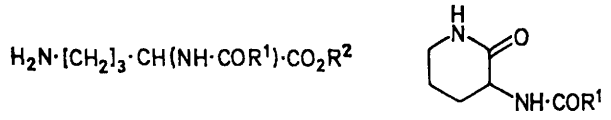
A number of 3-acylamino-2-piperidones having hydroxy-, oxo-, or vinyl groups in the acyl residue have been synthesized. The mechanism of formation by electron impact of the principal fragment ions of 3-(3-hydroxybutyrylamino)-2-piperidone has been investigated by examination of deuteriated analogues.

THE present investigation was carried out to assist in the determination by mass spectrometry of the structures of lipids of the type (I),[1] where R^1 and R^2 are alkyl chains which may contain double bonds and/or functional groups. Ornithine esters are known [2] to decompose thermally in the ion source of the mass spectrometer to give 2-piperidones. Since the latter compounds can be handled more easily than the free amino-compounds or their hydrochlorides, the synthesis and mass spectral examination of 3-acylamino-2-piperidones (II) was undertaken. A detailed examination of the mass spectrum of 2-piperidone has been made before.[3]

Synthetic Work.—Treatment of 3-amino-2-piperidone [4] with appropriately substituted carboxylic acid derivatives in the presence of *NN*-dicyclohexylcarbodi-imide [5] failed to give the required products. Accordingly a route involving prefential δ-acylation of L-ornithine was employed. The amino-acid copper(II) complex [6] was treated with benzyloxycarbonyl chloride [7] and the copper

[1] A. Gorchein, *Biochim. Biophys. Acta*, 1968, **152**, 358.
[2] K. Biemann, J. Seibl, and F. Gapp, *J. Amer. Chem. Soc.*, 1961, **83**, 3795.
[3] A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 5536.
[4] K. Golankiewicz and M. Wiewiorowski, *Acta Biochim. Polon.*, 1963, **10**, 443.
[5] N. F. Albertson, *Org. Reactions*, 1962, **12**, 205.
[6] G. R. Brubaker and D. H. Busch, *Inorg. Chem.*, 1966, **5**, 2110.
[7] R. C. Barass and D. T. Elmore, *J. Chem. Soc.*, 1957, 3134.

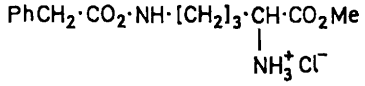
was then removed as the ethylenediaminetetra-acetic acid (EDTA) complex.[8] Esterification with anhydrous



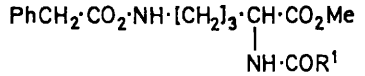
(I) (II)

a; $R^1 = CH_2{\cdot}COMe$
b; $R^1 = CH_2{\cdot}CH(OH)Me$
c; $R^1 = CH_2{\cdot}CH(OH)Et$
d; $R^1 = CH_2{\cdot}CH(OH)Pr$
e; $R^1 = CH_2{\cdot}CH(OH){\cdot}C_6H_{13}$-n
f; $R^1 = CH_2{\cdot}CH(OH){\cdot}CD_3$
g; $R^1 = CD_2{\cdot}CH(OH)Me$
h; $R^1 = CH_2{\cdot}CD(OH)Me$
i; $R^1 = CH{:}CH{\cdot}C_6H_{13}$-n
j; $R^1 = CH{:}CHEt$
k; $R^1 = CH{:}CHMe$

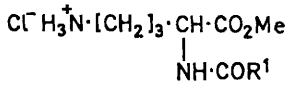
methanolic hydrogen chloride or (better) dimethyl sulphite [9] gave (+)-δ-*N*-benzyloxycarbonyl-L-ornithine



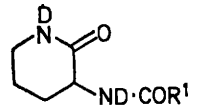
(III)



(IV)



(V)



(VI) a; $R^1 = CH_2{\cdot}COMe$
b; $R^1 = CH_2{\cdot}CH(OD)Me$

methyl ester hydrochloride (III). Condensation of the ester (III) with the appropriately substituted carboxylic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide [10] gave the acylamino-compound (IV) without significant racemization. The water-soluble carbodi-imide was employed as difficulties were experienced in separating the required product from dicyclohexylurea when the more common dicyclohexylcarbodiimide was used. Hydrogenolysis of the compound (IV) over 10% palladium–charcoal in the presence of hydrochloric acid (1 mol. equiv.) afforded the hydrochloride of the α-*N*-acylornithine methyl ester (V), which on filtration through an appropriate ion-exchange resin yielded the substituted 3-amino-2-piperidone (II).

Compound (IVa) was prepared by heating the isopropylidene derivative with acetone containing toluene-*p*-sulphonic acid. Deuteriation α to the amide carbonyl group was effected by boiling (IIa) with deuterium oxide; reduction of the product (VIa) with sodium borohydride in [^{2}H]ethanol and deuterium oxide afforded compound (IIg). Reduction of the ketone (IIa) with sodium [$^2H_4$]borohydride in ethanol gave the alcohol (IIh). Compound (IIf) was obtained by use of 3-hydroxy[4-$^2H_3$]-butyric acid in place of the protio-analogue in the synthesis of (IVb). Exchange of the hydroxy- and amino-protons was carried out in the usual way; thus treatment of compound (IIb) with deuterium oxide gave compound (VIb).

The olefins (IIj and k) were not prepared as such. Their mass spectra were obtained by introducing the alcohols (IIb and c) into the heated inlet of the mass spectrometer. Dehydration occurred rapidly in the hot flask. That the conjugated olefins were obtained is shown by the fact that there was no loss of deuterium when the compounds (IIf and h) were examined in this way but compound (IIg) lost one atom of deuterium.

Mass Spectra.—The lipid from *Rhodopseudomonas spheroides* and its hydrolysis product [1] show in their mass spectra prominent peaks at *m/e* 185, 156, 141, and 115 with a broad (metastable m_2*) peak at 71·5.[11] The mass spectra of the alcohols (IIb—e) show considerable similarities not only to each other but also to the spectrum of the lipid and particularly to the spectrum of its hydrolysis product; only that of (IIb) will be considered in detail (Figure 1).

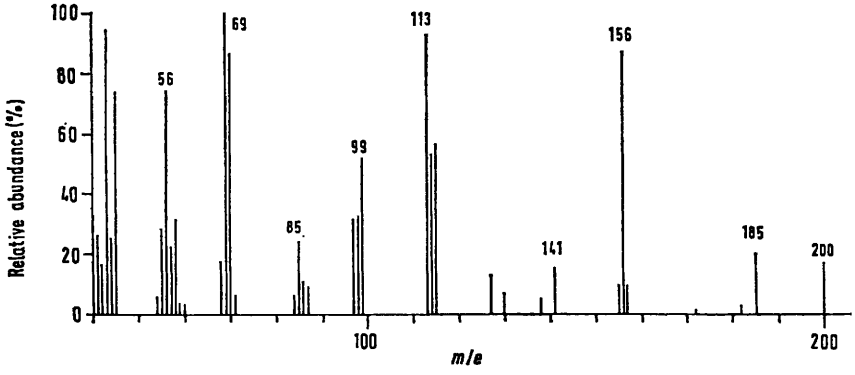


FIGURE 1 Mass spectrum of (+)-3-(3-hydroxybutyrylamino)-2-piperidone

The molecular ion ($M^{\cdot+}$) from (IIb) loses a methyl

[8] R. Ledger and C. Stewart, *Austral. J. Chem.*, 1965, **18**, 933.
[9] P. A. Cruickshank and J. C. Sheehan, *Analyt. Chem.*, 1964, **36**, 1191.
[10] J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, 1961, **26**, 2525; J. C. Sheehan and P. A. Cruickshank, *Org. Synth.*, 1968, **48**, 83.
[11] Unpublished observations.

radical to give a fragment, *m/e* 185 ($C_8H_{13}N_2O_3$), which in turn decomposes to form the ion, *m/e* 115 ($C_5H_{11}N_2O$), showing a metastable peak (m_2*) at 71·5. This process requires a double-hydrogen rearrangement and was further investigated by examination of the deuteriated compounds (IIf—h) and (VIb) (Figure 2). The mass

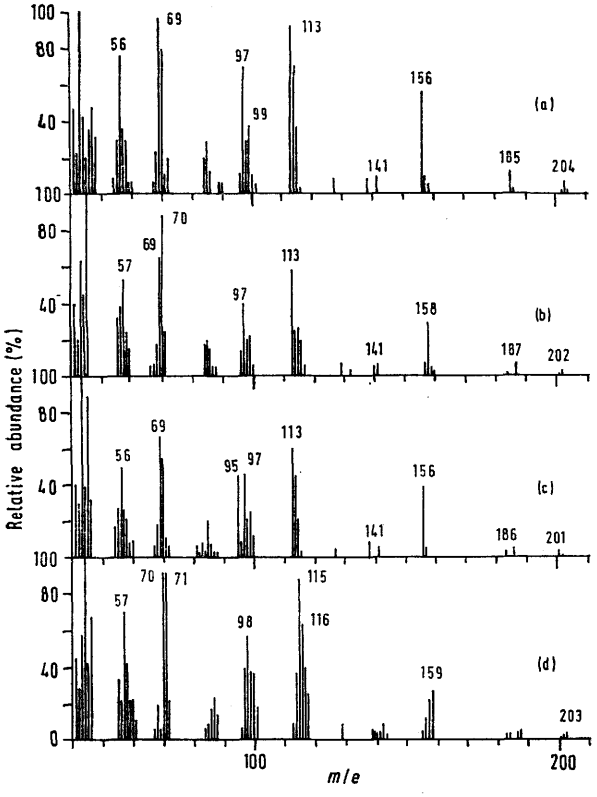
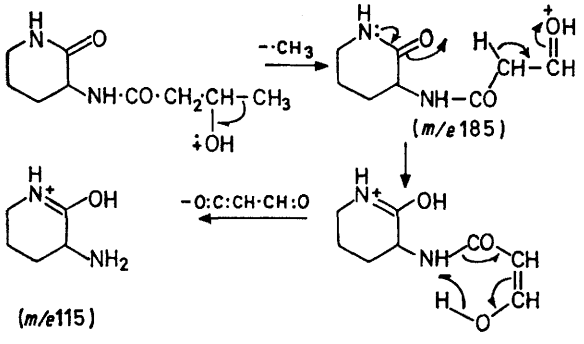
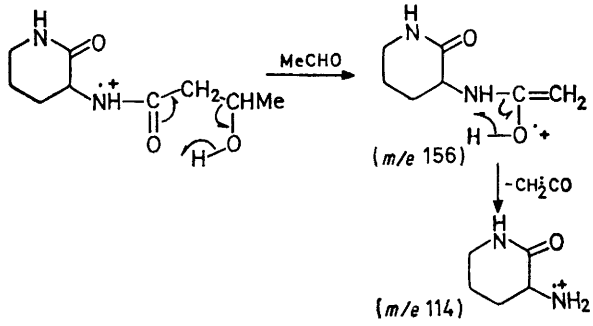


FIGURE 2 Mass spectra of (a) (+)-3-(3-hydroxy-[4-$^2H_3$]-butyrylamino)-2-piperidone, (b) (+)-3-(3-hydroxy[2-$^2H_2$]-butyrylamino)-2-piperidone, (c) (+)-3-(3-hydroxy-[3-^2H]-butyrylamino)-2-piperidone, and (d) (+)-3-(3-[^2H]hydroxy-butyryl[^2H]amino)-2-[1-^2H]piperidone

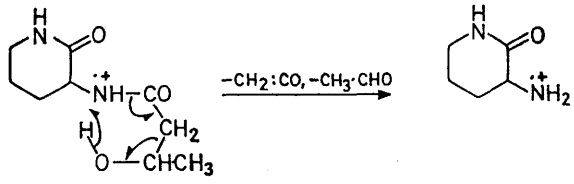
spectra of the latter leave little doubt that one of the methylenic hydrogen atoms α to the amide carbonyl group is involved.



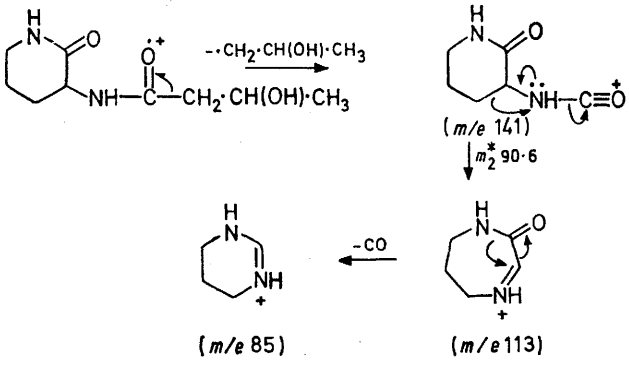
A transition in the first field-free region of the mass spectrometer (m_1*) shows that the ion, *m/e* 115, is also formed directly from the molecular ion. Evidently the same rearrangements as depicted for the $(M - CH_3)^+$ species can also occur in $M^{\cdot+}$, O:C:CH·CHMe·O· being eliminated. The ion, *m/e* 156, clearly arises by a McLafferty rearrangement with the elimination of acetaldehyde from the molecular ion. Loss of keten, indicated by a metastable peak (m_2*) at 83·3, leads to the



ion, *m/e* 114 ($C_5H_{10}N_2O$). The latter ion is formed (m_1*) in a one-step process from the molecular ion; support for such a process is to be found in the pyrolysis

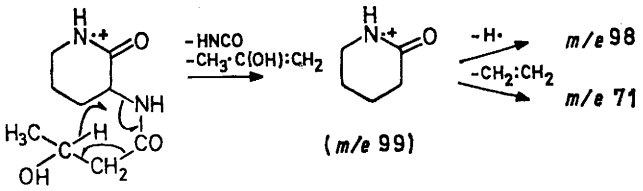


experiment described later. The ion *m/e* 113 ($C_5H_9N_2O$) has three precursors, $M^{\cdot+}$ and the ions *m/e* 156 and 141. It is likely that a mechanism similar to that illustrated for the molecular ion, operates in all three reactions. Loss of carbon monoxide from the ion, *m/e* 113, leads to the ion, *m/e* 85 ($C_4H_9N_2$).

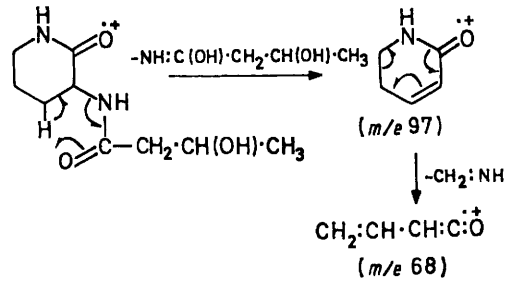


The mass spectra of the deuteriated compounds show that the ion, *m/e* 99, derived from the molecular ion, contains the carbinol hydrogen atom. Transfer of this hydrogen atom by way of a six-membered transition state with expulsion of NH:CO and CH_3·C(OH):CH_2 leads to the molecular ion of 2-piperidone, which can decompose further, for example, by loss of a hydrogen

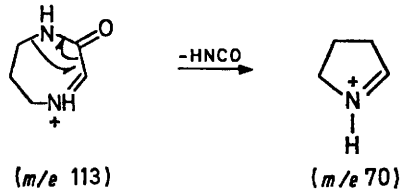
atom giving *m/e* 98, or of ethylene giving *m/e* 71. A McLafferty rearrangement involving the hydrogen atom



at C-4 of the piperidone ring can account for the formation of the ion *m/e* 97. The latter can undergo a retro-Diels–Alder reaction to give the ion, *m/e* 68.



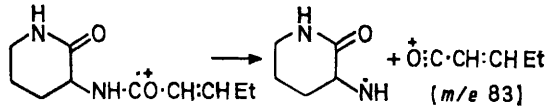
The formation of the abundant ion, *m/e* 70, from 2-piperidone has been noted by Duffield *et al.*,[3] who have proposed a mechanism involving a triradical species. Such a high energy intermediate seems most improbable and formation of the ion, *m/e* 70, from *m/e* 113 by loss of HNCO as shown seems more plausible.



The base peak (*m/e* 69) of the spectrum of compound (IIb) consists of three isobaric ions, C_5H_9, C_4H_7N, and C_4H_5O in the intensity ratio 9 : 3·9 : 1. Plausible mechanisms can be written for the formation of all these ions, for the intense ion, *m/e* 56, and for the ions of lower *m/e*, but since their parent ions are in doubt there seems little value in the exercise.

The spectrum of the ketone (IIa) does not show the ions *m/e* 156 and 115, but does show, as would be expected on the basis of the mechanisms proposed, the ions *m/e* 113, 98, 97, 70, and 69, which are all reasonably intense. The ion *m/e* 114 has about half the intensity of this species in the specum of (IIb).

The olefins (IIi) and (IIj) (Figure 3) show ions at *m/e* 156 and 115, but of much lower abundance than those derived from the corresponding alcohols (IIc and d). The ions, *m/e* 113, 97, 70, and 69, are again prominent, but the base peak is obtained by cleavage of the amido-group, the charge going with the acetyl fragment.



In an attempt to confirm the structures of some of the major fragment ions, the pyrolysis of (+)-3-(3-hydroxy-nonanoylamino)-2-piperidone (IIe) at 500° and 1 mmHg in a quartz tube was investigated. Keten was trapped as acetanilide by passing the pyrolysate into a solution of aniline in methylene chloride. The remainder of the volatile pyrolysate trapped at −196° contained five

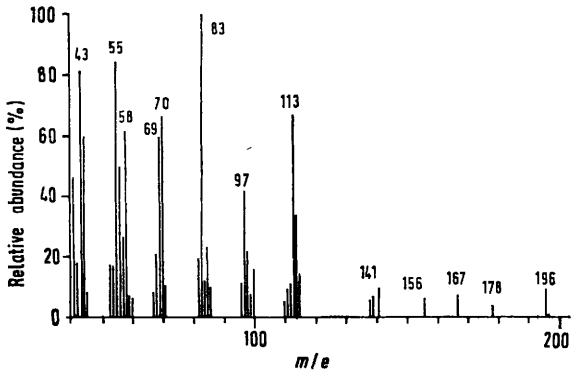


FIGURE 3 Mass spectrum of 3-(pent-2-enoylamino)-2-piperidone

products, as shown by t.l.c. The liquid product was identified as n-heptanal and the four solids, which were separated by preparative t.l.c., as starting material, (+)-3-amino-2-piperidone, (±)-3-acetamido-2-piperidone, and (±)-3-(*trans*-non-2-enoylamino)-2-piperidone. The formation of (+)-3-amino-2-piperidone, keten, and n-heptanal is analogous to the mass spectral fragmentation giving the ion, *m/e* 114. (±)-3-Acetamido-2-piperidone arises either by a process analogous to the mass spectral fragmentation forming the ion, *m/e* 156, followed by ketonization of the enol, or alternatively by reaction of 3-amino-2-piperidone with keten produced in the pyrolysis. In view of the fact that the 3-amino-2-piperidone isolated is optically active and it seems improbable that its acetylation would result in an inactive product, the former mechanism is preferred.

EXPERIMENTAL

Mass spectra were measured with an A.E.I. MS9 spectrometer operated at 8 kV accelerating voltage, 70 eV ionizing energy, and 100 μA trap current. Mass measurements were carried out at a resolving power of approximately 10,000 with heptacosafluorotri-n-butylamine as standard. Samples were introduced directly into the ion source at the minimum source temperature (130—190°). Metastable transitions in the first field-free region were determined by the standard A.E.I. ' defocusing ' technique.

N.m.r. spectra were recorded with Varian A-60 and HA-100 spectrometers, tetramethylsilane being used as an internal reference.

The purity of all compounds was checked by t.l.c. on silica gel and alumina. M.p.s were determined with a Kofler micro-hot-stage apparatus.

3-Ethylenedioxybutyric Acid.—A mixture of ethyl acetoacetate (2·0 g), ethylene glycol (1·0 g) and toluene-*p*-sulphonic acid (1 mg) in benzene (25 ml) was refluxed for 16 h under a Dean–Stark separator. The solvent was removed under reduced pressure and the residue distilled to give ethyl 3-ethylenedioxybutyrate (2·36 g), b.p. 96—104° at 2 mmHg. The ester (0·77 g) was dissolved in ethanol (3 ml), aqueous potassium hydroxide (0·0048M; 9·5 ml) was added dropwise, and the solution was heated at 75° for 3 h. The solvent was removed under reduced pressure and the residual white solid was dissolved in 50% aqueous methanol and filtered through Amberlite resin IR-20(H^+). The acidic filtrate was concentrated *in vacuo* to give the title compound (0·62 g); $\nu_{max.}$ (film) 1720 cm^{-1}; δ ($CDCl_3$), 11·17 (s, OH), 3·98 (4H, s), 2·70 (2H, s), and 1·52 p.p.m. (3H, s).

3-Hydroxybutyric Acid.—To a solution of ethyl 3-hydroxybutyrate [12] (1·0 g) in ethanol (5 ml) at 0°, aqueous potassium hydroxide (0·01 M; 20 ml) was added dropwise with stirring. Stirring was continued at 0° for 4 h, and the mixture was then kept at room temperature for 18 h. Evaporation to dryness gave a white solid which was dissolved in 50% aqueous methanol and filtered through Amberlite resin IR-20(H^+). Concentration of the acidic filtrate *in vacuo* gave 3-hydroxybutyric acid (0·53 g); $\nu_{max.}$ (film) 1709 cm^{-1}; δ ($CDCl_3$) 5·85 (s, OH), 4·22 (1H, sextet, *J* 6·40 Hz), 3·71 (s, OH), 2·46 (2H, d, *J* 6·40 Hz), and 1·25 p.p.m. (3H, d, *J* 6·40 Hz).

Ethyl 3-Hydroxy[4-$^2H_3$]*butyrate.*—To zinc dust (2·0 g; washed with N-hydrochloric acid, followed successively by water, ethanol, acetone, and diethyl ether, and dried *in vacuo* at 100° [13]), a mixture of freshly distilled ethyl bromoacetate (4·17 g) and [$^2H_3$]acetaldehyde [14] (1·41 g) in dry benzene (8 ml) and anhydrous ether (2 ml) was added under nitrogen in the usual manner of a Reformatski reaction.[15] The mixture was refluxed for 30 min, cooled, and poured into vigorously stirred 2N-sulphuric acid (30 ml) at 0°. The organic layer was washed successively with N-sulphuric acid (2 × 5 ml), 10% sodium carbonate (5 ml), N-sulphuric acid (5 ml), and water (2 × 5 ml). The aqueous acid extracts were washed with ether (2 × 5 ml) and the combined organic solutions were dried ($MgSO_4$). Removal of the solvent and distillation of the residue gave ethyl 3-hydroxy[4-$^2H_3$]butyrate (0·92 g); $\nu_{max.}$ (film), 3500, 2250, and 1730 cm^{-1}; δ ($CDCl_3$) 3·82—4·35 (2H, q, *J* 7·3 Hz, superimposed on complex, 1H), 2·98 (s, OH), 2·43 (2H, d, *J* 6·6 Hz), and 1·25 (3H, t, *J* 7·3 Hz); no signal at δ 1·25 p.p.m. corresponding to the 4-CH_3 group.

3-Hydroxyvaleric Acid.—Ethyl 3-hydroxyvalerate, prepared by the Reformatski reaction from n-propanol,[15] was saponified as described before to yield 3-hydroxyvaleric acid; $\nu_{max.}$ (film), 3400, 2650, and 1716 cm^{-1}. In the same way, 3-hydroxyhexanoic and 3-hydroxynonanoic (m.p. 61°) acids were also prepared.

δ-N-*Benzoyloxycarbonyl-*L*-ornithine.*[7,8]—To L-ornithine monohydrochloride (2·23 g) in boiling water (25 ml) was added basic copper carbonate (2·50 g). The mixture was cooled, unchanged copper carbonate was filtered off, and the filtrate was cooled (0°); magnesium oxide (2·30 g) was added with stirring. To the resultant mixture was added benzyl chloroformate (2·3 ml) in portions during 30 min. When precipitation of the blue copper complex was complete, it was collected and washed successively with water, ethanol, and ether. The complex (4·5 g) was dissolved in 2N-hydrochloric acid (75 ml) and ethylenediaminetetra-acetic acid (0·1N; 150 ml) was added. The solid which precipitated on cooling was filtered off, washed with water, and crystallized from 50% aqueous ethanol giving δ-*N*-benzyloxycarbonyl-L-ornithine (3·12 g), m.p. 255—256° (lit.,[7] 253—255°).

δ-N-*Benzyloxycarbonyl-*L*-ornithine Methyl Ester Hydrochloride.*—A suspension of δ-*N*-benzyloxycarbonyl-L-ornithine (1·00 g) in anhydrous methanol (5 ml) at 5° was saturated with anhydrous hydrogen chloride. Dimethyl sulphite (2·20 g) was added and the mixture was heated to 60° for 30 min. Removal of the solvent under reduced pressure gave the title compound (1·10 g), m.p. 134—135° (from acetone) (lit.,[16] 132—134°).

α-{N-(3-*Hydroxy*[4-$^2H_3$]*butyryl*)}-δ-(N-*benzyloxycarbonyl*)-L-*ornithine Methyl Ester Hydrochloride.*—3-Hydroxy[4-$^2H_3$]-butanoic acid (0·350 g) was added to a cooled (0°) solution of the foregoing ester (1·043 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide (0·527 g) in methylene chloride (25 ml). The solution was kept at 0° for 4 h, then washed successively with water, N-hydrochloric acid, water, N-potassium carbonate, and water, dried (Na_2SO_4), and evaporated under reduced pressure leaving the title compound (1·0 g), m.p. 73—74°; $\nu_{max.}$ (Nujol), 3350, 2250, 1742, 1684, and 1642 cm^{-1}; δ ($CDCl_3$), 7·28 (s, 5H), 6·60br (NH), 4·89—5·12 (2H, s, superimposed on broad NH), 4·30—4·67 (1H, m), 4·12 (s, OH), 3·64 (3H, s), 3·00—3·30 (2H, m), 2·20—2·35 (2H, m), and 1·32—1·92 p.p.m. (4H, m).

The m.p.s of five other derivatives prepared by the same method are listed in the Table.

	(IV)		(V)	(II)							
						Found (%)			Required (%)		
Compound	Yield (%)	M.p. (°C)	Yield (%)	Yield (%)	M.p. (°C)	C	H	N	C	H	N
(a)			90								
(b)	53	70—72	92	98	126—128	54·0	8·15	14·2	54·0	8·05	14·0
(c)	80	67—68	98	95	109—110	55·95	8·2	13·15	56·05	8·45	13·1
(d)	76	68—69	97	90	101—102	57·85	8·7	12·3	57·85	8·85	12·25
(e)	80	77—78	91	95	116—117	62·05	9·6	10·35	62·2	9·7	10·35
(f)	83	73—74	89	94	127—128						
(g)				65							
(h)				67							

[12] R. Mozingo, D. F. Wolff, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, 1944, **66**, 1859.
[13] R. L. Shriner, *Org. Reactions*, 1942, **1**, 1.
[14] J. E. Baldwin and R. G. Pudussery, *Chem. Comm.*, 1969, 679.
[15] F. Adickes and G. Andresen, *Annalen*, 1944, **555**, 41.
[16] R. L. M. Synge, *Biochem. J.*, 1948, **42**, 99.

α-[N-(3-*Oxobutyryl*)]-δ-(N-*benzyloxycarbonyl*)-L-*ornithine Methyl Ester* (IVa).—A mixture of α-[*N*-(3-methylenedioxybutyryl)]-δ-(*N*-benzyloxycarbonyl)-L-ornithine methyl ester (1·50 g), acetone (20 ml), and toluene-*p*-sulphonic acid (1 mg) was refluxed (*ca.* 15 h) until starting material had disappeared [t.l.c. in $CHCl_3$–MeOH (9 : 1) on silica gel]. Concentration of the solution under reduced pressure afforded an oil which was dissolved in methylene chloride; the solution was washed with N-potassium hydrogen carbonate, followed by water, dried (Na_2SO_4), and evaporated under vacuum to give the title compound (1·30 g); δ ($CDCl_3$) 7·26 (5H, s), 5·02 (2H, s), 4·33—4·73 (1H, m), 3·70 (3H, s), 3·40 (2H, s), 2·95—3·40 (2H, m), 2·23 (3H, s), and 1·36—1·90 p.p.m. (4H, m).

α-[N-(3-*Oxobutyryl*)]-L-*ornithine Methyl Ester Hydrochloride* (Va).—The ester (IVa) (1·30 g) in 80% aqueous methanol (40 ml) and N-hydrochloric acid (3·6 ml) was hydrogenated at atmospheric pressure and room temperature over 10% palladium–charcoal (0·6 g). The residue after removal of the catalyst and solvent was partitioned between ethyl acetate and water (1 : 1). The aqueous layer was concentrated under reduced pressure and dried *in vacuo* (KOH), affording the ester hydrochloride as a glass (0·86 g); $\nu_{max.}$ ($CHCl_3$) 1724 and 1650 cm^{-1}; δ (Me_2SO) 7·80—8·20 (m, NH_3^+), 4·10—4·40 (1H, m), 3·58 (3H, s), 3·32 (2H, s), 2·60—2·90 (2H, m), 2·10 (3H, s), and 1·40—1·82 p.p.m. (4H, m).

Five other benzyloxycarbonyl-L-ornithine derivatives were converted in this manner in the yields listed in the Table.

3-(3-*Oxobutyrylamino*)-2-*piperidone* (IIa).—To the foregoing ester hydrochloride (0·483 g) dissolved in 50% aqueous methanol (10 ml) silver oxide (0·245 g) was added with stirring. After 16 h the precipitate was filtered off and washed with methanol. The filtrate and washings were saturated with hydrogen sulphide and then filtered through activated charcoal. The filtrate on concentration under reduced pressure gave the *title compound* (0·35 g), m.p. 83—84° (from ethyl acetate) (Found: C, 54·55; H, 7·15; N, 14·1. $C_9H_{14}N_2O_3$ requires C, 54·55; H, 7·1; N, 14·15%).

3-(3-*Hydroxybutyrylamino*)-2-*piperidone* (IIb).—α-[*N*-(3-Hydroxybutyryl)]-L-ornithine methyl ester hydrochloride (0·483 g) was dissolved in 50% aqueous methanol (10 ml) and passed through Amberlite resin IR-45 (25 g; 60—80 mesh). Concentration of the filtrate under vacuum afforded the *piperidone* (IIb) (0·196 g), m.p. 126—128° (from methylene chloride), $\nu_{max.}$ (CH_2Cl_2) 1670 and 1659 cm^{-1}; $[\alpha]_D^{25}$ ($CHCl_3$) + 38°.

The same method was used for the substituted 2-piperidones whose m.p.s and analytical data are shown in the Table.

(+)-3-(3-*Oxo*[2-$^2H_2$]*butyryl*[N-^{2}H]*amino*)-2-[1-^{2}H]*piperidone*.—To 3-(3-oxobutyrylamino)-2-piperidone (0·10 g) dissolved in ethan[^{2}H]ol [17] (0·50 ml) was added deuterium oxide (0·10 ml) and the mixture was stirred for 24 h. Evaporation under reduced pressure left a white solid; this treatment was carried out three times and thus afforded the title compound (0·10 g), m.p. 84—85°. The n.m.r. spectrum did not show the singlet signal (δ *ca.* 3·4 p.p.m.) attributable to the 2-CH_2 group.

(+)-3-(3-*Hydroxy*[2-$^2H_2$]*butyrylamino*)-2-*piperidone* (IIg).—The foregoing ketone (0·10 g) dissolved in ethan[^{2}H]ol [17] (1 ml) was added to sodium borohydride (0·009 g) in ethan[^{2}H]ol and deuterium oxide (0·3 ml; 1 : 2). After being stirred for 30 min the mixture was concentrated under vacuum and the product was isolated by preparative t.l.c. [$CHCl_3$–MeOH (9 : 1) on silica gel] as a gum (0·065 g), $M^{\cdot+}$ 202. The i.r. spectrum showed no band at 1715 cm^{-1} (ketone C=O); the n.m.r. spectrum showed a doublet at δ 1·23 p.p.m. (CH_3) and no signal at δ 2·31 (CH_2·CO).

(+)-3-(3-[^{2}H]*Hydroxybutyryl*[^{2}H]*amino*)-2-[1-^{2}H]*piperidone*.—A mixture of (+)-3-(3-hydroxybutyrylamino)-2-piperidone (0·100 g), ethan[^{2}H]ol [17] (0·1 ml), and deuterium oxide (0·2 ml) was stirred for 24 h at room temperature and then concentrated under reduced pressure. Two successive repetitions of this procedure gave the title compound (0·100 g).

Pyrolysis of (+)-3-(3-*Hydroxynonanoylamino*)-2-*piperidone* (IIe).—The piperidone (0·200 g) was distilled slowly through a silica tube at 500° and 1 mmHg into a receiver at −195°. A liquid collected in the receiver and a solid in the neck of the receiver. The liquid was warmed to 50° and the gas evolved passed into 2,4-dinitrophenylhydrazine solution. No solid formed, indicating the absence of acetaldehyde. The liquid, however, gave a 2,4-dinitrophenylhydrazone, m.p. 106°. Its identity as n-heptanal was confirmed by combined g.l.c.–mass spectrometry (GC–MS) ($M^{\cdot+}$ 114) and mixed m.p. of the derivative with an authentic specimen. G.l.c.–m.s. indicated the presence in the liquid of a second component which was identified as keten by placing a solution of aniline in methylene chloride in the cooled receiver. Removal of the solvent under reduced pressure gave a solid whose i.r. spectrum was identical with that of acetanilide. The mixture of solid products from the pyrolysis was separated by t.l.c. and shown to contain starting material (0·047 g; m.p. 116—117°), (+)-3-amino-2-piperidone [4] (0·003 g; m.p 192—194°), (±)-3-acetamido-2-piperidone (0·046 g; m.p. 185—187°), and 3-(*trans*-non-2-enoylamino)-2-piperidone (IIi) (0·011 g; m.p. 200°). The identity of the first three compounds was proved by comparison of m.p.s and i.r. spectra with those of authentic specimens; the structure of compound (IIi) followed from its i.r., u.v., mass, and n.m.r. (100 MHz) spectra.

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