1216. *Studies on Some* O-*Acyl* N-*Substituted Hydroxylamines*

By P. G. Sammes

Several *O*-acyl *N*-substituted hydroxylamine derivatives have been prepared and studied as potential acylating agents. *NO*-Diacylhydroxylamines react with amines to give the corresponding amide and hydroxamic acid. Under forcing conditions, certain α-carbamoylhydroxylamines undergo the amino-acyl insertion reaction.

The amino-acyl insertion reaction for peptide synthesis (*e.g.*, I ⟶ II) has not gained widespread use mainly because of the difficulty in preparing suitable salicyloyl esters.[1] The use of diacyl hydrazides in place of the salicyloyl esters has been recommended.[2] In the present work alternative substrates for the amino-acyl insertion reaction were examined.

O-Acyl hydroxylamine derivatives were studied since, first, the " α-effect " of the nitrogen atom enables the hydroxyl group of the parent hydroxylamine to be readily acylated,[3] and, secondly, the electronegativity of the nitrogen atom " activates " the acylated derivatives.[4]

Treatment of *NO*-dibenzoylhydroxylamine[5] with benzylamine gave good yields of *N*-benzoylbenzamide and *N*-benzoylhydroxylamine. No evidence of Lossen rearrangement, which generally requires heating with a strong base,[6] was found. However, since it has been reported that heating of *NO*-dibenzoylhydroxylamine with cyclohexylamine does cause Lossen rearrangement,[7] some derivatives of *N*-methylhydroxylamine were prepared. In these, rearrangement is avoided by methyl blocking. *NO*-Dianisoyl-*N*-methylhydroxylamine reacted with benzylamine to give *N*-benzylanisamide and *N*-anisoyl-*N*-methylhydroxylamine. *N*-Anisoyl-*O*-acetyl-*N*-methylhydroxylamine reacted similarly with benzylamine. Thus, the diacylhydroxylamines are comparable to the esters of *N*-hydroxyphthalimide[8a] and *N*-hydroxysuccinimide[8b] in acting as acylating agents.

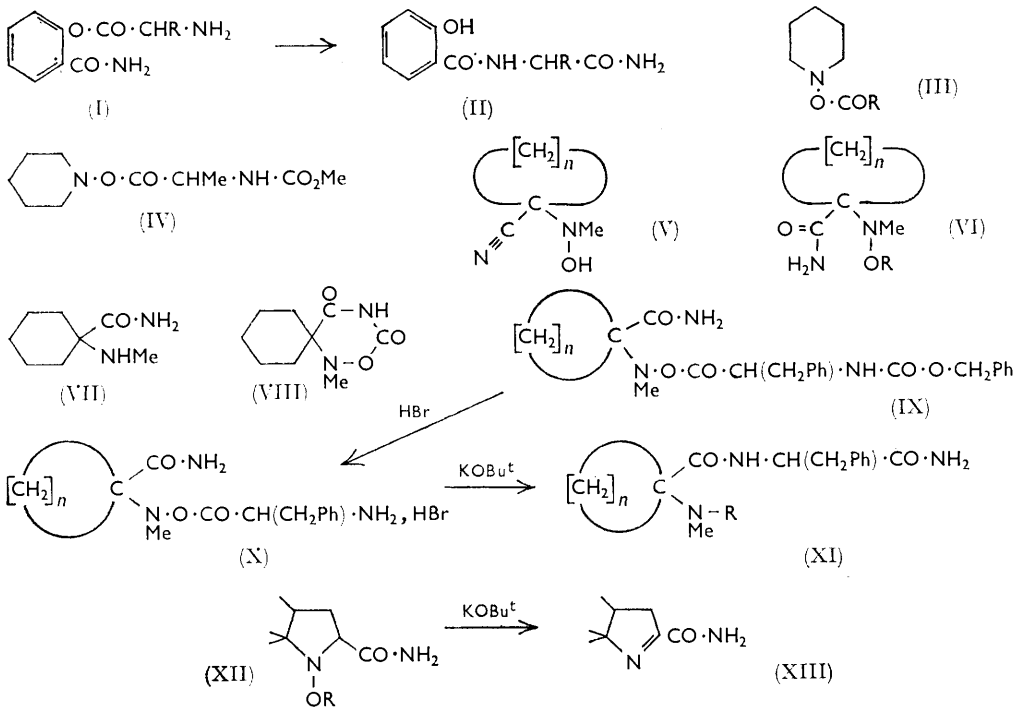
Some derivatives of *NN*-dialkyl hydroxylamines were also studied. *N*-Benzoyloxypiperidine (III; R = Ph) reacted with benzylamine to give *N*-benzylbenzamide in 80% yield. With ethyl aminoacetate, ethyl hippurate was formed, indicating the preferred reaction of this amine with the benzoate ester rather than with itself. In contrast, the weaker base aniline was not benzoylated, but *N*-acetoxypiperidine (III; R = Me) was much more reactive than the benzoate and converted aniline into acetanilide. Recently, it was demonstrated that the reactions of esters of *N*-hydroxypiperidine with amines can be catalysed by acetic acid.[9]

Reaction of *N*-hydroxypiperidine with L-α-alanine-*N*-carboxyanhydride and triethylamine at −40° in tetrahydrofuran, followed by treatment with excess diazomethane,[10] gave the alanyl ester (IV).

Since the above activated esters of the hydroxylamine models were readily synthesised by direct acylation, some α-carbamoyl-*NN*-dialkylhydroxylamines were prepared in order to study their participation in the amino-acyl insertion reaction. Treatment of cyclohexanone with sodium cyanide and *N*-methylhydroxylamine hydrochloride in aqueous

[1] M. Brenner, J. P. Zimmermann, J. Wehrmüller, P. Quitt, A. Hartmann, W. Schneider, and U. Beglinger, *Helv. Chim. Acta*, 1957, **40**, 1497.
[2] M. Brenner and W. Hofer, *Helv. Chim. Acta*, 1961, **44**, 1794, 1798.
[3] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.
[4] Cf. N. F. Albertson, *Org. Reactions*, 1962, **12**, 157.
[5] C. D. Hurd and J. W. Fan, *J. Amer. Chem. Soc.*, 1951, **73**, 110.
[6] E. C. Franklin, *Chem. Rev.*, 1934, **14**, 219.
[7] J. K. Sutherland and D. A. Widdowson, *J.*, 1964, 4651.
[8] (*a*) G. H. L. Nefkens and G. I. Tesser, *J. Amer. Chem. Soc.*, 1961, **83**, 1263. (*b*) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, 1963, **85**, 3039.
[9] S. M. Beaumont, B. O. Handford, J. H. Jones, and G. T. Young, *Chem. Comm.*, 1965, 53.
[10] J. L. Bailey, *J.*, 1950, 3461.

ethanol gave the adduct (V; $n = 5$), which, on hydrolysis with sulphuric acid, furnished the corresponding amide (VI; $n = 5$, R = H); hydrogenation of this over palladium gave 1-methylaminocyclohexanecarboxyamide (VII). Both *N*-hydroxy-compounds (V; $n = 5$) and (VI; $n = 5$, R = H) could be acylated with acetic anhydride, and with benzyl chloroformate the latter gave the benzyl carbonate (VI; $n = 5$, R = $PhCH_2 \cdot O \cdot CO$), which was unaffected by triethylamine but was converted into the cyclic urethane (VIII) with potassium t-butoxide. Coupling of the amide (VI; $n = 5$, R = H) to *N*-benzyloxycarbonyl-DL-phenylalanine by the use of dicyclohexylcarbodi-imide, followed by removal of the benzyloxycarbonyl group with hydrogen bromide in nitromethane,[11] gave the hydrobromide (X; $n = 5$). This product reacted slowly with triethylamine to form the amide (VI; $n = 5$, R = H) and an amorphous solid, presumably polymeric DL-phenylalanine, but with potassium t-butoxide a rapid reaction occurred to give a new compound (XI; $n = 5$, R = OH), formed by the amino-acyl insertion reaction. The latter compound was also obtained when the amide (VI; $n = 5$, R = H) was treated with DL-phenyl-



alanine-*N*-carboxyanhydride in tetrahydrofuran at −20° followed by treatment with potassium t-butoxide. The rearrangement product was reduced catalytically to the corresponding amine (XI; $n = 5$, R = H). When the *N*-benzyloxycarbonyl-L-phenylalanine derivative was used, the optically inactive rearrangement product was formed. Hydrolysis of the latter compound gave DL-phenylalanine.

To investigate the generality of the amino-acyl insertion reaction in these systems, the amide (VI; $n = 4$, R = H) was prepared. The initial adduct (V; $n = 4$) from cyclopentanone, sodium cyanide, and *N*-methylhydroxylamine hydrochloride was not isolated [12] but directly converted into the amide by hydrolysis with sulphuric acid. Coupling to

[11] N. F. Albertson and F. C. McKay, *J. Amer. Chem. Soc.*, 1953, **75**, 5323.
[12] Cf. H. C. Brown, J. H. Brewster, and H. Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.

N-benzyloxycarbonyl-DL-phenylalanine was again achieved with dicyclohexylcarbodiimide. Removal of the protecting group, followed by treatment with potassium t-butoxide gave the rearranged amide (XI; $n = 4$, R = H).

One further substrate was prepared. Hydrolysis of 2-cyano-1-hydroxy-4,5,5-trimethylpyrrolidine[13] with sulphuric acid afforded the amide (XII; R = H). Since the amide and hydroxyl functions were now held sterically closer than in the previous models (because of absence of rotation about the adjoining bond), greater participation of the amide group in the amino-acyl insertion step was expected. In the event, no reaction occurred on treatment of the benzyl carbonate (XII; R = $PhCH_2 \cdot O \cdot CO$) with mild base, and with potassium t-butoxide elimination to the imine (XIII) occurred.

Experimental

Melting points were determined on a Kofler hot-stage apparatus. Infrared spectra were recorded on a Unicam S.P. 200 spectrophotometer. Light petroleum refers to the fraction of boiling range 40—60°.

NO-*Dianisoyl*-N-*methylhydroxylamine*.—*N*-Methylhydroxylamine hydrochloride (3·3 g.) in triethylamine (10 ml.) was added to a solution of anisoyl chloride (3·4 g.) in pyridine (20 ml.) at room temperature. After 2 hr. the solution was poured into water (100 ml.), extracted with ethyl acetate (2 × 50 ml.), and the extract washed with N-hydrochloric acid (50 ml.) and saturated sodium hydrogen carbonate solution (50 ml.). Removal of solvent from the dried (Na_2SO_4) solution and recrystallisation of the residue from ethyl acetate–light petroleum afforded prisms of the *ester* (2·05 g.), m. p. 81°, $\nu_{max.}$ (Nujol) 1755 and 1660 cm.$^{-1}$ (diacylhydroxylamine) (Found: C, 64·55; H, 5·3; N, 4·7. $C_{17}H_{17}NO_5$ requires C, 64·8; H, 5·4; N, 4·45%).

Treatment of the ester (0·31 g.) with benzylamine (0·11 g.) in tetrahydrofuran (10 ml.) at room temperature overnight, followed by addition of water and extraction with chloroform, gave, from the organic phase, *N*-benzylanisamide (0·20 g., 89%), m. p. 129—130° (lit.,[14] 131°). The aqueous phase, on evaporation afforded *N*-anisoyl-*N*-methylhydroxylamine (0·15 g., 83%), m. p. 96—102° (lit.,[15] 102—103°). In a similar manner, *NO*-dibenzoylhydroxylamine (0·23 g.) with benzylamine (0·11 g.) in chloroform (5 ml.) for 15 hr. at room temperature afforded *N*-benzylbenzamide (0·20 g.) and *N*-benzoylhydroxylamine (0·10 g.), both identical with authentic samples.

O-*Acetyl* N-*Anisoyl*-N-*methylhydroxylamine*.—*N*-Anisoyl-*N*-methylhydroxylamine (0·18 g.) in acetic acid (10 ml.) was treated with acetic anhydride (0·2 ml.) in the presence of imidazole (37 mg.) at room temperature. After 5 hr. the solvent was removed *in vacuo* and water was added. Extraction with ethyl acetate afforded the *acetate*, b. p. 70° (air-bath)/10^{-2} mm., $\nu_{max.}$ (film) 1785 and 1660 cm.$^{-1}$ (diacylhydroxylamine) (Found: C, 59·4; H, 6·05; N, 6·1. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9; N, 6·0%).

N-*Benzoyloxypiperidine*.—Benzoyl peroxide (7·26 g.) in ether (100 ml.) at −10° was stirred while piperidine (5·1 g.) was added dropwise during 15 min. After a further 1 hr. at −10°, the mixture was poured into saturated sodium hydrogen carbonate solution and extracted with ether, to give colourless plates of the benzoate[16] (III; R = Ph) (1·6 g.), m. p. 58—61°, $\nu_{max.}$ (Nujol) 1765 cm.$^{-1}$ (ester).

Reaction of the Benzoate with Amines.—The following is illustrative. A mixture of the benzoate (0·52 g.) and benzylamine (0·25 g.) in ether (5 ml.) was left at room temperature until its infrared spectrum showed disappearance of the ester absorption. Evaporation of the solvent afforded crystals of *N*-benzylbenzamide (0·42 g., 79%), m. p. and mixed m. p. 108—109°. Similarly, ethyl aminoacetate (0·15 g.) gave ethyl hippurate (0·096 g.), m. p. 63—67° (lit.,[17] 67·5°). With aniline no amide was isolated.

Reaction of N-*Acetoxypiperidine with Amines*.—In a similar fashion to the benzoate, the acetate[18] gave with aniline (6 days) acetanilide (44%), with benzylamine (10 hr.) *N*-benzylbenzamide (98%), and with ethyl aminoacetate (6 days) ethyl *N*-acetylaminoacetate (87%).

[13] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J.*, 1959, 2094.
[14] E. Plapinger, *J. Org. Chem.*, 1959, **24**, 802.
[15] E. Beckmann, *Ber.*, 1904, **37**, 4136.
[16] S. Gambarian, *Ber.*, 1925, **58**, 1775.
[17] E. Fischer, *Ber.*, 1905, **38**, 605.
[18] S. Gambarian and L. Kazarian, *J. Gen. Chem.* (*U.S.S.R.*), 1933, **3**, 222.

O-(N-*Methoxycarbonyl*-L-α-*alanyl*)-N-*hydroxypiperidine* (IV).—A solution of L-α-alanine-*N*-carboxyanhydride [10] (0·23 g.) and *N*-hydroxypiperidine (from 0·28 g. of the hydrochloride) in tetrahydrofuran (5 ml.) at −40° was treated with triethylamine (0·23 g.) for 3 hr. Excess of ethereal diazomethane was added, and the mixture left at 0° overnight. Evaporation, and recrystallisation of the residue from tetrahydrofuran–ether, gave needles of the *hydroxylamine ester* (0·20 g., 45%), m. p. 69°, $[\alpha]_D^{25}$ −5·9° (*c* 2·0 in $CHCl_3$), $\nu_{max.}$ (Nujol) 3270 (N–H), 1753 (ester), and 1720 (urethane) cm.$^{-1}$ (Found: C, 44·5; H, 7·2; N, 14·5. $C_{10}H_{18}N_2O_4$ requires C, 44·2; H, 7·4; N, 14·7%).

1-*Cyano*-1-(N-*methylhydroxylamino*)*cyclohexane* (V; *n* = 5).—Cyclohexanone (0·25 g.) in ethanol (5 ml.) was added to a suspension of sodium cyanide (0·10 g.) and *N*-methylhydroxylamine hydrochloride (0·24 g.) in 80% aqueous ethanol (10 ml.). The mixture was stirred at room temperature overnight, then concentrated *in vacuo*, diluted with tetrahydrofuran, and filtered. Evaporation of the solvent, followed by washing of the filtrate with ice-cold water, afforded the *nitrile* (0·33 g., 84%), m. p. 73—76°. It sublimed at 65° (air-bath)/2 × 10^{-3} mm. and then had m. p. 77°, $\nu_{max.}$ (Nujol) 3300 (OH), 2265 (C⋮N) cm.$^{-1}$ (Found: C, 62·2; H, 9·1; N, 18·05. $C_8H_{14}N_2O$ requires C, 62·3; H, 9·15; N, 18·2%).

With acetic anhydride in ethyl acetate, in the presence of saturated sodium hydrogen carbonate solution, needles of the *acetate* (91%) were obtained, m. p. 52°, $\nu_{max.}$ ($CHCl_3$) 2260 (C⋮N), and 1765 (ester) cm.$^{-1}$ (Found: C, 61·2; H, 8·2; N, 14·2. $C_{10}H_{16}N_2O_2$ requires C, 61·2; H, 8·2; N, 14·3%).

1-*Carbamoyl*-1-(N-*methylhydroxylamino*)*cyclohexane* (VI; *n* = 5, R = H).—The nitrile (V; *n* = 5) (1·50 g.) was added in portions to concentrated sulphuric acid (10 ml.), with shaking and cooling in an ice-bath. After 4 hr. at room temperature, the solution was poured into crushed ice (150 g.) and made alkaline (cooling) with ammonia (15 ml.; *d* 0·88). Extraction with ethyl acetate gave prisms of the *amide* (0·79 g., 47%), m. p. 139° (from ethyl acetate), $\nu_{max.}$ (Nujol) 3460, 3200 (amide), 3300 (OH), and 1663 (amide) cm.$^{-1}$ (Found: C, 56·2; H, 9·3; N, 16·25. $C_8H_{16}N_2O_2$ requires C, 55·8; H, 9·4; N, 16·3%).

The amide, after acetylation with acetic anhydride as described above, yielded needles of the *acetate* (VI; *n* = 5, R = Ac) (88%), m. p. 108° (from ethyl acetate–light petroleum), $\nu_{max.}$ (Nujol) 3500, 3300 (amide), 1760 (ester), and 1690 (amide) cm.$^{-1}$ (Found: C, 55·8; H, 8·3; N, 12·8. $C_{10}H_{18}N_2O_3$ requires C, 56·1; H, 8·5; N, 13·1%). In a similar manner, benzyl chloroformate gave the *benzyl carbonate* (VI; *n* = 5, R = $PhCH_2$·O·CO) (65%), m. p. 91—92° (from tetrahydrofuran–petroleum), $\nu_{max.}$ (Nujol) 3500, 3200 (amide), 1760 (carbonate), and 1673 (amide) cm.$^{-1}$ (Found: C, 62·8; H, 7·1; N, 9·1. $C_{16}H_{22}N_2O_4$ requires C, 62·75; H, 7·2; N, 9·1%).

Action of Potassium t-Butoxide on the Benzyl Carbonate (VI; *n* = 5, R = $PhCH_2$·O·CO).—The carbonate (0·23 g.) in anhydrous tetrahydrofuran (5 ml.) was treated with potassium t-butoxide in t-butyl alcohol (0·8 ml.; 1·25N) at room temperature for 1 hr. Acetic acid (0·2 ml.) was added, and the product extracted with ethyl acetate, to yield needles of 1-*methyl*-1,4-*diaza*-2-*oxaspiro*[5,5]*undecane*-3,5-*dione* (VIII) (96 mg.), m. p. 128° (from ether–light petroleum), $\nu_{max.}$ (Nujol) 3250, 3150 (N–H), 1750, 1710 (imide) cm.$^{-1}$ (Found: C, 54·6; H, 7·1; N, 14·2. $C_9H_{14}N_2O_3$ requires C, 54·5; H, 7·1; N, 14·1%).

The benzyl carbonate gave no reaction with triethylamine.

1-*Carbamoyl*-1-(N-*methylamino*)*cyclohexane* (VII).—The amide (VI; *n* = 5, R = H) (49 mg.), in ethanol (3 ml.) containing 2 drops of concentrated hydrochloric acid, was hydrogenated over palladised charcoal (19 mg.; 10%) at room temperature and atmospheric pressure. After 15 min., when hydrogen uptake had ceased (5·5 ml.), sodium hydrogen carbonate was added, the mixture filtered, and the solution evaporated, to give needles of the *amine* (24 mg., 59%), m. p. 134°, $\nu_{max.}$ (Nujol) 3430, 3330, 3180 (N–H), and 1665 (amide) cm.$^{-1}$ (Found: C, 61·5; H, 10·2; N, 18·1. $C_8H_{16}N_2O$ requires C, 61·5; H, 10·1; N, 17·9%).

1-*Carbamoyl*-1-[N-*methyl*-O-(N-*benzyloxycarbonyl*-DL-*phenylalanyl*)*hydroxylamino*]*cyclohexane* (IX; *n* = 5).—The amide (VI; *n* = 5) (0·80 g.) and *N*-benzyloxycarbonyl-DL-phenylalanine (1·39 g.) were coupled with dicyclohexylcarbodi-imide (1·1 g.) in ethyl acetate (10 ml.) at room temperature, to give, from benzene–ether, needles of the *phenylalanyl ester* (1·01 g.), m. p. 138°, $\nu_{max.}$ (Nujol) 3520, 3470 (N–H), 1755 (ester), 1720 (urethane), 1680 (amide) cm.$^{-1}$ (Found: C, 66·0; H, 7·0; N, 9·1. $C_{25}H_{31}N_3O_5$ requires C, 66·2; H, 6·9; N, 9·3%).

The ester (0·71 g.) was treated with hydrogen bromide in acetic acid (1·2 ml.; 45% w/v) and

nitromethane (8 ml.) at room temperature for 4 hr. Addition of ether precipitated an amorphous solid which was washed with ether by decantation before being dissolved in acetone (3 ml.). When stored at 0° overnight the solution deposited the *hydrobromide* (X; $n = 5$) (0·22 g.), m. p. 132—134° (decomp.), $\nu_{max.}$ (Nujol) 1760 (ester), 1684 (amide) cm.$^{-1}$ (Found: Br, 19·7. $C_{17}H_{25}N_3O_3$,HBr requires Br, 19·9%).

Rearrangement of the Hydrobromide (X; $n = 5$).—(a) *With triethylamine.* The hydrobromide (0·136 g.) was shaken with triethylamine (0·4 g.) in chloroform (9·6 ml.) at room temperature. After 14 days the infrared spectrum showed that most of the ester had disappeared. The mixture was filtered and extracted with hydrochloric acid (5 ml.; 2N). The organic phase yielded a gummy solid (25 mg.) of similar properties to phenylalanine anhydride. The acid extract was neutralised with sodium hydrogen carbonate and re-extracted with ethyl acetate, to give a pale yellow oil shown, by thin-layer chromatography and its infrared spectrum, to be a mixture of amide (VI; $n = 5$, R = H) and some of the starting ester.

(b) *With potassium t-butoxide.* To a suspension of the hydrobromide (0·30 g.) in tetrahydrofuran (8 ml.) at room temperature was added potassium t-butoxide (in t-butyl alcohol) (1·5 ml.; N). After 2 hr., acetic acid (0·15 ml.) was added and the mixture was poured into water. Extraction with ethyl acetate afforded needles of the *amide* (XI; $n = 5$, R = OH) (79 mg.), m. p. 169° (from ethyl acetate), $\nu_{max.}$ (Nujol) 3510, 3400 (N–H), 3220 (OH), 1680, 1660 (amide) cm.$^{-1}$ (Found: C, 63·9; H, 8·0; N, 13·0. $C_{17}H_{25}N_3O_3$ requires C, 63·9; H, 7·9; N, 13·2%). This material was homogeneous to thin-layer chromatography.

Reaction of Amide (VI; $n = 5$, R = H) *with* DL-*Phenylalanine* N-*Carboxyanhydride.*[19]—Phenylalanine *N*-carboxyanhydride (0·12 g.), in tetrahydrofuran (5 ml.) at −30° in the presence of triethylamine (0·5 ml.), was treated with the amide (0·117 g.). The solution was kept at −20° for 6 hr. then allowed to warm to room temperature before the addition of potassium t-butoxide in t-butyl alcohol (2 ml.; N). After a further 1 hr., acetic acid (0·2 ml.) was added, the mixture poured into ethyl acetate and worked up in the usual manner. Crystallisation from ethyl acetate gave the rearranged amide (XI; $n = 5$, R = OH) (42 mg.), m. p. 158—162°.

Reduction of Rearranged Amide (XI; $n = 5$, R = OH).—Reduction of the rearranged amide (66 mg.) in ethanol (3 ml.) over palladium–charcoal (25 mg.; 10%) in the presence of hydrochloric acid (0·25 ml.; N) gave the *amide* (XI; $n = 5$, R = H), m. p. 160° (from ethyl acetate) $\nu_{max.}$ (Nujol) 3350, 3200 (N–H), 1690, 1640 (amide) cm.$^{-1}$ (Found: C, 67·0; H, 8·35; N, 14·1. $C_{17}H_{25}N_3O_2$ requires C, 67·3; H, 8·3; N, 13·9%).

Use of L-*Phenylalanine.*—The amide (VI; $n = 5$, R = H) (0·56 g.) was coupled to *N*-benzyloxycarbonyl-L-phenylalanine under the conditions described for the racemate. The product, which would not crystallise, had $[\alpha]_D^{18}$ +6° (*c* 2·0 in $CHCl_3$). Treatment of the ester with hydrogen bromide in nitromethane, as described above, was followed by rearrangement with potassium t-butoxide. After chromatography on silica gel (Woelm, neutral; 20 g.), prisms of the amide (XI; $n = 5$, R = OH) (0·174 g.), m. p. 155—162°, were obtained which showed no optical rotation. Hydrolysis of this product (80 mg.) with hydrochloric acid (3 ml.; 8N) at 100° for 20 hr., followed by chromatography through a cation-exchange resin (Amberlite IR 120; 40 g.), using water and then 0·5N-ammonium hydroxide for elution, gave phenylalanine (23 mg.), identical with authentic material by paper-chromatographic comparison, but showing no optical activity.

1-*Carbamoyl*-1-(*N-methylhydroxylamino*)*cyclopentane* (VI; $n = 4$, R = H).—Cyclopentanone (8·4 g.) was added to a solution of sodium cyanide (5·0 g.) and *N*-methylhydroxylamine hydrochloride (10·0 g.) in 50% aqueous ethanol (25 ml.) at 0°. The solution was allowed to warm to room temperature overnight and then extracted with ethyl acetate, to give an oil (2·5 g.). This was immediately dissolved in cold concentrated sulphuric acid (10 ml.), left at room temperature overnight, poured into ice–water (30 g.), neutralised with ammonia, and extracted with ethyl acetate, to afford prisms of the *amide* (0·43 g.), m. p. 115°, $\nu_{max.}$ (Nujol) 3400, 3200 (N–H), 3300br (OH), 1660 (amide) cm.$^{-1}$ (Found: C, 53·2; H, 8·65; N, 17·9. $C_7H_{14}N_2O_2$ requires C, 53·1; H, 8·9; N, 17·7%).

1-*Carbamoyl*-1-[*N-methyl*-O-(*N-benzyloxycarbonyl*-DL-*phenylalanyl*)*hydroxylamino*]*cyclopentane* (IX; $n = 4$).—The amide (VI; $n = 4$, R = H) (0·71 g.) and *N*-benzyloxycarbonyl-DL-phenylalanine (1·5 g.) in ethyl acetate (20 ml.) were coupled with dicyclohexylcarbodi-imide (1·1 g.), to give the *ester* (1·52 g.), m. p. 107° (from ethyl acetate), $\nu_{max.}$ (Nujol) 3430, 3310, 3210

[19] H. Leuchs and W. Geiger, *Ber.*, 1908, **41**, 1721.

(N–H), 1765 (ester), 1715 (urethane), 1675 (amide) cm.$^{-1}$ (Found: C, 65·6; H, 6·8; N, 9·9. $C_{24}H_{29}N_3O_5$ requires C, 65·6; H, 6·7; N, 9·6%).

Rearrangement of the Cyclopentyl Amide Ester (IX; $n = 4$).—The ester (0·56 g.) was added to nitromethane (4 ml.) containing hydrogen bromide in acetic acid (0·6 ml.; 45% w/v) at 0°. After 2 hr. the solvent was decanted from the crystalline hydrobromide which was washed with ether and then treated with potassium t-butoxide (5 ml., N) in tetrahydrofuran for 2 hr. The oily product, on chromatography through silica gel (Woelm, neutral) (20 g.), using acetone–light petroleum (1 : 3) (200 ml.) as eluant, afforded prisms of the *amide* (XI; $n = 4$, R = OH) (68 mg.), m. p. 185° (from ethyl acetate), $\nu_{max.}$ (Nujol) 3450, 3340 (N–H), 3250br (OH), 1700, 1680 (amide) cm.$^{-1}$ (Found: N, 13·6. $C_{16}H_{23}N_3O_3$ requires N, 13·8%). The product was homogeneous to thin-layer chromatography.

1-*Hydroxy*-5-*carbamoyl*-2,2,3-*trimethylpyrrolidine* (XII; R = H).—1-Hydroxy-5-cyano-2,2,3-trimethylpyrrolidine [12] (2·7 g.) was added to cold concentrated sulphuric acid (10 ml.). The solution was left at room temperature overnight, then warmed to 60° for 30 min.; working up in the usual way gave the *amide* (1·85 g.), m. p. 163° (from ethyl acetate), $\nu_{max.}$ (Nujol) 3400, 3230 (N–H and OH), 1690 (amide) cm.$^{-1}$ (Found: C, 55·9; H, 9·3; N, 16·5. $C_8H_{16}N_2O_2$ requires C, 55·8; H, 9·4; N, 16·3%).

1-*Benzyloxycarbonyloxy*-5-*carbamoyl*-2,2,3-*trimethylpyrrolidine* (XII; R = $PhCH_2{\cdot}O{\cdot}CO$).—The amide (0·69 g.) in ethyl acetate (10 ml.) was treated with benzyl chloroformate, in the manner described previously, to give the *benzyl carbonate* (1·02 g.), m. p. 121° (from ethyl acetate), $\nu_{max.}$ (Nujol) 3450, 3200 (N–H), 1755 (carbonate), 1680 (amide) cm.$^{-1}$ (Found: C, 63·0; H, 7·1; N, 9·1. $C_{16}H_{22}N_2O_4$ requires C, 62·7; H, 7·2; N, 9·1%).

Action of Base on the Benzyl Carbonate (XII; R = $PhCH_2{\cdot}O{\cdot}CO$).—To a solution of the benzyl carbonate (0·31 g.) in tetrahydrofuran (10 ml.) was added potassium t-butoxide in t-butyl alcohol (0·55 ml.; 2N). After 15 min. at room temperature, acetic acid (0·2 ml.) was added, and the mixture was extracted with ethyl acetate. Sublimation of the product at 65°(air-bath)/10^{-3} mm. gave fine needles of 2-*carbamoyl*-4,5,5-*trimethyl*-1-*pyrroline* (XIII), m. p. 123—124°, $\nu_{max.}$ (Nujol) 3350, 3200 (N–H), 1695, 1660 (amide), and 1620 (imine) cm.$^{-1}$. Its n.m.r. spectrum (Varian A60) showed ($CDCl_3$) τ 9·05 and 8·91 (doublet, secondary methyl), 8·94 and 8·70 (singlets, tertiary methyls), and 2·75 and 3·5 (broad, primary amide) (Found: C, 62·4; H, 9·1; N, 18·5. $C_8H_{14}N_2O$ requires C, 62·3; H, 9·1; N, 18·2%).

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Chemistry Department, Imperial College, London S.W.7. [*Received, March 9th*, 1965.]