The Epimeric (±)-3-*Amino*cyclo*hexanecarboxylic Acids.*

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cis- and *trans*-3-Amino*cyclo*hexanecarboxylic acids have been prepared by a stereochemically specific method. A cyclic lactam (II) has been reduced to 1-aza*bicyclo*[3 : 2 : 1]octane (IV). The first dissociation constants of the amino-acids have been determined.

BAUER and EINHORN (*Annalen*, 1901, **319**, 329) obtained a 3-amino*cyclo*hexanecarboxylic acid of m. p. 268—269°, and a similar product, m. p. 268°, was described by Orthner and Hein (*Biochem. Z.*, 1933, **262**, 461), but in neither case did the authors make a configurational assignment. More recently, Greenstein and Wyman (*J. Amer. Chem. Soc.*, 1938, **60**, 2341) prepared crystalline samples of the amino-acid by platinum-catalysed hydrogenation of *m*-aminobenzoic acid in acid and in neutral solution, giving products, m. p. 264° and 278° respectively, which they considered to be identical. The last authors, by comparison of the dielectric increments of the 2-, 3-, and 4-amino*cyclo*hexanecarboxylic acids plotted against the mean-square distances separating the charged groups with the straight line obtained for this function of the simple aliphatic amino-acids, concluded that the 2- and 4-amino-acids probably occur in the *cis*-configuration, and the 3-isomer in the *trans*-configuration. They recognised that their arguments were somewhat artificial but apparently did not consider the possibility that their preparations were epimeric mixtures. Moreover, they made no mention of the work of Orthner and Hein (*loc. cit.*) who clearly described the preparation of both geometrical isomers of 4-amino*cyclo*hexanecarboxylic acid. Similar preparations have since been described by Wendt (*Ber.*, 1942, **75**, 425), and by Ferber and Brückner (*Ber.*, 1943, **76**, 1019), and Hünig and Kahanek (*Ber.*, 1953, **86**, 518) have prepared both *cis*- and *trans*-2-amino*cyclo*hexanecarboxylic acids. These results, taken in conjunction with the usual steric course of catalytic hydrogenation (Barton, *J.*, 1953, 1029; Bose, *Experientia*, 1953, **9**, 256), suggest that Greenstein and

Wyman's 2- and 4-amino-acids are epimeric mixtures richer in the *trans*-epimer, while their 3-isomer is probably a mixture richer in the *cis*-epimer, *i.e.*, the configurations are the reverse of those suggested by them.

It appeared possible to clarify the matter in the case of the 3-amino-acid by applying the Schmidt reaction, found to proceed with retention of molecular configuration and asymmetry by Campbell and Kenyon (*J.*, 1946, 25) in their particular case, to the epimeric hexahydro*iso*phthalic acids, the configurations of which have been established with certainty by resolution of the *trans*-acid (Böeseken and Peek, *Rec. Trav. chim.*, 1925, **44**, 845), and by anhydride formation from the *cis*-acid (Baeyer and Villiger, *Annalen*, 1893, **276**, 261; Goodwin and Perkin, *J.*, 1905, **87**, 841). If both epimers of the amino-acid are stable each should be formed stereochemically pure from the appropriate epimer of hexahydro*iso*phthalic acid.

In an attempt to obtain greater selectivity we used methyl hydrogen *cis*-hexahydro*iso*-phthalate with one equivalent of sodium azide, for hydrazoic acid appears to react more readily with carboxyl than with alkoxycarbonyl groups (Smith, "Organic Reactions," Vol. 3, p. 364). No amino-ester could be isolated, however, the product being identified through its benzoyl derivative as the amino-acid itself. The absence of the amino-ester may be explained either by assuming that in this case hydrazoic acid reacts more readily with the methoxycarbonyl group, or more probably by the extreme ease with which many esters are hydrolysed in concentrated sulphuric acid (Gillespie and Leisten, *Quart. Reviews*, 1954, **8**, 40).

Best yields (80%) of the amino-acid were obtained by slow addition of hydrazoic acid in chloroform to a sulphuric acid solution of the hexahydro*iso*phthalic acid itself. The use of hydrazoic acid rather than sodium azide was necessitated both by the greater control over the rate of addition and by the subsequent method of isolation. As the reaction was rather slow, the possibility of isomerisation was ruled out by blank experiments in which the hydrazoic acid was omitted. The characteristics of the two epimeric 3-amino*cyclo*-hexanecarboxylic acids so obtained from the corresponding hexahydro*iso*phthalic acids are shown below.

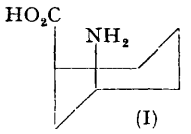
	M. p., *cis*	M. p., *trans*
3-Amino*cyclo*hexanecarboxylic acid	284°	290—291°
Benzoyl derivative	166—167	195—196
p-Bromophenacyl ester of the benzoyl derivative	211—212	182
α-Naphthylcarbamoyl derivative	207	213—214

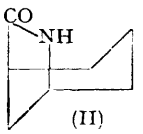
Benzoylation of the amino-acid obtained by platinum-catalysed hydrogenation of *m*-aminobenzoic acid in acid solution gave a derivative identical with that obtained from the Schmidt reaction on methyl hydrogen *cis*-hexahydro*iso*phthalate and on the acid itself. Confirmation is thus provided for the suggested reversal of configuration of the 3-amino*cyclo*hexanecarboxylic acid prepared by Greenstein and Wyman.

Further evidence that the configurations assigned to these 3-amino-acids on the basis of the stereochemical specificity of the Schmidt reaction are correct was provided by formation of the lactam (II). The two substituents in the diaxial conformation of the *cis*-amino-acid (I) are favourably situated for the elimination of water, and pyrolysis of the *cis*-amino-acid gave a 30% yield of a lactam. However, the same lactam was obtained in 13% yield by pyrolysis of the *trans*-amino-acid. That the lactam is derived from the *cis*-amino-acid was proved by hydrolysis with barium hydroxide, which afforded only this acid. Orthner and Hein (*loc. cit.*) observed a similar partial isomerisation in the formation of the lactam of 4-amino*cyclo*hexanecarboxylic acid, but this could not be verified by Wendt (*loc. cit.*).

A complication arose in that the molecular weight (Rast's method) of the lactam was almost double that required by (II). As the dipeptide (III) had been described by Mazza (*Chem. Abs.*, 1929, **23**, 2957), the possibility of a bimolecular structure had to be considered. Inspection of models showed that dipeptide formation from either epimer in the 3-amino-series was only possible from a pair of diaxially substituted amino-acids involving considerable steric hindrance. To establish the unimolecular structure of the lactam experimentally, the latter was reduced with lithium aluminium hydride by the method of Ruzicka,

Kobelt, Häfliger, and Prelog (*Helv. Chim. Acta*, 1949, **32**, 544) to a crystalline base. The molecular weights of both the α-naphthylurethane and the *p*-nitrobenzoyl derivative closely correspond to those for derivatives of 6-aza*bicyclo*[3 : 2 : 1]octane (IV). Further evidence that the lactam possesses the unimolecular structure (II) was provided by pyrolysis of *cis*-3-benzamido*cyclo*hexanecarboxylic acid, which gave the *N*-benzoyl derivative (V), the molecular weight of which corresponded to the structure shown. Although


(I)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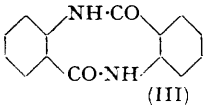
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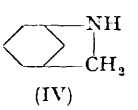
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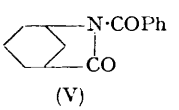
(V)

some benzoic acid was obtained from this pyrolysis, none of the lactam itself could be isolated. The bimolecular association shown by the lactam in solution in camphor is probably attributable to hydrogen bonding between the very favourably situated atoms. Ferber and Brückner (*loc. cit.*) report a similar phenomenon with the lactam of 4-amino-*cyclo*hexanecarboxylic acid.

The reversal of the Auwers–Skita rule for 1 : 3-disubstituted *cyclo*hexanes (Pitzer *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 977, 2488; *Science*, 1947, **105**, 647; Hassel *et al.*, *Acta Chem. Scand.*, 1947, **1**, 929; 1950, **4**, 597) implies that in general the m. p.s of *cis*-1 : 3-compounds should be higher than those of their *trans*-epimers. From the foregoing Table it can be seen that for 3-amino*cyclo*hexanecarboxylic acid and its derivatives this condition is fulfilled in only one instance. A similar situation exists for *cyclo*hexane-1 : 3-diol where the *cis*-epimer has the lower m. p. (Rigby, *J.*, 1949, 1586, 1588). Although m. p.s are the least reliable criteria for the application of the Auwers–Skita rule, and the m. p.s of amino-acids are as a rule merely temperatures of decomposition, we found these two exceptions suggestive. Kuhn (*J. Amer. Chem. Soc.*, 1952, **74**, 2492) has provided firm evidence that *cis-cyclo*hexane-1 : 3-diol is stabilised in the diaxial conformation by hydrogen bonding, a possibility suggested by Hassel and Ottar (*loc. cit.*, 1947), and as the physical properties with which the rule is concerned appear to depend largely on the compactness of the molecule, it seemed possible that the discordant m. p.s in the case of the 3-amino-acid might arise from a similar cause.

From the high m. p.s and extreme insolubility in organic solvents, and by analogy with aliphatic amino-acids, these 3-amino*cyclo*hexanecarboxylic acids must be assumed to be largely in the form of dipolar ions. Consequently, the attraction between the oppositely charged groups might be expected to hold the *cis*-amino-acid in the diaxial conformation, overcoming the destabilisation due to steric factors. Empirically it is improbable that this destabilisation would seriously exceed the 6 kcal./mole calculated for the diaxial form of *cis*-1 : 3-dimethyl*cyclo*hexane (Pitzer and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 977), since it is known that the methyl is more effective than the carboxyl group in hindering the rotation of diphenyls. Albrecht and Corey (*ibid.*, 1939, **61**, 1087) have shown that in crystalline glycine the nitrogen atom is separated from the oxygen atoms of a carboxyl group in the same plane by 2·76 and 2·88 Å. These distances may be compared with a value of 2·8 Å in the diaxial form where the nitrogen atom is equidistant from the two oxygen atoms. For the vapour phase, where the effective dielectric constant will be approximately unity, simple calculation gives an electrostatic stabilisation energy of approximately 70 kcal./mole for the diaxial form, which would thus be expected to be the more stable form. In solution, however, the evaluation of effective dielectric constants (Kirkwood and Westheimer, *J. Chem. Phys.*, 1938, **6**, 506; Sarmousakis, *ibid.*, 1944, **12**, 277) is complicated by the choice of suitable models.

The first dissociation constants of the epimeric amino-acids were therefore determined by using a glass electrode and Tague's method of correction for the solvent (*ibid.*, 1920, **42**, 173). The pK_1 values of 3·70 and 3·85 obtained for the *cis*- and the *trans*-epimer respectively at 15° are close to those obtained for the crude 3- and epimeric 4-amino*cyclo*hexane-carboxylic acids (Orthner and Hein, *loc. cit.*; Greenstein and Wyman, *loc. cit.*), and are

considerably larger (*ca.* 1 pK unit) than those found by these authors for crude 2-amino*cyclo*hexanecarboxylic acid. On these grounds alone it appears unlikely that the *cis*-3-amino-acid is stabilised in the diaxial form in aqueous solution. If the difference of 0·15 in the pK_1 values for the isomeric acids is significant the following argument may be applied. As the two charged groups are separated by the same number of carbon atoms in each geometrical isomer, the inductive effect may be assumed to be the same in both isomers, any difference in dissociation constant being due to an electrostatic effect. Thus the dipolar structure is most stable when the two charged groups are closest together, *i.e.*, the closer the groups the stronger the acid and base. From the relevant equilibrium $^+NH_3{\cdot}R{\cdot}CO_2^- + H^+ \rightleftharpoons {}^+NH_3{\cdot}R{\cdot}CO_2H$, it can be seen that the stronger acid will have the larger pK_1 value. The expected order of acidity from the relative separation of the groups is *cis*-1a : 3a > *trans*-1a : 3e ≏ *trans*-1e : 3a > *cis*-1e : 3e. It thus appears that the *cis*-epimer, being the weaker acid, is more stable in the diequatorial form in solution. Further evidence for this conclusion is provided by Greenstein and Wyman's observation (*loc. cit.*) that, if the attraction of oppositely charged groups could give rise to conformations of lower energy content, the dielectric increment found for the 2-amino-acid should not be less than that for the 3- and 4-isomers, whereas in fact it is.

Experimental

cis- and *trans*-Hexahydro*iso*phthalic acids were prepared as described previously (*J.*, 1954, 700) with the exception that hydrogenation was carried out at 70° under an initial pressure of 1000 lb./sq. in. The hydrogenations were then usually complete in 3 hr., and the proportion of the *trans*-epimer produced was only slightly less than that obtained under atmospheric conditions. Both epimers were recovered stereochemically pure after stirring their solutions in sulphuric acid with chloroform for 6 hr. at 60°.

Solutions of hydrazoic acid in chloroform, obtained as described in "Organic Reactions" (1946, Vol. 3, p. 327), were analysed by titration with standard alkali; they showed no sign of deterioration after 6 months' storage over anhydrous sodium sulphate at 0°. The usual safety precautions were adopted.

Hydrogenation of m-*Aminobenzoic Acid.*—*m*-Aminobenzoic acid (7 g.), four times recrystallised from water, was hydrogenated exactly as described by Greenstein and Wyman (*loc. cit.*). The reaction was stopped when the theoretical amount of hydrogen had been absorbed. Three precipitations of the crude 3-amino*cyclo*hexanecarboxylic acid (4·6 g.) from aqueous solution by acetone gave microcrystals, m. p. 279° (decomp.). Benzoylation of this product in aqueous sodium carbonate, followed by recrystallisation from chloroform–hexane, gave 3-*benzamido*-cyclo*hexanecarboxylic acid* (50%) as prisms, m. p. 166—167° (Found: C, 68·3; H, 6·7; N, 5·6. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%). Recrystallisation from aqueous ethanol gave plates, m. p. 167—168°.

cis-3-*Amino*cyclo*hexanecarboxylic Acid.*—(a) *From* cis-3-*methoxycarbonyl*cyclo*hexanecarboxylic acid.* The methoxy-acid, b. p. 136—140°, m. p. 59—60°, was prepared (see Vavon and Peignier, *Bull. Soc. chim.*, 1929, **45**, 300) from the anhydride of *cis*-hexahydro*iso*phthalic acid. Powdered sodium azide (0·5 g.) was added portionwise (90 min.) to a well-stirred solution of this *cis*-monoester (1·3 g.) in chloroform (30 ml.) and concentrated sulphuric acid (5 ml.), kept at 40°. The temperature was then raised to 50°, and stirring continued for a further 30 min. When cool, the mixture was poured on crushed ice and separated. Evaporation of the chloroform gave a negligible residue. The solution was made just alkaline with sodium hydroxide and continuously extracted with ether: however, no residue was obtained on evaporation of the dried ($MgSO_4$) ethereal extract. The solution was then made neutral to phenolphthalein with sulphuric acid and concentrated to *ca.* 40 ml. under reduced pressure. Ethanol (15 ml.) was carefully added to this warm solution, and after two days the precipitated sodium sulphate was filtered off. The filtrate was evaporated to dryness under reduced pressure and the solid residue, which appeared to be almost free from sodium sulphate, was benzoylated as described above. Recrystallisation from aqueous ethanol gave plates, m. p. 165—166°, mixed m. p. with the benzoyl derivative of the amino-acid obtained by hydrogenation 166—167°.

(b) *From* cis-*hexahydro*iso*phthalic acid.* A solution of hydrazoic acid in chloroform (8·4%; 20·3 ml.) was added dropwise (75 min.) to a well-stirred mixture, at 35°, of chloroform (60 ml.) and a solution of *cis*-hexahydro*iso*phthalic acid (6 g.) in concentrated sulphuric acid (18 ml.).

Stirring was continued at 40° for 75 min., and finally at 50° for 30 min., evolution of nitrogen then having practically ceased. When cool, the layers were separated. Evaporation of the chloroform left no residue. The sulphuric acid layer was diluted with ice (60 g.), and a solution of crystalline barium hydroxide (120 g.) added. Dilute sulphuric acid was added dropwise to the filtrate until the barium was removed quantitatively. Concentration of the filtered solution under reduced pressure to *ca.* 30 ml., followed by precipitation with acetone, gave the crude cis-3-*amino*cyclo*hexanecarboxylic acid* (4·8 g.). Sublimation at 270°/0·01 mm. and two more such precipitations gave microcrystals, m. p. 284° (decomp.) (Found : C, 58·6; H, 9·4; N, 9·7. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%).

Derivatives of cis-3-*amino*cyclo*hexanecarboxylic acid.* The benzoyl derivative prepared as described above had m. p. 166—167°, undepressed on admixture with that of the amino-acid obtained by hydrogenation. Treatment of this benzoyl derivative with *p*-bromophenacyl bromide gave p-*bromophenacyl* cis-3-*benzamido*cyclo*hexanecarboxylate* (58%), which crystallised from acetone–ethanol as needles, m. p. 211—212° (Found : C, 59·6; H, 4·8. $C_{22}H_{22}O_4NBr$ requires C, 59·4; H, 5·0%). Treatment of the amino-acid with α-naphthyl *iso*cyanate gave the *α-naphthylcarbamoyl derivative*, which after many recrystallisations from ethanol was obtained as microcrystals, m. p. 207° (Found : N, 8·6. $C_{18}H_{20}O_3N_2$ requires N, 9·0%).

trans-3-*Amino*cyclo*hexanecarboxylic Acid.*—Method (b) for the preparation of the *cis*-amino-acid when applied to *trans*-hexahydro*iso*phthalic acid gave trans-3-*amino*cyclo*hexanecarboxylic acid* in similar yield. Purification by sublimation at 250°/0·01 mm., and precipitation with acetone from aqueous solution gave microcrystals, m. p. 290—291° (decomp.) (Found : C, 58·8; H, 9·3; N, 9·5%), depressed to 273—275° on admixture with the *cis*-epimer. Both amino-acids were completely insoluble in organic solvents—even methylformamide—nor did they give copper salts when their aqueous solutions were boiled with freshly prepared cupric hydroxide.

Derivatives of trans-3-*amino*cyclo*hexanecarboxylic acid.* These were obtained by the foregoing methods and in similar yields. trans-3-*Benzamido*cyclo*hexanecarboxylic acid* crystallised from chloroform–hexane as prisms, m. p. 195—196° (Found : C, 68·4; H, 6·8; N, 5·9%), depressed to 144—147° on admixture with the *cis*-epimer. The p-*bromophenacyl ester* crystallised from ethanol as needles, m. p. 182° (Found : C, 59·3; H, 4·7%), depressed to 170—173° on admixture with the *cis*-epimer. The *α-naphthylcarbamoyl derivative* was obtained from ethanol as microcrystals, m. p. 213—214° (Found : N, 9·3%), depressed to 200—202° on admixture with the *cis*-epimer.

Pyrolysis of cis-3-*Amino*cyclo*hexanecarboxylic Acid.*—The *cis*-amino-acid (1 g.), in an N-shaped tube open at one end, was gently heated in a luminous flame until the volatile matter had been driven into the middle limb, where it partly solidified. The distillates from three such operations were taken up in hot ethanol. Removal of the solvent gave a residue (2·4 g.), which was extracted with hot benzene during 20 min., and the extract filtered from a very hygroscopic residue. Evaporation of the benzene gave a crystalline residue which was sublimed at 140°/0·1 mm. Several recrystallisations of the sublimate (1·2 g.) from hexane afforded the *lactam* as waxy prisms (0·75 g.), m. p. 198—199° (Found : C, 67·3; H, 8·8; N, 11·3%; *M*, 240. $C_7H_{11}ON$ requires C, 67·2; H, 8·9; N, 11·2%; *M*, 125). The same product (80 mg.) was obtained by pyrolysis of the *trans*-amino-acid (800 mg.).

The lactam (250 mg.) was hydrolysed by boiling aqueous barium hydroxide [10 ml. of 20% solution] during 2 hr. After quantitative removal of the barium as sulphate, the filtrate was evaporated, and the residue identified as *cis*-3-amino*cyclo*hexanecarboxylic acid by preparation of the benzoyl derivative (90 mg.), m. p. and mixed m. p. 166—167°.

6-*Aza*bicyclo[3 : 2 : 1]*octane.*—The lactam (250 mg.) in dry ether (25 ml.) was added to a suspension of lithium aluminium hydride (80 mg.) in ether (35 ml.), and the mixture heated under reflux for 4 hr. When cool, the excess of hydride was decomposed with water, followed by sulphuric acid (10%; 10 ml.), and the clear solutions were separated. Two more ethereal extracts of the aqueous layer were combined with the first and dried ($CaCl_2$), and the solvent was removed, leaving a residue (30 mg.) smelling strongly of the unreduced lactam.

The aqueous layer, which gave positive tests with both Mayer's and Wagner's reagents, was made sufficiently alkaline with sodium hydroxide to dissolve the precipitated alumina, and continuously extracted with ether. Removal of the solvent from the dried (K_2CO_3) extract left a crystalline residue of 6-aza*bicyclo*[3 : 2 : 1]octane, which had a strongly basic smell and fumed in air. The base was characterised as its *α-naphthylurethane*, which crystallised from benzene–hexane as prisms, m. p. 216—217° (Found : C, 77·0; H, 7·1; N, 9·7%; *M*, 301. $C_{18}H_{20}ON_2$ requires C, 77·1; H, 7·2; N, 10·0%; *M*, 280), and its p-*nitrobenzoyl derivative* which, after chromatography on alumina and elution with hexane–benzene (4 : 1) followed by

crystallisation from benzene–hexane, was obtained as needles, m. p. 128—129° (Found: C, 64·6; H, 6·2; N, 10·7%; *M*, 254. $C_{14}H_{16}O_3N_2$ requires C, 64·3; H, 6·6; N, 10·7%; *M*, 261).

Pyrolysis of cis-3-*Benzamido*cyclo*hexanecarboxylic Acid.*—This acid (500 mg.) was pyrolysed in the manner described for the amino-acids. The partly solidified distillate was extracted from the tube with ethanol, the ethanol removed, and the residue extracted with three portions of boiling hexane. Evaporation of the hexane left an oil which was taken up in ether and extracted with aqueous sodium carbonate. The ethanol layer was dried ($MgSO_4$) and evaporated, leaving a residue which on crystallisation from hexane afforded the N-*benzoyl derivative* of the lactam as needles (40 mg.), m. p. 106—107° (Found: C, 73·9; H, 6·9; N, 6·3%; *M*, 236. $C_{14}H_{15}O_2N$ requires C, 73·3; H, 6·6; N, 6·1%; *M*, 229). Acidification of the aqueous layer, extraction with ether, and recrystallisation of the residue from chloroform–hexane yielded unchanged *cis*-3-benzamido*cyclo*hexanecarboxylic acid (20 mg.), m. p. and mixed m. p. 165—166°. Benzoic acid (120 mg.), m. p. and mixed m. p. 121°, was deposited on concentration of the mother-liquors.

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