Synthesis and Stereochemistry of 1,4-Diazabicyclo[4,3,0]nonane-2,5,9-triones

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1,4-Diazabicyclo[4,3,0]nonane-2,5,9-triones have been prepared by two synthetic routes. The first (Scheme 1) involves cyclisation of α-aminoacyl glutamic acids to 3,6-dioxo-2-piperazinepropionic acids, which undergo a second cyclisation on refluxing with an acid anhydride. In the second (Scheme 2) the bicyclic system is obtained by direct cyclisation of α-acetamidoacyl glutamic acids. N.m.r. studies and optical rotations have been used in the elucidation of the stereochemistry of the products.

L-GLUTAMIC ACID and its decarboxylation product, 4-aminobutyric acid, are known to be involved in the biochemistry of the central nervous system. 3-Phthalimidoglutarimide (thalidomide) and related compounds exhibit profound central nervous system depressant activity. I here describe part of an investigation into the synthesis of novel cyclic imides derived from glutamic acid derivatives, for evaluation as central nervous system depressants.

It had previously been reported [1] that 3,6-dioxo-2-piperazinepropionic acid (9) was the product obtained on heating glycyl-L-glutamic acid (1), but no attempt to further cyclise the diketopiperazine had been made.

On refluxing (9) with excess of trifluoroacetic anhydride, 1,4-diazabicyclo[4,3,0]nonane-2,5,9-trione (16) was obtained (Scheme 1). Refluxing (16) with acetic anhydride gave 4-acetyl-1,4-diazabicyclo[4,3,0]nonane-2,5,9-trione (23). The *N*-acetyl derivative (23) was also obtained directly from (9) by refluxing with acetic anhydride.

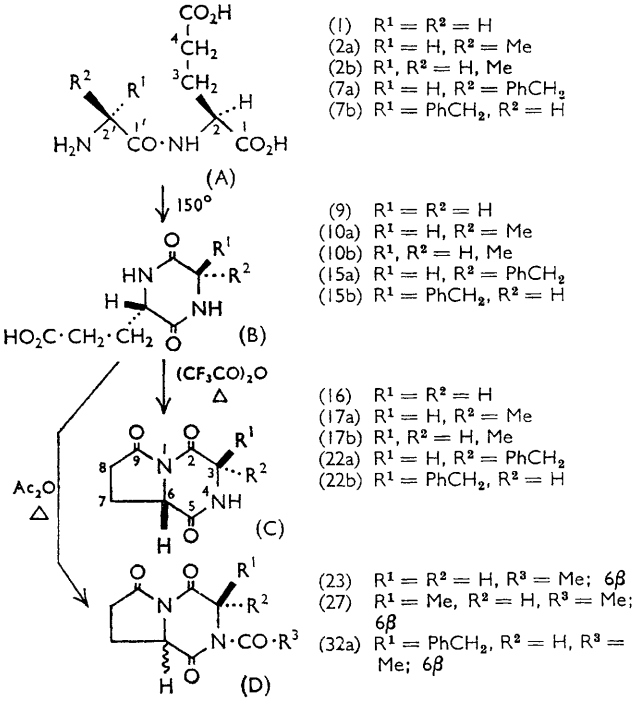
That the formation of the above bicyclic system is favoured over the alternative bridged structure (16a) that would be obtained by reaction of the carboxy-function with the amide nitrogen at the 4-position, is as expected, since (16) presents a more favourable situation for π-bonding between the imide carbonyl carbon atoms and nitrogen. Amide nitrogens at bridgehead positions similar to that occupied by the nitrogen in structure (16a) have been reported [2] but only when π-bonding between the amide carbonyl carbon and an adjacent carbon atom occurs as an alternative to π-bonding to the nitrogen atom, as in the case of conjugation with an aromatic system.

Nuclear magnetic resonance studies (Tables 10 and 11) provided conclusive evidence for the bicyclic structure (16). In compounds (16) and (23) the two protons at

[1] E. Aberhalden, K. Weichert, H. Schumann, and E. Haase, *Fermentforschung*, 1940, **16**, 182.

[2] H. Von Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron*, 1965, **21**, 2257.

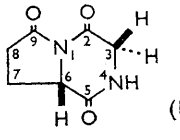
C-3 are magnetically non-equivalent and give rise to an AB quartet (J = 17 c./sec.). In (16) one of the protons of the AB system is further coupled to the N-4 proton (J = 5 c./sec.). This additional splitting disappears on deuterium exchange and on acetylation. In (16a) there

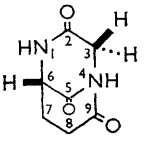


Scheme 1

6β defines 6-H as *cis* to R¹

is no N-4 proton adjacent to the AB system and additional coupling could not therefore occur. Furthermore, the C-6 proton appears as a simple triplet (J = 8 c./sec.) whereas in structure (16a) additional coupling of this


(16)


(16a)

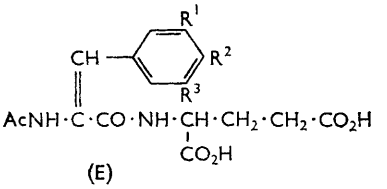
proton to the N-1 proton would be expected. Additional evidence in favour of the bicyclic system (16) is that the centre of the AB pattern is shifted further downfield (0·58 p.p.m.) on acetylation of the nitrogen atom than is the triplet for the C-6 proton (0·30 p.p.m.) whereas the opposite would be expected for (16a).

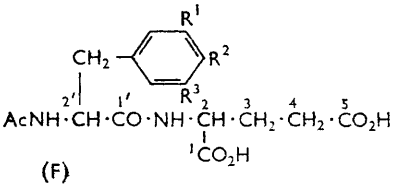
The n.m.r. spectra of other acylated derivatives (24), (25), and (26) obtained by cyclisation of (9) with the appropriate carboxylic acid anhydrides, were similar to that of (23) (Table 12).

A series of compounds (17a)—(22b) (Table 9) and(27)—(32a) (Table 11) substituted at the 3-position was prepared in the same manner from the appropriate glutamic acid dipeptides, which with the exception of DL-2-amino-2-methylbutanoyl-L-glutamic acid (5) were prepared by coupling benzyloxycarbonyl amino-acids with dibenzyl L-glutamate in pyridine solution in the presence of dicyclohexylcarbodi-imide. Concentrated solutions [3] were used and the reactants pre-cooled to 0° to minimise formation of acyl ureas.[4] The protecting groups were removed by hydrogenolysis.

Although preparation of peptides with amino-acids doubly substituted at the α-carbon atom has been reported to present some difficulty because of steric hindrance to the formation of the peptide linkage, coupling reactions involving the amino-function of α,α-disubstituted amino-acids are much more difficult to accomplish than those involving the carboxy-group.[5,6] In accordance with this it was found that coupling of the carboxy-function of hindered *N*-protected amino-acids with dibenzyl L-glutamate proceeded readily in high yield using the conditions described above, but the choice of suitable protecting groups for the amino-function did present some problems. 2-Benzyloxycarbonylamino-2-methylpropanoic acid was prepared [7] but attempts to prepare DL-2-benzyloxycarbonylamino-2-methylbutanoic acid were unsuccessful. DL-2-Trifluoroacetylamino-2-methylbutanoic acid was, however, readily obtained by reaction of the amino-acid with trifluoroacetic anhydride, and the protecting group could be removed from both the acyl amino-acid and the protected peptide by alkaline hydrolysis. The preparation of 2-trifluoroacetylamino-2-ethylbutanoic acid was accomplished in the same manner, but in this case steric hindrance was severe enough to prevent hydrolytic removal of the protecting group under conditions that would not also cause hydrolysis of a peptide linkage.

Sarcosyl-L-glutamic acid (8) could not be dehydrated to the *N*-methyl-dioxo-piperazine.

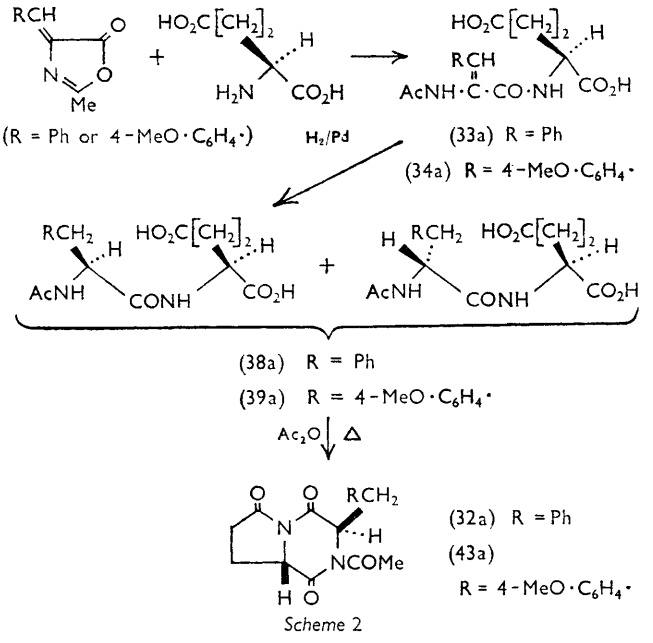

(E)


(F)

The *N*-acetyl compounds (32a—c) and (43a)—(46) (Table 11) were synthesised by an alternative route involving direct cyclisation with acetic anhydride of α-acetamidoacyl glutamic acids. These were obtained by hydrogenation of α-acetamidocinnamoyl glutamic acids prepared by addition of glutamic acid to unsaturated azlactones (Scheme 2).

[3] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley, New York and London, 1961, vol. 2, p. 1019.
[4] B. Helferich and H. Böshagen, *Chem. Ber.*, 1959, **92**, 2813.
[5] M. T. Leplawly, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, 1960, **11**, 39.
[6] G. Faust and H. Lange, *J. prakt. Chem.*, 1960, **11**, 153.
[7] Ref. 3, p. 895.

Hydrogenation of α-acetamidocinnamoyl L-glutamic acids (33a), (34a), and (35—37) (Table 5) with palladium–carbon catalyst in glacial acetic acid [8] at 60° yielded racemic mixtures of the two possible diastereoisomeric



Scheme 2

acetyl dipeptides (38c), (39c), and (40)—(42) (Table 7) which on cyclisation with acetic anhydride each led to a racemic mixture of only one of the two possible diastereoisomeric bicyclic compounds (32c), (43c), and (44)—(46), indicating a high degree of asymmetric induction. When the hydrogenation of (33a) and (34a) was carried out at 20°, however, racemisation of the glutamic acid did not occur and the acetyl DL,L-dipeptides (38a) and (39a) were obtained. On cyclisation with acetic acid these yielded the optically active bicyclic compounds (32a) ($[\alpha]_D^{25}$ + 8·2°) and (43a) ($[\alpha]_D^{25}$ + 64·3°). The material (32a) obtained from *N*-acetyl-DL-phenylalanyl-L-glutamic acid (38a) by this route was identical with that obtained from both of the optically pure diastereoisomers L-phenylalanyl-L-glutamic acid (7a) and D-phenylalanyl-L-glutamic acid (7b) by Scheme 1. Hydrogenation of the α-acetamidocinnamoyl D-glutamic acids (33b) and (34b) (Table 5) at 20° yielded the acetyl DL-D-dipeptides (38b) and (39b) which were cyclised with acetic anhydride to compounds (32b) and (43b). The latter two proved to be the enantiomers of (32a) and (43a), respectively.

Optical rotatory and n.m.r. measurements have permitted stereochemical assignments to be made to the products. When an L-α-aminoacyl L-glutamic acid derivative is used as the starting material for the bicyclic system, in the absence of epimerisation at either of the two asymmetric centres during the reaction, the substituent at C-3 is pseudoequatorial and *trans* with respect to the 6-proton. When a D,L-dipeptide or acetyldipeptide is used, the 3-substituent is pseudoaxial and *cis* with respect to the 6-proton in the product. In the event of epimerisation at either centre, mixtures of diastereoisomers with pseudoequatorial and pseudoaxial substituents would be obtained.

Comparison of the n.m.r. spectra of the products obtained on cyclisation of L-alanyl-L-glutamic acid (2a) and DL-alanyl-L-glutamic acid (2b) illustrates that no epimerisation occurs under the reaction conditions used either in the formation of dioxopiperazines or in the cyclisations with trifluoroacetic anhydride. Although it is not possible to differentiate in dimethyl sulphoxide between the two possible positions of the methyl group in the mixture of epimeric dioxopiperazines (10b) derived from (2b), the methyl groups are clearly separated as two doublets in deuterium oxide, one at δ 1·48 p.p.m. (J = 7 c./sec.) and the other at δ 1·43 p.p.m. (J = 7 c./sec.). In the spectrum of the dioxopiperazine (10a) derived from (2a) only the doublet at δ 1·48 p.p.m. can be seen. A similar observation is made on examination of the spectra of the bicyclic products. In the spectrum of the mixture of diastereoisomers (17b) derived from the DL,L-peptide (2b) methyl doublets appear at δ 1·49 p.p.m. (J = 7 c./sec.) and δ 1·56 p.p.m. (J = 7 c./sec.) and the mixture has $[\alpha]_D^{25}$ −0·1°. The spectrum of the compound (17a) derived from (2a) shows only the doublet at δ 1·56 p.p.m. and the compound has $[\alpha]_D^{25}$ −84·0°. The spectra of the diastereoisomers (22a) ($[\alpha]_D^{25}$ −108·9°) and (22b) ($[\alpha]_D^{25}$ +25·0°), derived from (7a) and (7b), respectively, also show differences indicating that no epimerisation occurs during the above reaction (Table 10).

With the exception of those compounds doubly substituted at C-3 (28) and (29) (Table 11) the n.m.r. spectra of *N*-acetyl bicyclic compounds synthesised by either route indicate that during the cyclisations with acetic anhydride epimerisation can occur at C-3, with the result that only one of the two possible isomers at that position is obtained, regardless of the original configuration of the 3-substituent. The n.m.r. spectrum of compound (27), obtained from both the L,L-dipeptide (2a) and the DL-L-dipeptide (2b) by Scheme 1, shows only one doublet for the 3-methyl substituent at δ 1·54 p.p.m. (J = 5 c./sec.). The spectrum of compound (32a), obtained from the L,L-dipeptide (7a) and the D,L-dipeptide (7b) by Scheme 1 and from *N*-acetyl-DL-phenylalanyl-L-glutamic acid (38a) by Scheme 2 shows one doublet for the benzyl methylene protons at δ 3·28 p.p.m. and a triplet for the 3-proton at δ 5·41 p.p.m. (J_{av} = 5 c./sec.).*

Since the enantiomers (32b) and (43b) of compounds (32a) and (43a) were obtained when α-acetamidoacyl D-glutamic acids (38b) and (39b) (Table 7), were cyclised with acetic anhydride, and racemic mixtures of enantiomers (32c) and (43c) were obtained from α-acetamidoacyl

* In the n.m.r. spectra of compounds with a benzyl methylene group adjacent to a proton on an asymmetric carbon atom a simple five line pattern is often obtained. The only value which can be derived from such a pattern is the average value of J_{AX} and J_{BX}.[9]

[8] M. Bergmann, F. Stern, and C. Witte, *Annalen*, 1926, **449**, 277.

[9] R. J. Abraham and H. J. Bernstein, *Canad. J. Chem.*, 1961, **39**, 216.

DL-glutamic acids (38c) and (39c), it must be concluded that no epimerisation occurs at C-6 and that the configuration of the 3-substituent in the final bicyclic product is determined by that of the glutamic acid.

Substituents occupying the pseudoaxial position suffer less from steric interaction with the neighbouring acyl group than do substituents occupying the pseudoequatorial position, and therefore in the event of thermodynamically controlled epimerisation would be expected to be favoured. Experimental confirmation of this observation was obtained from examination of the n.m.r. spectra of compounds with benzyl and substituted benzyl groups at C-3. The n.m.r. spectra in deuteriochloroform 6-proton falls in the region δ 4·00—4·67 p.p.m. The benzyl substituent in (22b) occupies the pseudoaxial position and in deuteriochloroform solution the 6-proton falls in the region δ 3·00—3·42 p.p.m. Other similar examples of long-range shielding have been reported.[10,11] The formation of an intramolecular collision complex, analogous to the intermolecular complexes of benzene with substituted formamides,[12,13] involving the aromatic ring of a pseudoaxial 3-benzyl substituent and the N(1)-imido-function would account for the rotamer in which the aromatic ring lies directly over the 6-proton being thermodynamically favoured and the very large shielding effect observed. Since

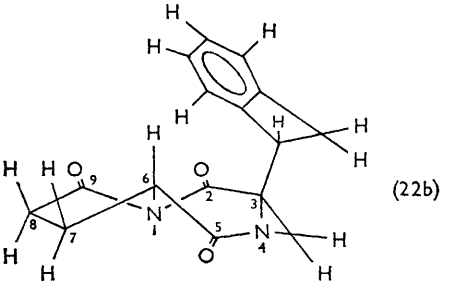
TABLE 1

N-α-aminoacyl-L-glutamic acids (A)

	Compound	$[\alpha]_D^{25}$ [a]	Yield [b] %	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N	I.r. absorption bands [c]: 1500—1800 cm.$^{-1}$ region (C=O stretching, NH_3^+ deformation)	I.r. absorption bands [c]: 3100—3500 cm.$^{-1}$ region (NH stretching)
(1)	Glycyl-L-glutamic acid	−6·3		$C_7H_{12}N_2O_5$							1530br, 1675, 1720	3315
(2a)	L-Alanyl-L-glutamic acid	−9·0		$C_8H_{14}N_2O_5$							1540, 1605, 1685, 1705	3200
(2b)	DL-Alanyl-L-glutamic acid	−17·3	88		44·0	6·5	12·8	43·7	6·7	12·6	1550br, 1670, 1710sh	3250sh
(3)	2-Amino-2-methylpropanoyl-L-glutamic acid	−8·3	67	$C_9H_{16}N_2O_5$	46·5	6·9	12·1	46·2	6·7	12·3	1560br, 1680, 1720	3320sh
(4)	DL-2-Amino-2-methylbutanoyl-L-glutamic acid	−1·0	70	$C_{10}H_{18}N_2O_5$	48·8	7·4	11·4	48·5	7·1	11·2	1560br, 1680, 1720sh	3300sh
(5)	DL-Valyl-L-glutamic acid	−19·0	69					48·5	7·2	11·1	1530br, 1655, 1700sh	3250sh
(6)	L-Leucyl-L-glutamic acid	+17·7	54	$C_{11}H_{20}N_2O_5$	50·8	7·8	10·8	51·0	7·9	10·6	1570, 1665, 1705	3360
(7a)	L-Phenylalanyl-L-glutamic acid	+20·3									1570br, 1670, 1700	3300
(7b)	D-Phenylalanyl-L-glutamic acid	−85·0	57	$C_{14}H_{18}N_2O_5$	57·1	6·2	9·5	57·1	6·1	9·4	1530, 1560, 1660, 1695	3340
(8)	Sarcosyl-L-glutamic acid	+1·2	54	$C_8H_{14}N_2O_5$	44·0	6·5	12·8	44·0	6·6	13·0	1535, 1660, 1680sh	3330

[a] In water. [b] Based on *N*-protected amino acid. [c] In addition to these bands, all spectra showed a broad absorption in the 2100—3600 cm.$^{-1}$ region.

of *N*-acetyl derivatives with 3-benzyl and substituted 3-benzyl substituents all show a remarkable degree of anisotropic shielding of the 6-proton by the aromatic substituent. For example, the 6-proton in the 3-benzyl-4-acetyl derivatives (32a) and (32b) falls at δ 3·07 p.p.m. whereas in the unsubstituted compound (23) it appears at δ 4·93 p.p.m. Examination of molecular models shows that it is possible for the aromatic ring of a pseudoaxial 3-benzyl substituent to lie directly over the 6-proton, whereas this is not possible when the benzyl substituent occupies the pseudoequatorial position and is *trans* to the 6-proton. The n.m.r. spectra of compounds (22a) and (22b) prove unequivocally that shielding of the 6-proton does occur only when the 3-benzyl substituent occupies the pseudoaxial position. The two bicyclic compounds (22a) and (22b) were obtained from (7a) and (7b), respectively, using the reaction sequence that has been shown above to involve no epimerisation at either of the asymmetric centres. The 3-benzyl substituent in (22a) therefore occupies the pseudoequatorial position and in deuteriochloroform solution the an increase in temperature might alter the rotamer population and thus reduce the degree of shielding of the 6-proton, the n.m.r. spectrum of the racemic material (32c) was measured in deuteriochloroform at 56°, showing that the shielding was reduced by 0·19 p.p.m. When



(22b)

the spectrum of (32c) was measured in pyridine and in dimethylsulphoxide solution however, the shielding was very much reduced, the 6-proton falling at δ 4·15 and 4·80 p.p.m., respectively. Co-ordination

[10] R. C. Pink, R. Spratt, and C. J. M. Stirling, *J. Chem. Soc.*, 1965, 5714.

[11] R. M. Horowitz and B. Gentili, *Chem. and Ind.*, 1966, 625.

[12] J. V. Hatton and R. E. Richards, *Mol. Phys.*, 1962, **5**, 139.

[13] L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, 1964, **86**, 337.

of pyridine or dimethylsulphoxide to specific sites in the bicyclic material (32c) could result in deshielding of the 6-proton by the solvating molecules.[14,15] In addition, solvation of the imide functions would be likely to weaken a collision complex involving the aromatic ring of the 3-benzyl group and alter the rotamer population in favour of rotamers in which the 6-proton is not shielded by the aromatic ring.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined in Nujol mulls with a Perkin-Elmer 521 grating spectrophotometer. N.m.r. spectra were determined in deuteriated solvents at 60 Mc./sec. with a Varian model A60 spectrometer. Tetramethylsilane was used as an internal standard except when the spectra were determined in deuterium oxide when the sodium salt of 3-trimethylsilyl-propane-1-sulphonic acid was used. Chemical shifts are given as δ values; coupling constants are given in c./sec. The calculations described by Pople, Schneider, and Bernstein [16] were used to evaluate chemical shifts and coupling constants for AB and ABX systems.

Optical rotations were measured on 1% solutions in 1 dm. polarimeter tubes with a Hilger-Watts polarimeter. Catalytic hydrogenations were carried out by Mr. M. Freifelder and Mr. D. A. Dunnigan of Abbott Laboratories. Elemental analyses were performed by Mr. O. Kolsto and his associates in the analytical department of Abbott Laboratories. Unless otherwise stated, all solid products were dried at 60° 1 mm. for 4 hr.

Starting Materials.— 2-Benzyloxycarbonylamino-2-methylpropanoic acid,[17] m. p. 78°, was prepared from the amino-acid by the method of Greenstein and Winitz [7] in 21% yield. All the other benzyloxycarbonyl amino-acids were commercially available.

DL-Trifluoroacetylamino-2-methylbutanoic acid, m. p. 129—131°, and 2-trifluoroacetylamino-2-ethylbutanoic acid, m. p. 115—117°, were prepared in quantitative yield by treatment of the amino-acid with excess of trifluoroacetic anhydride at room temperature for 1 hr., and addition of water to the residue obtained after concentration of the reaction mixture.

Toluene-*p*-sulphonyldibenzyl L-glutamate, m. p. 144—145°, was prepared as previously described [18] (74% yield).

4-(Substituted-benzylidene)-2-methyl-2-oxazolin-5-ones were prepared from substituted benzaldehydes and acetylglycine in yields of around 50% using the conditions described by Herbst and Shemin.[19] The physical properties of these compounds were as stated in the literature.[19-21]

N-α-*Aminoacyl-L-glutamic Acids* (A).—With the exception of DL-2-amino-2-methylbutanoyl-L-glutamic acid (4) and three peptides which were commercially available,* the dipeptides were synthesised by the reaction of the appropriate benzyloxycarbonyl amino-acid with dibenzyl L-glutamate in pyridine in the presence of dicyclohexylcarbodiimide. The protecting groups were removed by hydrogenolysis. The following procedure is typical.

TABLE 2

N.m.r. data [a] for compounds (A)

Compound (1)	2′-Substituents	2- and 2′-H	3- and 4-H_2
		2′-H_2, 3·86s 2-H, 4·28t, J = 7	1·83—2·58m
(2a) and (2b)	CH_3, 1·57d, J = 8	3·90—4·42m	1·83—2·58m
(3)	$(CH_3)_2$, 1·64s	2H, 4·23t, J = 7	1·83—2·58m
(4)	CH_3CH_2, 0·96t, J = 7 CH_3CH_2, with 3- and 4-H_2 CH_3, 1·64s	2H, 4·23t, J = 6·5	1·72—2·58m
(5)	$(CH_3)_2CH$, 1·04d, J = 7 $(CH_3)_2CH$, with 3- and 4-H_2	2′-H, 3·85d, J = 6 2-H, 4·25t, J = 7	1·72—2·58m
(6)	$(CH_3)_2CHCH_2$, 0·83—1·10m, 2 strong peaks at 0·91 and 1·00 $(CH_3)_2CHCH_2$, with 3- and 4-H_2	3·88—4·43m	1·17—2·60m
(7a)	Aromatic H, 7·35s Benzyl CH_2, 3·23d, J_{AX} = 7 (ABX system)	4·05—4·47m	1·67—2·53m
(7b)	Aromatic H, 7·35s Benzyl CH_2, 3·03—3·32q (ABX system)	3·97—4·42m	1·53—2·03m
(8)	NCH_3, 2·78s	2′-H_2, 3·93s 2-H, 4·29t, J = 6·5	1·75—2·67m

[a] Spectra measured in D_2O.

2-Amino-2-methylpropanoyl-L-glutamic acid (3). Toluene-*p*-sulphonyl dibenzyl L-glutamate (15·00 g., 0·03 mole) in chloroform (100 ml.) was shaken with sodium hydrogen carbonate (3·78 g., 0·045 mole) in water (50 ml.) until evolution of carbon dioxide ceased. The chloroform layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to a white solid (9·82 g.). The free base was dissolved in pyridine (25 ml.) and the protected amino-acid (5·93 g., 0·025 mole) in pyridine (25 ml.) added. The solution was cooled to 0° and dicyclohexylcarbodi-imide (5·16 g., 0·025 mole) added. After a few seconds dicyclohexylurea began to precipitate. The mixture was stored at 5° for 16 hr. Glacial acetic acid (1 ml.) was added, and after storage at 5° for a further hr., the mixture was filtered, and the filtrate concentrated under reduced pressure. The syrup obtained was dissolved in ethyl acetate (100 ml.), a small amount of insoluble material removed by filtration, and the ethyl acetate solution washed with water (25 ml.), N-hydrochloric acid (25 ml.), water (25 ml.), sodium hydrogen carbonate solution (50%, 25 ml.), and water (25 ml.),

* Glycyl-L-glutamic acid (1) was purchased from the Nutritional Biochemical Corporation, and L-alanyl-L-glutamic acid (2a) and L-phenylalanyl-L-glutamic acid (7a) from the Cyclo Chemical Corporation.

[14] R. M. Moriarty, *J. Org. Chem.*, 1963, **28**, 1296.
[15] J. V. Hatton and R. E. Richards, *Mol. Phys.*, 1962, **5**, 153.
[16] (*a*) J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High-Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, Toronto, London, 1959, p. 122; (*b*) p. 134.
[17] M. Bergmann, L. Zervas, J. S. Fruton, F. Schneider, and H. Schleich, *J. Biol. Chem.*, 1935, **109**, 325.
[18] M. Winitz and J. P. Greenstein, *J. Org. Chem.*, 1957, **22**, 1515.
[19] R. M. Herbst and D. Shemin, *Org. Synth.*, Coll. Vol. II, 1943, 1.
[20] S. Sugasawa and T. Tsuda, *J. Pharm. Soc. Japan*, 1935, **55**, 1050.
[21] R. M. Acheson, D. P. Dearnaley, A. O. Plunkett, and V. C. Porter, *J. Chem. Soc.*, 1963, 2085.

TABLE 3

3,6-Dioxo-2-piperazinepropionic acids (B)

	R^1	R^2	M. p.	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N	I.r. absorption bands: 1600—1800 $cm.^{-1}$ region (C=O stretching)	I.r. absorption bands: 3100—3500 $cm.^{-1}$ region (NH stretching)
(9)	H	H	233—235°	$C_7H_{10}N_2O_4$	45·2	5·4	15·1	44·9	5·7	15·2	1690, 1740	3200, 3300sh
(10a)	H	Me	211—213	$C_8H_{12}N_2O_4$	48·0	6·1	14·0	48·0	6·0	14·0	1660, 1730	3050, 3180, 3290sh
(10b)	Me and H		207—211					48·2	6·1	13·9	1670, 1705sh	3030, 3175, 3300
(11)	Me	Me	205—207	$C_9H_{14}N_2O_4$	50·5	6·6	13·1	50·2	6·9	13·4	1675, 1710, 1760sh	3030, 3175, 3300
(12)	Et and Me		270—273	$C_{10}H_{16}N_2O_4$	52·6	7·1	12·3	52·7	7·1	12·1	1670, 1730	3000, 3135, 3250sh
(13)	Pr^i and H		230—233	$C_{10}H_{16}N_2O_4$	52·6	7·1	12·3	52·3	7·2	12·4	1660, 1715sh	3030, 3175, 3300sh
(14)	H	Bu^s	213—216	$C_{11}H_{18}N_2O_4$	54·5	7·5	11·6	54·5	7·6	11·7	1675, 1715	3040, 3180, 3300sh
(15a)	H	Ph·CH_2	219—220	$C_{14}H_{16}N_2O_4$	60·8	5·8	10·1	60·7	5·9	10·2	1705, 1775	3000, 3140, 3260sh
(15b)	Ph·CH_2	H	220—222					60·8	5·9	10·0	1660, 1720, 1755	3010, 3165, 3280sh

TABLE 4

N.m.r. data for compounds (B)

Compound	Solvent	5-Substituents	NH	OH	Propionic CH_2·CH_2	2- and 5-H
(9)	DMSO	—	7·97b and 8·13b	7·67b	1·67—2·50m	3·73b
(10a)	D_2O	CH_3, 1·48d, J = 7			1·95—2·70m	3·95—4·43m
(10b)	DMSO	CH_3, 1·27d, J = 6·5	8·12b and 8·23b	6·72b	1·62—2·50m	3·62—4·17m
	D_2O	CH_3, 1·48d, J = 7 and 1·43d, J = 7			1·73—2·63m	3·93—4·43m
(11)	DMSO	$(CH_3)_2$, 1·32s	7·97b and 8·15b	6·45b	1·75—2·50m	3·94t, J = 4·5
(12)	DMSO	CH_3·CH_2, 0·76t, J = 7·5 CH_3·CH_2, 1·38—2·47m with propionic CH_2·CH_2 CH_3, 1·28s	7·95b and 8·08b	5·03b	1·38—2·47m	3·93t, J = 4·5
(13)	DMSO	$(CH_3)_2$·CH, 0·85d, J = 6 and 0·95d, J = 6 $(CH_3)_2$·CH, 1·63—2·50m with propionic CH_2·CH_2	7·98b and 8·13b	5·43b	1·63—2·50m	3·50—4·03m
(14)	DMSO	$(CH_3)_2$·CH·CH_2, 0·88d, J = 5 $(CH_3)_2CHCH$, 1·33—2·50m with propionic CH_2·CH_2	8·05b and 8·17b	4·60b	1·33—2·50m	3·50—4·10m
(15a)	DMSO	Aromatic H, 7·27s Benzyl CH_2, 2·88—3·23m	8·15b	7·27b under aromatic H	1·00—2·17m	3·72b and 4·22b
(15b)	DMSO	Aromatic H, 7·22s Benzyl CH_2, 3·06d, J_{av} = 5 (ABX system)	7·97b and 8·10b	7·22b under aromatic H	1·00—2·43m	3·73b and 4·15b

TABLE 5

α-Acetamidocinnamoyl glutamic acids (E)

	Compound	M. p.	$[\alpha]_D^{25}$ [a]	Yield %	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N	I.r. absorption bands: 1600—1800 $cm.^{-1}$ region (C=O and C=C stretching)	I.r. absorption bands: 3100—3500 $cm.^{-1}$ region (NH stretching)
(33a)	α-Acetamidocinnamoyl-L-glutamic acid	166—168°	−4·8	59	$C_{16}H_{18}N_2O_6$	57·5	5·4	8·4	57·3	5·4	8·4	1620, 1650, 1700, 1715	3150, 3200, 3350
(33b)	α-Acetamidocinnamoyl-D-glutamic acid	169—171	−35·3	78					57·7	5·3	8·3	1620, 1650, 1685, 1710	3150, 3200, 3350
(34a)	α-Acetamido-4-methoxy cinnamoyl-L-glutamic acid	189—191	−38·2	74	$C_{17}H_{20}N_2O_7$	56·0	5·5	7·7	56·1	5·5	7·8	1620, 1660, 1690, 1740	3165, 3260, 3300
(34b)	α-Acetamido-4-methoxy-cinnamoyl-D-glutamic acid	192—194	−42·0	66					56·3	5·3	7·7	1615, 1650, 1690, 1715	3140, 3195, 3350
(35)	α-Acetamido-3,4-dimethoxy-cinnamoyl-L-glutamic acid	136—137	−55·4	90	$C_{18}H_{22}N_2O_8$	54·8	5·6	7·1	54·8	5·9	7·0	1615, 1645, 1690, 1715	3130, 3200, 3350
(36)	α-Acetamido-3,4,5-trimethoxy-cinnamoyl-L-glutamic acid	206—208	−46·7	89	$C_{19}H_{24}N_2O_9$	53·8	5·7	6·6	54·0	5·6	6·8	1615, 1650, 1700, 1725	3220, 3335
(37)	α-Acetamido-3,4-methylenedi-oxycinnamoyl-L-glutamic acid	182—184	−47·4	77	$C_{17}H_{18}N_2O_8$	54·0	4·8	7·4	53·8	5·0	7·1	1610, 1645, 1690, 1710	3130, 3190, 3345

[a] In dimethylformamide.

TABLE 6

N.m.r. data [a] for compounds (E)

Compound	CH_3CO	Aromatic substituents	Aromatic H	Vinyl C*H*	Glutamic acid CH	Glutamic acid CH_2·CH_2	Glutamic acid N*H*	CH_3CONH	COO*H*
(33a, b)	2·25s		7·12—7·45m (with solvent)	7·67s	5·33b	2·50—3·33m	8·87d, J = 7	10·63b	11·68s
(34a, b)	2·28s	CH_3O, 3·63s	6·91, 7·65 AB quartet J = 9	7·73 (under part of AB pattern of Aromatic H)	5·32b	2·50—3·33m	8·92d, J = 7	10·58b	11·38s
(35)	2·31s	$(CH_3O)_2$, 3·73s	6·72—7·50m (with solvent)	7·80s	5·33b	2·50—3·33m	8·91d, J = 7	10·56b	11·12s
(36)	2·32s	3,5-CH_3O, 3·73s 4-CH_3O, 3·84s	7·00s	7·70s	5·32b	2·50—3·33m	9·06d, J = 7·5	10·62b	13·28s
(37)	2·24s	CH_2O_2, 5·90s	6·79, 7·28 AB quartet J = 8 7·05s	7·68s	5·33b	2·50—3·33m	8·98d, J = 7	10·58b	10·37s

[a] Spectra measured in pyridine.

TABLE 7

α-Acetamidoacyl glutamic acids (F)

	Compound	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N	a $[\alpha]_D^{25}$	I.r. absorption bands: 1500—1800 cm.$^{-1}$ region (C=O stretching)	I.r. absorption bands: 3100—3500 cm.$^{-1}$ region (NH stretching)
(38a)	*N*-Acetyl-DL-phenylalanyl-L-glutamic acid					57·1	5·8	8·5	−5·1		
(38b)	*N*-Acetyl-DL-phenylalanyl-D-glutamic acid	$C_{16}H_{20}N_2O_6$	57·2	6·0	8·3	57·1	6·0	8·5	+5·3	1540, 1595sh, 1615, 1700	3275b
(38c)	*N*-Acetyl-DL-phenylalanyl-DL-glutamic acid					57·4	6·3	8·3	−0·3		
(39a)	*N*-Acetyl-DL-4-methoxyphenylalanyl-L-glutamic acid					55·5	6·1	7·8	−4·2		
(39b)	*N*-Acetyl-DL-4-methoxyphenylalanyl-D-glutamic acid	$C_{17}H_{22}N_2O_7$	55·7	6·1	7·7	55·4	6·3	7·7	+4·9	1540, 1610, 1650, 1710	3270, 3310
(39c)	*N*-Acetyl-DL-4-methoxyphenylalanyl-DL-glutamic acid					55·7	6·0	7·8	−0·1		
(40)	*N*-Acetyl-DL-3,4-dimethoxyphenylalanyl-DL-glutamic acid	$C_{18}H_{24}N_2O_8$	54·6	6·1	7·1	54·6	6·2	7·1	−0·9	1540, 1590sh, 1635, 1710	3290b
(41)	*N*-Acetyl-DL-3,4,5-trimethoxyphenylalanyl-DL-glutamic acid	$C_{19}H_{26}N_2O_9$	53·5	6·2	6·6	53·5	6·4	6·5	+0·2	1535, 1590, 1635, 1715	3280, 3310
(42)	*N*-Acetyl-DL-3,4-methylenedioxyphenylalanyl-DL-glutamic acid	$C_{17}H_{20}N_2O_8$	53·7	5·3	7·4	53·9	5·4	7·4	−0·6	1540, 1615, 1645, 1715	3270, 3310

[a] In dimethylformamide.

TABLE 8

N.m.r. data [a] for compounds (F)

Compound	CH_3CON	Benzyl CH_2	Aromatic H	Aromatic substituents	2- and 2′-H	3- and 4-H_2	COO*H*	N*H*
(38a, b, c)	2·02s	3·17—3·75m	7·07—7·53m		5·00—5·83m	2·33—3·17m	13·83s	8·95d, J = 8 and 9·31d, J = 8·5
(39a, b, c)	2·02s	3·20—3·53m	6·70—7·52m	CH_3O, 3·58s and 3·65s	5·00—5·73m	2·33—3·10m	13·12s	8·95d, J = 8·5 and 9·18d, J = 8
(40)	2·08s	3·15—3·62m	6·80—7·17m	CH_3O, 3·73s and 3·68s 3·76s and 3·71s	5·00—5·83m	2·43—3·08m	14·01s	8·91d, J = 8·5 and 9·34d, J = 8·5
(41)	2·09s	3·27—3·53m	6·73s	3,5-CH_3O 3·70s and 3·84s 4-CH_3O 3·60s and 3·70s	5·00—5·83m	2·33—3·17m	11·30s	8·93d, J = 8 and 9·48d, J = 8
(42)	2·09s	3·17—3·57m	6·70—7·13m	CH_2O_2, 5·85s and 5·95s	5·00—5·72m	2·33—3·10m	14·05s	8·97d, J = 8·5 and 9·36d, J = 8·5

[a] Spectra measured in pyridine.

TABLE 9

1,4-Diazabicyclo[4,3,0]nonane-2,5,9-triones (C)

Compound	R_1	R_2	Starting material	Yield %	Recryst. solvent	M. p.	$[\alpha]_D^{25}$ [a]	I.r. absorption bands: 1620—1850 cm.$^{-1}$ region (C=O stretching)	I.r. absorption bands: 3000—3400 cm.$^{-1}$ region (NH stretching)
(16)	H	H	(1)	79	ethanol–ether	184—187°	−70·5	1710, 1785	3235, 3280
(17a)	H	Me	(2a)	72	ethanol	220—222	−84·0	1640, 1680, 1760	3255
(17b)	H and Me		(2b)	68	ethanol	187—191	−0·1	1680, 1775	3080, 3185
(18)	Me	Me	(3)	77	ethanol–ether	258—261	−9·2	1675, 1770	3070, 3185
(19)	Me and Et		(4)	28	acetone	222—225	−2·8	1655, 1750	3040, 3150
(20)	H and Pr^i		(5)	19	ethanol	190—220	−13·7	1680, 1760	3065, 3180
(21)	H	Bu^s	(6)	23	ethanol	215—218	−10·5	1675, 1775	3060, 3180
(22a)	H	$PhCH_2$	(7a)	57	methanol–ether	192—194	−108·9	1720, 1780	3350
(22b)	$PhCH_2$	H	(7b)	69	ethanol	196—198	+25·0	1695, 1765	3280

[a] In dimethylformamide.

Analysis of compounds (C)

Compound	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N
(16)	$C_7H_8N_2O_3$	50·0	4·8	16·7	50·2	4·7	16·8
(17a)	$C_8H_{10}N_2O_3$	52·7	5·5	15·4	52·5	5·5	15·4
(17b)					52·8	5·4	15·6
(18)	$C_9H_{12}N_2O_3$	55·1	6·2	14·3	54·9	6·5	14·3
(19)	$C_{10}H_{14}N_2O_3$	57·1	6·7	13·3	57·2	6·6	13·1
(20)	$C_{10}H_{14}N_2O_3$	57·1	6·7	13·3	57·2	6·7	13·2
(21)	$C_{11}H_{16}N_2O_3$	58·9	7·2	12·5	59·0	7·2	12·6
(22a)	$C_{14}H_{14}N_2O_3$	65·1	5·5	10·9	64·8	5·7	11·0
(22b)					65·1	5·4	10·9

TABLE 10

N.m.r. data for compounds (C)

Compound	Solvent	N(4)-H	3-Substituents	7- and 8-H_2	6-H
(16)	DMSO	8·20b	H^{ax}, 4·12d; H^{eq}, 3·64q; ABX System $J_{AB} = 17$, $J_{AX} = 0$, $J_{BX} = 5$	1·33—1·83m	4·63t, $J = 8$
(17a)	C_5H_5N	7·78b	CH_3^{eq}, 1·56d; H^{ax}, 4·32q; $J = 7$	2·17—2·67m	4·77t, $J = 8$
(17b)	C_5H_5N	7·78b	CH_3^{eq}, 1·56d; H^{ax}, 4·32q; $J = 7$ CH_3^{ax}, 1·49d; H^{eq}, 4·32q; $J = 7$	2·00—2·67m	4·77t, $J = 8$
(18)	DMSO	8·32b	CH_3, 1·34s and 1·38s	1·83—2·83m	4·75t, $J = 8$
(19)	DMSO	8·28b and 8·40b	CH_3, 1·30s and 1·37s CH_3CH_2, 0·77t, $J = 7$ and 0·88t, $J = 7$ CH_3CH_2, 1·50—2·50m (with 7,8-H_2 and solvent)	1·50—2·50m	4·90t, $J = 8$
(20)	C_5H_5N	4·83b (under 6-H)	H^{ax}, 4·19d, $J = 2·5$ H^{eq}, 3·91q, $J_{CH} = 7·5$, $J_{NH} = 5$ $(CH_3)_2CH$, 0·95—1·26m (7 of 8 theoretical peaks visible) $CH(CH_3)_2$, under 7,8-H_2	1·83—3·00m	4·86t, $J = 7·5$
(21)	C_5H_5N	7·43b and 8·00b	H, 4·00—4·50m $(CH_3)_2CHCH_2$, 0·78—1·03m $(CH_3)_2CHCH_2$, 1·50—2·67m (with 7,8-H_2)	1·50—2·67m	4·83t, $J = 8$
(22a)	$CDCl_3$	5·75b	Aromatic H, 7·33b Benzyl CH_2 H^A, 2·87q H^B, 3·60q H^{ax}, 4·00—4·67m (with 6-H); ABX System $J_{AB} = 15$, $J_{AX} = 10$, $J_{BX} = 4$	2·22—2·67m	4·00—4·67m (with 3-H)
(22b)	$CDCl_3$	6·63d, $J = 5$	Aromatic H, 7·28b Benzyl CH_2, 3·00—3·42m (with 6-H) H^{eq}, 4·34q	1·67—2·67m	3·00—3·42m (with benzyl CH_2)

dried ($MgSO_4$), and concentrated at reduced pressure to a clear intractable syrup (11·90 g.).

The syrup was dissolved in 50% aqueous ethanol (100 ml.) and hydrogenated over 5% palladium–carbon (2·4 g.) at 50° and 2·7 atmos. for 16 hr. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. A syrup was obtained which on treatment with a (9·82 g., 0·03 mole) in pyridine (50 ml.) in the presence of dicyclohexylcarbodi-imide (5·16 g., 0·025 mole) as described.

Hydrogenation of the protected peptide under the same conditions yielded the trifluoroacetyl peptide as an intractable syrup (7·36 g.).

The syrup was dissolved in ethanol (50 ml.) and N-sodium hydroxide added to pH 12. The solution was allowed to

TABLE 11

4-Acyl-1,4-diazabicyclo[4,3,0]nonane-2,5,9-triones (D)

Compound	R^1	R^2	R^3	Configuration of 6-proton	Starting material	Yield %	Recryst. solvent	M. p.	$[\alpha]_D^{25}$ [a]	I.r. absorption [b] bands in 1620—1850 cm.$^{-1}$ region (C=O stretching)
(23)	H	H	Me	β	(1)	78	EtOH	148—150°	−7·7	1730, 1795
(24)	H	H	Et	β	(1)	66	EtOH–Et_2O	158—160	−3·9	1735, 1795
(25)	H	H	Pr^n	β	(1)	36	Me_2CO–Et_2O	121—123	+0·5	1700, 1765
(26)	H	H	Pr^i	β	(1)	25	C_6H_6–Et_2O	148—150	+11·3	1725, 1790
(27)	Me	H	Me	β	(2a)	48	EtOH	183—185	+8·0	1715, 1780
					(2b)	37				
(28)	Me	Me	Me	β	(3)	47	Me_2CO	163—166	−25·4	1700, 1745, 1790
(29)	Me and Et		Me	β	(4)	26	Me_2CO–H_2O	129—131	−3·2	1750, 1780, 1830
(30)	Pr^i	H	Me	β	(5)	63	EtOH	178—180	−34·4	1720, 1780
(31)	Bu^s	H	Me	β	(6)	32	EtOH	158—160	+0·2	1715, 1780
(32a)	$PhCH_2$	H	Me	β	(7a)	63	EtOAc–pet [d]	164—166	+8·2	
					(7b)	59				
					(38a)	56				
(32b)	H	$PhCH_2$	Me	α	(38b)	60	EtOAc	164—166	−8·3	1715, 1780
(32c [c])	$PhCH_2$	H	Me	β	(38c)	49	EtOAc–pet [d]	162—164	0·0	
	H	$PhCH_2$	Me	α						
(43a)	4-MeO·C_6H_4·CH_2	H	Me	β	(39a)	54	EtOAc	200—202	+64·3	
(43b)	H	4-MeO·C_6H_4·CH_2	Me	α	(39b)	51	EtOAc	200—202	−64·5	1710, 1775
(43c [c])	4-MeO·C_6H_4·CH_2	H	Me	β	(39c)	55	EtOAc–pet [d]	168—169	+0·3	
	H	4-MeO·C_6H_4·CH_2	Me	α						
(44 [c])	3,4-$(MeO)_2$·C_6H_3·CH_2	H	Me	β	(40)	42	EtOAc–pet [d]	172—173	0·0	1710, 1775
	H	3,4-$(MeO)_2$·C_6H_3·CH_2	Me	α						
(45 [c])	3,4,5-$(MeO)_3$·C_6H_2·CH_2	H	Me	β	(41)	40	EtOAc	162—164	−0·1	1710, 1780
	H	3,4,5-$(MeO)_3$·C_6H_2·CH_2	Me	α						
(46 [c])	3,4-(CH_2O_2)·C_6H_3·CH_2	H	Me	β	(42)	42	EtOAc	172—174	+0·2	1715, 1780
	H	3,4-(CH_2O_2)·C_6H_3·CH_2	Me	α						

[a] In dimethylformamide. [b] Spectra measured in chloroform. [c] Racemate. [d] Light petroleum, b. p. 40—60°.

Analysis of compounds (D)

Compound	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N
(23)	$C_9H_{10}N_2O_4$	51·4	4·8	13·3	51·7	4·9	13·6
(24)	$C_{10}H_{12}N_2O_4$	53·6	5·4	12·5	53·9	5·7	12·7
(25)	$C_{11}H_{14}N_2O_4$	55·5	5·9	11·8	55·3	6·2	11·7
(26)					55·3	5·7	11·7
(27)	$C_{10}H_{12}N_2O_4$	53·6	5·4	12·5	53·7	5·2	12·7
(28)	$C_{11}H_{14}N_2O_4$	55·5	5·9	11·8	55·6	6·2	11·7
(29)	$C_{12}H_{16}N_2O_4$	57·1	6·4	11·1	57·4	6·5	11·2
(30)					56·9	6·2	11·0
(31)	$C_{13}H_{18}N_2O_4$	58·6	6·8	10·5	58·6	6·9	10·5

Compound	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N
(32a)					64·1	5·4	9·5
(32b)	$C_{16}H_{16}N_2O_4$	64·0	5·4	9·3	63·7	5·5	9·3
(32c)					64·2	5·4	9·2
(43a)					61·7	5·5	8·4
(43b)	$C_{17}H_{18}N_2O_5$	61·8	5·5	8·5	61·6	5·3	8·5
(43c)					61·7	5·7	8·4
(44)	$C_{18}H_{20}N_2O_6$	60·0	5·6	7·8	60·2	5·7	7·8
(45)	$C_{19}H_{22}N_2O_7$	58·5	5·7	7·2	58·7	5·7	7·1
(46)	$C_{17}H_{16}N_2O_6$	59·3	4·7	8·1	59·2	4·4	8·1

mixture of ethanol (50 ml.) and ether (50 ml.) yielded a hygroscopic white solid (5·03 g.). This material was dissolved in methanol (50 ml.) and reprecipitated with ether (250 ml.). The white solid obtained was filtered and dried (3·89 g., 67%, $[\alpha]_D^{25}$ −8·3°).

DL-2-*Amino-2-methylbutanoyl-*L*-glutamic acid* (4). Dibenzyl DL-2-trifluoroacetylamino-2-methylbutanoyl-L-glutamate (11·75 g.) was prepared by the reaction of the protected acid (5·33 g., 0·025 mole) with dibenzyl L-glutamate

stand at room temperature for 2 days and then acidified with N-hydrochloric acid.* The solution was concentrated under reduced pressure and the residue treated with methanol (50 ml.) and filtered. On addition of ether (500

* Prior experimentation had established these as the mildest conditions under which the trifluoroacetyl group could be removed from the 2-amino-2-methyl acid. Hydrolytic cleavage of the trifluoroacetyl group from the 2-ethyl analogue did not occur under these conditions.

ml.) to the methanol solution a white precipitate was obtained (5·30 g.). This was dissolved in methanol (50 ml.), filtered, and reprecipitated with ether (500 ml.). The product was filtered and dried (4·31 g., 70%, $[\alpha]_D^{25}$ −1·0°).

3,6-*Dioxo-2-piperazinepropionic Acids* (B).—5-Substituted dehydropeptides were prepared by a procedure similar to that described by Bergmann, Stern, and Witte.[8]

α-*Acetamido-4-methoxycinnamoyl-L-glutamic acid* (34*a*). To L-glutamic acid (44·1 g., 0·3 mole) in acetone (300 ml.), N-sodium hydroxide (600 ml.) was added with stirring, and

TABLE 12

N.m.r. data for compounds (D)

Compound	Solvent	N(4)-Acyl substituent	3-Substituents	7- and 8-H_2	6-H
(23)	DMSO	CH_3, 2·45s	H, 4·73d and 4·18d AB system J = 16	1·17—1·83m	4·93t, J = 8
(24)	DMSO	CH_3, 1·04t; CH_2, 2·89q; J = 7·5	H, 4·78d and 4·19d AB system J = 17	2·00—2·67m	4·93t, J = 8
	$CDCl_3$	CH_3, 1·17t; CH_2, 2·98q; J = 7	H, 5·16d and 3·99d AB system J = 17	2·17—2·67m	4·75t, J = 7·5
(25)	$CDCl_3$	CH_3, 0·97t, J = 7 CH_2CH_3CO, 1·33—2·00m CH_2CH_2CO, 2·94t, J = 7·5	H, 5·11d and 4·01d AB system J = 17·5	2·17—2·67m	4·79t, J = 7·5
(26)	$CDCl_3$	CH_3, 1·18d, J = 7 and 1·21d, J = 7 $>CH-$, 3·33—4·00m	H, 5·14d and 3·98d AB system J = 17·5	2·17—2·83m	4·71t, J = 7·5
(27)	$CDCl_3$	CH_3, 2·58s	CH_3, 1·54d; H, 5·20q; J = 7·5	2·33—2·83m	4·72t, J = 8
(28)	DMSO	CH_3, 2·40s	CH_3, 1·57s and 1·60s	1·83—2·83m	4·93t, J = 8
(29)	DMSO	CH_3, 2·47s	CH_3, 1·53s and 1·61s CH_3CH_2, 0·65t, J = 7·5 and 0·86t, J = 7·5 CH_3CH_2, 1·83—2·67m (with 7,8-H_2 and solvent)	1·83—2·67m	4·93t, J = 8
(30)	$CDCl_3$	CH_3, 2·58s	$(CH_3)_2CH$, 1·00d, J = 10 and 1·12d, J = 10 H, 4·97d, J = 10 $CH(CH_3)_2$ under 7,8-H_2	2·17—2·83m	4·75t, J = 8
(31)	$CDCl_3$	CH_3, 2·56s	H, 5·03t, J = 6 $(CH_3)_2CHCH_2$, 0·83—1·17m $(CH_3)_2CHCH_2$, 1·33—2·00m	2·33—2·67m	4·68t, J = 8
(32a, b, c)	$CDCl_3$	CH_3, 2·57s	Aromatic H, 7·00—7·50m Benzyl CH_2, 3·28d; H_{eq}, 5·41t; J_{av} = 5	2·00—2·50m	3·07t, J = 8
(32c)	$CDCl_3$, 56°	CH_3, 2·57s	Aromatic H, 7·00—7·50m Benzyl CH_2, 3·28d; H_{eq}, 5·41t; J_{av} = 5	2·00—2·50m	3·26t, J = 8
	C_5H_5N	CH_3, 2·59s	Aromatic H, 7·33s Benzyl CH_2, 3·35d; H_{eq}, 5·74t; J_{av} = 6·5	2·17—2·67m	4·51t, J = 8
	DMSO	CH_3, 2·35s	Aromatic H, 7·24s Benzyl CH_2, 3·13d; H_{eq}, 5·14t; J_{av} = 7	2·00—2·67m	4·80t, J = 8
(43a, b, c)	$CDCl_3$	CH_3, 2·58s	Aromatic H, 6·81d and 7·05d, J = 9 $-OCH_3$, 3·80s Benzyl CH_2, 3·23d; H_{eq}, 5·37t; J_{av} = 5	2·00—2·50m	3·15t, J = 8
(44)	$CDCl_3$	CH_3, 2·58s	Aromatic H, 6·50—6·83m OCH_3, 3·81s and 3·87s Benzyl CH_2, 3·17—3·29q H_{eq}, 5·41t, J_{av} = 5	2·00—2·50m	3·05t, J = 8
(45)	$CDCl_3$	CH_3, 2·58s	Aromatic H, 6·32s *p*-OCH, 3·80s *m*-OCH_3, 3·78s Benzyl CH_2, 3·00—3·33m (with 6-H) H_{eq}, 5·38t, J_{av} = 5	2·00—2·50m	3·00—3·33m (with benzyl CH_2)
(46)	$CDCl_3$	CH_3, 2·57s	Aromatic H, 6·33—7·00m CH_2O_2, 5·95s Benzyl CH_2, 3·18d; H_{eq}, 5·37t; J_{av} = 5	2·00—2·50m	3·47t, J = 8

3,6-dioxo-2-piperazinepropionic acids were prepared by heating the appropriate *N*-α-aminoacyl-L-glutamic acid at 150—160°/1 mm. for 30 min. The products were used without further purification in the subsequent cyclisation reactions. The dioxopiperazines were purified for characterisation by precipitation from dimethylformamide solution with ether–light petroleum.

α-*Acetamidocinnamoyl Glutamic Acids* (E).—The acetyl after several min. 2-methyl-4-(4-methoxybenzylidene)-2-oxazolin-5-one (65·2 g., 0·3 mole). The mixture was stirred at room temperature for 3 hr. during which time all of the oxazolinone went into solution. N-hydrochloric acid (600 ml.) was added with stirring and the clear solution concentrated under reduced pressure to remove the acetone. A white crystalline precipitate was obtained. The mixture was stored at 5° overnight and filtered. The crude product

was recrystallised from propan-2-ol and dried (80·9 g., 74%, m. p. 189—191°).

N-α-*Acetamidoacyl-glutamic Acids* (F).—Compounds (38c), (39c), (40), (41), and (42) were prepared by hydrogenation of the appropriate α-acetamidocinnamoyl glutamic acid using a procedure similar to that described by Bergmann, Stern, and Witte.[8]

N-*Acetyl*-DL-3-(4-*methoxyphenyl*)*alanyl*-DL-*glutamic acid* (39*c*). α-Acetamido-4-methoxycinnamoyl-L-glutamic acid (50·0 g.) was hydrogenated in glacial acetic acid (250 ml.) at 60° and 2·7 atmos. in the presence of 5% palladium–carbon (7·5 g.). The uptake of hydrogen was complete after 1 hr., but the hydrogenation was allowed to run for a further hr. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. The last traces of acetic acid were removed from the white solid product (50·3 g., quantitative yield) at 50°/1 mm. for 40 hr.

Compounds (38a), (38b), (39a), and (39b) were prepared in the same manner except that the hydrogenation was carried out at 20°.

1,4-*Diazabicyclo*[4,3,0]*nonane*-2,5,9-*triones* (C).—*Method* 1. 1,4-*Diazabicyclo*[4,3,0]*nonane*-2,5,9-*trione* (16). The dioxopiperazine (9) derived from glycyl-L-glutamic acid (2·0 g.) was refluxed for 1 hr. with trifluoroacetic anhydride (20 ml.). The solution was cooled and concentrated at reduced pressure to a syrup which on treatment with ether (10 ml.) yielded a pale yellow solid (1·86 g.). The product was purified by reprecipitation from ethanol (10 ml.) with ether (25 ml.), filtered, and dried (1·30 g., 79%, m. p. 184—187°).

Compounds (17a), (17b), (18), (20), (21), (22a), and (22b) [general formula (C)] were prepared in the same manner. In some cases it was possible to isolate the pure bicyclic product by recrystallisation of the crude material from ethanol.

The *N*-acetyl derivatives (23), (27), (28), (30), (31), and (32a) [general formula (D)] were synthesised by the same procedure except that acetic anhydride was used in place of trifluoroacetic anhydride.

Compound (23) was also prepared by refluxing (16) with acetic anhydride for 30 min. (37% yield).

The *N*-acyl derivatives (24), (25), and (26) were prepared by a similar procedure, but in these experiments it was necessary to use a mixture of dimethylformamide (20 ml.) and the appropriate acid anhydride (20 ml.) to dissolve the dioxopiperazine.

3-*Ethyl*-3-*methyl*-1,4-*diazabicyclo*[4,3,0]*nonane*-2,5,9-*trione* (19) *and* 4-*acetyl*-3-*ethyl*-3-*methyl*-1,4-*diaza-bicyclo*-[4,3,0]*nonane*-2,5,9-*trione* (29). The dioxopiperazine (12) (2 g.) was refluxed for 1 hr. with acetic anhydride. The solution was cooled and concentrated under reduced pressure to a syrup, which on treatment with ether (10 ml.) yielded a buff solid (1·52 g.). The solid was recrystallised from acetone (15 ml.) and yielded (19) as a white crystalline solid (0·48 g., 28%, m. p. 222—225°).

The supernatant acetone solution was concentrated at reduced pressure and a water insoluble solid (0·59 g.) obtained. The solid was treated with water (15 ml.), filtered, washed with water (2 × 5 ml.) and dried to give pure (29) (0·54 g., 26%, m. p. 129—131°).

Method 2. (—)-4-*Acetyl*-3-*benzyl*-1,4-*diazabicyclo*[4,3,0]-*nonane*-2,5,9-*trione* (32*b*). *N*-Acetyl-DL-phenylalanyl-D-glutamic acid (38b) (5·0 g.) was refluxed with acetic anhydride (50 ml.) for 1 hr. The solution was concentrated under reduced pressure and a white solid obtained. Recrystallisation from ethyl acetate afforded pure (32b) (2·7 g., 60%, m. p. 164—166°).

Compounds (32a), (32c), (43a), (43b), (43c), (44), (45), and (46) were also prepared by this procedure.

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