861. *Amino-acids of the Cyclohexane Series. Part I.*

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Several alkyl-1-aminocyclohexanecarboxylic acids have been synthesised by the Bucherer hydantoin and the Strecker synthesis. While the latter synthesis leads to one geometrical isomer in each case, the former gives both possible isomers, the opposite geometric isomer greatly preponderating.[1] Evidence is presented for the configurations assigned, which are based on the resistance to hydrolysis of the 1-amino-4-t-butyl- and -4-isopropyl-cyclohexanenitrile hydrochlorides, on infrared spectra, and on the dissociation constants of the amino-acids.

Steric hindrance to the hydration of cupric chelate derivatives of α-amino-acids has a marked effect on their solubilities in water.[2] Further illustration of this effect required the synthesis of 2-, 3-, and 4-alkyl-1-aminocyclohexanecarboxylic acids; these were prepared from the corresponding ketones by the Strecker and the Bucherer synthesis. 1-Aminocyclohexanecarboxylic acid has been prepared by the Strecker route by numerous workers, the yields (where quoted) being poor (~10%).[3] In the present work, the yields varied from 15% to 20%.

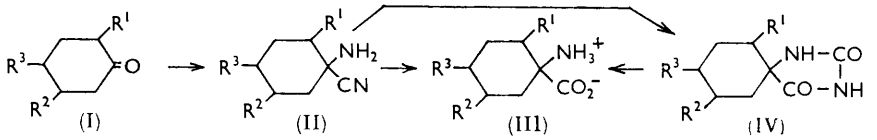
The 2-, 3-, and 4-methyl derivatives were also prepared by both methods, the yields

[1] Preliminary note, Munday, *Nature*, 1961, **190**, 1103.
[2] Graddon and Munday, *Chem. and Ind.*, 1959, 122.
[3] Baddar and Iskander, *J.*, 1954, 203.

being much better by the hydantoin route. In the Strecker synthesis the intermediate 1-amino-3- and -4-methylcyclohexanenitrile hydrochlorides were readily hydrolysed to the corresponding amino-acids by 20% hydrochloric acid at 100° in 10 hours; 1-amino-2-methylcyclohexanenitrile required heating with concentrated hydrochloric acid in a sealed tube at 140° for 10 hours, as Skita and Levi reported;[4] this resistance to hydrolysis seems to be an obvious result of the direct spatial effect of the adjacent 2-methyl group.

But resistance to hydrolysis of the amino-nitrile hydrochlorides was also encountered with higher homologues such as the 4-isopropyl and the 4-t-butyl derivatives where the direct spatial effect is not possible. The explanation of this unexpected effect[5] provided a clue to the configuration of the Strecker products. Hydrolysis of these compounds was achieved by 60% sulphuric acid at 140° in 12 hours.

The Bucherer hydantoin synthesis was applied in the synthesis of higher homologous cyclohexane amino-acids substituted in the 2- or the 4-position.



Several workers have made the 2-, 3-, and 4-methyl derivatives by the hydantoin route, and have assumed the identity of these products with those of the Strecker synthesis, presumably on the basis that the hydantoins (IV) are synthesised from the same amino-nitriles (II) involved in the Strecker synthesis, as suggested by Bucherer and Steiner.[6]

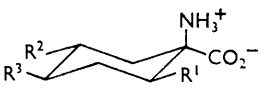
No work has been published on the stereochemistry of the substituted 1-aminocyclohexanecarboxylic acids produced by the two methods. We found the Strecker synthesis to produce only one geometrical isomer, since the crude product yielded only one spot on a paper chromatogram. The crude Bucherer product yielded two spots, one at a different and a much weaker one at the same R_F value as that of the Strecker product. Further differences in properties which show the non-identity of the two products are as follows: (1) The 1-amino-4-methyl-, 4-ethyl-, -4-isopropyl-, and -4-t-butyl-cyclohexanecarboxylic acids produced by the Strecker route are anhydrous when crystallised from 50% acetic acid and dried at 120°/25 mm. The corresponding acids made by the Bucherer route are hemi-hydrated on similar treatment, and the water of crystallisation is removed only with difficulty. (2) The melting points of the isomeric amino-acids are different, as are those of the acetyl and benzoyl derivatives of the 2- and 4-methyl compounds. The 3- and 4-methyl compounds made by the Strecker synthesis are converted by heating them with potassium cyanate solution into the ureido-acids and these in refluxing 10% hydrochloric acid yield hydantoins. The melting points of these hydantoins are different from those of the hydantoins produced directly from 3- and 4-methylcyclohexanone by Bucherer's synthesis. The 1-amino-2-methylcyclohexanecarboxylic acid produced by the Strecker synthesis could not be converted into a hydantoin by this method. (3) The infrared spectra of the corresponding amino-acids of the two series, determined for potassium chloride discs, are different, especially in the region 6—8 μ. Thus, in the case of the 2-methyl derivatives, the Strecker products alone give well-defined amino-acid bands. To ensure that the differences in the 4-alkyl compounds are not due to the presence of the half-molecule of water the 4-methyl compound was dehydrated. This necessitated heating the hemi-hydrate at 190°/0·01 mm. for 12 hours. Differences in the spectra still existed. (4) The R_F values on Whatman 3 MM. paper with butan-1-ol–acetic acid–water as eluant are different.

Evidence for the geometrical configuration of the 4-alkyl derivatives was first indicated

[4] Skita and Levi, *Ber.*, 1908, **41**, 2925.
[5] Munday, *Chem. and Ind.*, 1960, 1057.
[6] Bucherer and Steiner, *J. prakt. Chem.*, 1934, **140**, 291.

by the resistance to hydrolysis of the intermediate 1-amino-4-t-butyl- and -4-isopropyl-cyclohexanenitrile hydrochlorides obtained in the Strecker synthesis.[5] This suggested that the nitrile group is in the axial position (cf. V), the normal flexibility of the cyclohexane ring being restricted by the large alkyl groups so that transformation into the alternative chair form is energetically unfavourable. These assignments are supported by the

(V) Strecker product



(VI) Hydantoin product

infrared spectra. The 2- and 4-alkyl-acids made by the Strecker reaction give strong and well-resolved bands at 6·2 and 6·5 μ which have been ascribed to N–H deformational modes.[7] These bands are weak and not well resolved in the spectra of the hydantoin products, especially for the 2-methyl (II; $R^2 = R^3 = H$, $R^1 = Me$) and 4-t-butyl derivative (II; $R^1 = R^2 = H$, $R^3 = Bu^t$), which could be explained by restriction of their N–H bond deformations in the more crowded axial position, especially for 1-amino-2-methylcyclohexanecarboxylic acid.

Measurements of the first and second dissociation constants, pK_1' and pK_2', were made. Unfortunately the low solubilities of the 4-isopropyl- and 4-t-butyl derivatives (even in

TABLE 1.

p*K*'s of 1-aminocyclohexanecarboxylic acids.

Acid	pK_1'	pK_2'	pK_1'	pK_2'
Unsubst.	2·27	9·85		
	Strecker product		Hydantoin product	
4-Me	2·53	9·40	2·25	9·78
4-Et	3·33	9·585	2·74	9·93
3-Me	2·67	9·59	2·23	10·06
2-Me	2·25	9·675	2·02	9·795
2-Et	2·96	10·30	2·30	10·18
2-Pr^n			2·55	10·17
2-Pr^i-5-Me			2·58	10·10
2-Bu^n			2·20	9·92
1-Aminocyclopentanecarboxylic acid	2·54	10·33		
1-Aminocycloheptanecarboxylic acid	2·67	9·78		

acid or alkaline media, and also in dimethylformamide) prevented determination of their acidity constants by this method. The first dissociation constants (which refer to the ionisation of the carboxyl group) for the 2- and 4-alkyl-hydantoin products are greater than for the isomeric Strecker products. This supports the belief that the carboxyl group is preferentially equatorial in the hydantoin product, and axial in the Strecker product. The difference in dissociation constants is usually ascribed to the greater ionic solvation possible in the equatorial position, which stabilises the carboxylate ion.[8] The second dissociation constant, referring to the loss of a proton by the substituted ammonium ion, is weaker for the 2- and 4-alkyl Bucherer products. This is contradictory to available evidence and to accepted principles of conformational analysis. Bird and Cookson [9] have studied the base strengths of epimeric equatorial and axial primary amino- and dimethylamino-groups in various positions of the steroid nucleus and have found that in general axial amino-groups are less basic than their equatorial epimers. The exceptions are readily explicable in terms of intramolecular effects in the steroid molecule. The strength of an axial basic group is considered to be weaker than for the same group in an equatorial position because solvation, which would assist salt formation, is more restricted for the axial group. For the present equilibrium, $^+NH_3{\cdot}R{\cdot}CO_2^- \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} NH_2{\cdot}R{\cdot}CO_2^-$, solvation effect might be less easily interpreted.

[7] Bellamy, " Infra-red Spectra of Complex Molecules," Methuen, London, 1959, p. 238.
[8] Stolow, *J. Amer. Chem. Soc.*, 1959, **81**, 5806.
[9] Bird and Cookson, *J.*, 1960, 2343.

Paper chromatography was used to examine both the pure and the crude amino-acids produced by the two routes. Butan-1-ol–acetic acid (4 : 1) saturated with water was used as ascending eluant. While the crude 3- and 4-methylcyclohexane Strecker products yielded only one spot, the crude hydantoin products gave one strong spot and a much fainter spot at the same R_F value as the isomeric Strecker product. The crude 3- and 4-methylcyclohexane-1-spiro-5′-hydantoins produced by the Bucherer synthesis were analysed by partition chromatography on a cellulose column with butan-1-ol–acetic acid as eluant. About 0·2% of material having the melting point of the opposite isomer was obtained and 99% of the pure main product was recovered. Fractional crystallisation was also applied to determine the proportions of the isomers, and the proportion of the minor constituent found was again about 0·2%.

Experimental

Products were dried at 120°/25 mm. over $CaCl_2$ unless otherwise stated.

1-Aminocyclohexanecarboxylic acid was prepared by a Strecker synthesis from cyclohexanone. Yields averaged 15—20%; the m. p. was 320—325° (decomp.) (Found: C, 58·2; H, 9·0; N, 9·8. Calc. for $C_7H_{13}NO_2$: C, 58·7; H, 9·15; N, 9·8%).

1-*Amino*-cis-4-*methylcyclohexanecarboxylic Acid.*—4-Methylcyclohexanone (45 g., 0·4 mole), potassium cyanide (30 g., 0·4 mole), and ammonium chloride (22·0 g., 0·4 mole) were dissolved in water (300 ml.) and alcohol (250 ml.) and kept at room temperature for 6 days. The dark solution was diluted with water (300 ml.) and saturated with hydrogen chloride. After a further 2 days 1-amino-*cis*-4-methylcyclohexanenitrile hydrochloride (62·2 g., 88%) had crystallised. This hydrochloride (60 g.) was refluxed with 20% hydrochloric acid for 12 hr., the solution evaporated to dryness, and the residue extracted (Soxhlet) with ethanol–ether (9 : 1) for 8 hr. After removal of the solvent, the residue was basified with aqueous ammonia (*d* 0·880), to yield 1-amino-*cis*-4-methylcyclohexanecarboxylic acid (45·5 g.), needles [from acetic acid–water (1 : 1)], m. p. 356—360° (sublimes), R_F 0·69 (Found: C, 61·6; H, 9·7; N, 8·4. Calc. for $C_8H_{15}NO_2$: C, 61·1; H, 9·6; N, 9·0%). The N-*acetyl derivative* crystallised from ethanol–water as needles, m. p. 220—222° (Found: C, 60·1; H, 8·65; N, 6·8. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%). The N-*benzoyl derivative*, prepared by heating the amino-acid in pyridine with benzoyl chloride was obtained as needles (from ethanol–water), m. p. 209—210° (Found: C, 68·9; H, 7·6; N, 5·4. $C_{15}H_{19}NO_3$ requires C, 68·9; H, 7·3; N, 5·4%).

cis-4-*Methylcyclohexane*-1-*spiro*-5′-*hydantoin.*—1-Amino-*cis*-4-methylcyclohexanecarboxylic acid (1·0 g.) and potassium cyanate (0·6 g.) in water (10 ml.) were refluxed for 30 min. The cooled solution was acidified with hydrochloric acid, to precipitate the ureido-acid, which was converted without purification by heating it with 20% hydrochloric acid (20 ml.) for 30 min. into cis-4-*methylcyclohexane*-1-*spiro*-5′-*hydantoin*, plates (from ethanol), m. p. 215—216° (Found: C, 58·8; H, 7·4; N, 15·35. $C_9H_{14}N_2O_2$ requires C, 59·3; H, 7·7; N, 15·4%).

1-*Amino*-trans-4-*methylcyclohexanecarboxylic Acid.*—Bucherer's hydantoin synthesis [10] was followed. 4-Methylcyclohexanone (22·4 g., 0·2 mole), potassium cyanide (14·0 g., 0·22 mole), and ammonium carbonate (87 g., 0·9 mole) in water (100 ml.) and ethanol (100 ml.) were heated at 50—55° for 5 hr. and at 90—95° for 1 hr., then kept overnight. *trans*-4-Methylcyclohexane-1-spiro-5′-hydantoin was precipitated (29·8 g., 82%), having m. p. 281—282°. Henze and Speer [11] reported m. p. 279—280°. This hydantoin (10 g.) was heated with 60% sulphuric acid (57 ml.) at 150° for 24 hr. On cooling and dilution with water, a small amount of a pale straw-coloured solid was precipitated. The filtrate was neutralised with barium hydroxide, then made just acid with dilute sulphuric acid, and filtered hot. (If the solution was alkaline much of the amino-acid remained behind, presumably as barium salt.) The filtrate was evaporated to about 20 ml. and neutralised with aqueous ammonia (*d* 0·88), to produce 1-*amino*-trans-4-*methylcyclohexanecarboxylic acid* (8·0 g.). Crystallisation from acetic acid–water (1 : 1) afforded needles, m. p. 305—310° (sublime), R_F 0·57 (Found: C, 57·9; H, 9·8; N, 8·5. $C_8H_{15}NO_2,\frac{1}{2}H_2O$ requires C, 57·8; H, 9·75; N, 8·4%).

In order to remove the water, it was necessary to heat the compound at 190°/0·01 mm. over P_2O_5 for 12 hr. (Found: C, 60·2; H, 9·6. Calc. for $C_8H_{15}NO_2$: C, 61·1; H, 9·6%). The

[10] Bucherer and Lieb, *J. prakt. Chem.*, 1934, **141**, 5.
[11] Henze and Speer, *J. Amer. Chem. Soc.*, 1942, **64**, 522.

N-*acetyl derivative* crystallised from ethanol water as needles, m. p. 223—224·5° (Found: C, 60·4; H, 8·8; N, 6·8. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%). Equal weights of this acetyl derivative and of the acetyl derivative of the *cis*-4-methyl-amino-acid gave, when mixed, m. p. 170—185°. The N-*benzoyl derivative*, prepared as above, formed needles (from ethanol–water), m. p. 234—236° (Found: C, 68·7; H, 7·4; N, 5·2. $C_{15}H_{19}NO_3$ requires C, 68·9; H, 7·3; N, 5·4%).

4-*Ethylcyclohexanone*.—4-Ethylphenol was catalytically hydrogenated to 4-ethylcyclohexanol which was oxidised with potassium dichromate and dilute sulphuric acid to the ketone b. p. 191—194°; von Braun, Mannes, and Reuter [12] record b. p. 192—194°.

1-*Amino*-cis-4-*ethylcyclohexanenitrile Hydrochloride*.—4-Ethylcyclohexanone was converted by the method used for the 4-methyl analogue into the *amino-nitrile hydrochloride*, plates, m. p. 187—190° (decomp.), from ethanol–hydrochloric acid. The crystals were washed with ether, and dried at room temperature *in vacuo* over paraffin wax (Found: C, 56·6; H, 9·2; N, 15·35; Cl, 19·15. $C_9H_{17}N_2Cl$ requires C, 57·3; H, 9·1; N, 14·9; Cl, 18·8%).

1-*Amino*-cis-4-*ethylcyclohexanecarboxylic Acid*.—The amino-nitrile hydrochloride (6·0 g.) was heated with 70% sulphuric acid (16 ml.) at 140° for 18 hr. The dark solution was cooled, poured into water (40 ml.), neutralised with barium hydroxide, made slightly acid with dilute sulphuric acid, and filtered hot. The filtrate was evaporated, then treated with ammonia to precipitate the amino-acid, needles [from acetic acid–water (1 : 1)], m. p. 360—370° (sinter) (Found: C, 63·0; H, 9·3; N, 8·6. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%).

trans-4-*Ethylcyclohexane*-1-*spiro*-5′-*hydantoin*.—4-Ethylcyclohexanone was converted by Bucherer's method [10] in 64% yield into the *hydantoin*, plates (from aqueous ethanol), m. p. 265—266° (Found: C, 61·5; H, 8·0; N, 14·3. $C_{10}H_{16}N_2O_2$ requires C, 61·5; H, 8·2; N, 14·3%).

1-*Amino*-trans-4-*ethylcyclohexanecarboxylic Acid*.—The hydantoin was hydrolysed by 60% sulphuric acid as for the 4-methyl derivative, to the *amino-acid*, needles (from acetic acid–water), m. p. 306—308° (sublime) (Found: C, 60·7; H, 10·45; N, 7·7. $C_9H_{17}NO_2,\frac{1}{2}H_2O$ requires C, 60·0; H, 10·3; N, 7·8%).

4-*Isopropylcyclohexanone, etc.*—This ketone was made from *p*-isopropylphenol *via* the 4-isopropylcyclohexanol as for the 4-ethyl analogue, and had b. p. 125—130°/25 mm. Cahn, Penfold, and Simonsen [13] reported b. p. 139—140°/100 mm. This was converted by the same methods as for the 4-ethylcyclohexanone into 1-*amino*-cis-4-*isopropylcyclohexanenitrile hydrochloride* (92%), plates (from ethanol–hydrochloric acid), m. p. 213—215° (char) (Found: C, 60·0; H, 9·6; N, 13·8; Cl, 17·6. $C_{10}H_{19}N_2Cl$ requires C, 59·2; H, 9·5; N, 13·8; Cl, 17·5%), 1-*amino*-cis-4-*isopropylcyclohexanecarboxylic acid*, plates (from acetic acid–water), m. p. 321—323° (chars) (Found: C, 64·8; H, 10·2; N, 7·4. $C_{10}H_{19}NO_2$ requires C, 64·8; H, 10·4; N, 7·6%), and trans-4-*isopropylcyclohexane*-1-*spiro*-5′-*hydantoin* (78%), plates (from aqueous dioxan), m. p. 300·5—301·5° (Found: C, 62·9; H, 8·6; N, 13·0. $C_{11}H_{18}N_2O_2$ requires C, 62·9; H, 8·6; N, 13·3%).

1-*Amino*-trans-4-*isopropylcyclohexanecarboxylic Acid*.—The hydantoin was hydrolysed with 60% sulphuric acid in a similar manner to the 4-ethyl derivative, but after dilution with water the *amino-acid hydrogen sulphate* was precipitated as a dark grey solid. This, after decolorisation with charcoal in aqueous acetic acid, yielded white plates, m. p. >360° [Found: N, 5·8; SO_4, 20·9. $(C_{10}H_{20}NO_2)_2SO_4$ requires N, 6·0; SO_4, 20·6%]. This on treatment with ammonia yielded the *amino-acid*, plates [from aqueous acetic acid (1 : 1)], m. p. 317—318° (sublime) (Found: C, 62·5; H, 10·6; N, 7·6. $C_{10}H_{19}NO_2,\frac{1}{2}H_2O$ requires C, 61·8; H, 10·4; N, 7·2%).

4-*t-Butylcyclohexanone, etc.*—The ketone was obtained by oxidation of commercial 4-t-butylcyclohexanol with potassium dichromate and dilute sulphuric acid, and had b. p. 176—182°/140 mm., m. p. 48—50°. It was converted by the above methods into 1-*amino*-cis-4-*t-butylcyclohexanenitrile hydrochloride* (90%), plates (from ethanolic hydrochloric acid), m. p. 320—325° (decomp.) (Found: C, 61·0; H, 9·8; N, 12·8; Cl, 16·5. $C_{11}H_{21}ClN_2$ requires C, 60·95; H, 9·8; N, 13·0; Cl, 16·4%) (recovered unchanged after 20 hours' heating with 20% hydrochloric acid at 100°), 1-*amino*-cis-4-*t-butylcyclohexanecarboxylic acid* (by hydrolysis with 65% sulphuric acid at 140° for 40 hr.), plates [from acetic acid–water (1 : 1)], m. p. 345—350° (Found: C, 66·1; H, 10·8; N, 6·9. $C_{11}H_{21}NO_2$ requires C, 66·3; H, 10·6; N, 7·0%), *trans*-4-*t-butylcyclohexane*-1-*spiro*-5′-*hydantoin* (~100%), plates (from aqueous ethanol), m. p. 322° (Found: C, 64·7; H, 9·2; N, 12·3. $C_{12}H_{20}N_2O_2$ requires C, 64·3; H, 9·0; N, 12·5%), and 1-*amino*-trans-4-*t-butylcyclohexanecarboxylic acid* (by hydrolysis with 70% sulphuric acid to the amino-acid sulphate

[12] von Braun, Mannes, and Reuter, *Ber.*, 1933, **66**, 1499.
[13] Cahn, Penfold, and Simonsen, *J.*, 1931, 1369.

and treatment with ammonia), plates [from aqueous acetic acid (1 : 1)], m. p. 300—304° (sublime) (Found: C, 63·1; H, 10·2; N, 7·1. $C_{11}H_{21}NO_2,\frac{1}{2}H_2O$ requires C, 63·4; H, 10·6; N, 6·7%).

1-*Amino*-trans-3-*methylcyclohexanecarboxylic Acid.*—3-Methylcyclohexanone (22·5 g., 0·2 mole), potassium cyanide (15·6 g., 0·24 mole), and ammonium chloride (12·7 g., 0·24 mole) in 1 : 1 water–ethanol (200 ml.) were kept for 60 hr. The dark solution was diluted with water (100 ml.), saturated with hydrogen chloride, and refluxed for 16 hr. The solution was evaporated and the residue extracted (Soxhlet) with ethanol–ether (400 ml.; 9 : 1). Removal of the solvent afforded the crude hydrochloride, which on treatment with ammonia yielded the *amino-acid* (5·3 g., 31%), needles (from water), m. p. 360—365° (sublime) R_F 0·73 (Found: C, 60·95; H, 9·8; N, 8·6. $C_8H_{15}NO_2$ requires C, 61·15; H, 9·6; N, 9·0%).

trans-3-*Methylcyclohexane*-1-*spiro*-5′-*hydantoin* was prepared by the action of potassium cyanate on the Strecker amino-acid as for the 4-methyl compound. It formed needles, m. p. 237—238°, from ethanol (Found: C, 59·5; H, 7·9; N, 15·1. $C_9H_{14}N_2O_2$ requires C, 59·3; H, 7·7; N, 15·4%).

cis-3-*Methylcyclohexane*-1-*spiro*-5′-*hydantoin.*—3-Methylcyclohexanone (22·4 g.), potassium cyanide (26 g.), and ammonium carbonate (90 g.) were heated in 1 : 1 aqueous ethanol (200 c.c.) at 50—55° for 5 hr., then for 1 hr. at 90—95°. Next morning the hydantoin was collected (30·8 g., 84%); it formed needles, m. p. 274°, from ethanol. Henze and Speer [11] reported m. p. 268·5—269°.

1-*Amino*-cis-3-*methylcyclohexanecarboxylic Acid.*—The previous hydantoin (20·0 g.) in 70% sulphuric acid (120 ml.) was heated at 140° for 30 hr. The solution was cooled, diluted with water, and neutralised with barium carbonate. After being heated to the b. p. the solution was made just acid with dilute sulphuric acid and filtered. The filtrate was evaporated to ~40 ml. and neutralised with aqueous ammonia (*d* 0·88), to yield the crude *amino-acid*, needles (from water), m. p. 312—315° (sublime) R_F 0·65 (Found: C, 60·5; H, 9·6; N, 9·0. $C_8H_{15}NO_2$ requires C, 61·15; H, 9·6; N, 9·0%).

1-*Amino*-cis-2-*methylcyclohexanenitrile hydrochloride*, prepared by a Strecker synthesis from 2-methylcyclohexanone in 42% yield, had m. p. 192—195° (Found: C, 54·5; H, 9·0; N, 16·1. Calc. for $C_8H_{15}ClN_2$: C, 55·0; H, 8·6; N, 16·4%). Skita and Levi [3] reported m. p. 182°.

1-Amino-*cis*-2-methylcyclohexanecarboxylic Acid.—The amino-nitrile hydrochloride (3·9 g.) and concentrated hydrochloric acid (30 ml.) were heated in 4 sealed tubes at 140° for 10 hr. The tubes were cooled in acetone–solid carbon dioxide before being opened (high pressure). In some experiments, violent explosions occurred when the tubes were opened. Dilution with water (100 ml.) gave an oil that was identified as 2-methylcyclohexanone by its b. p.; the aqueous layer was evaporated to dryness and treated with ammonia, yielding the *amino-acid*, needles (from water), m. p. 355—360° (Skita and Levi [4] reported m. p. >300°), R_F 0·33 with *s*-collidine (see below) (Found: C, 60·6; H, 10·3; N, 8·7. Calc. for $C_8H_{15}NO_2$: C, 61·15; H, 9·6; N, 9·0%). The N-*acetyl derivative* formed needles, m. p. 220—221°, from aqueous ethanol (Found: C, 60·1; H, 8·7. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6%). The N-*benzoyl derivative* formed needles, m. p. 174—175°, from aqueous ethanol (Found: C, 68·55; H, 7·3. $C_{15}H_{19}NO_3$ requires C, 68·9; H, 7·3%). Refluxing the amino-acid (0·6 g.) and potassium cyanate (0·6 g.) in water (25 ml.) for 40 min., then cooling and acidifying the mixture gave 50 mg. of precipitate; this dissolved completely when boiled with dilute hydrochloric acid.

1-*Amino*-trans-2-*methylcyclohexanecarboxylic Acid.*—This was prepared by the method of Connors and Ross,[14] and had m. p. 300°, R_F 0·27 with *s*-collidine. The N-*acetyl derivative* formed prisms, m. p. 181—181·5°, from aqueous ethanol (Found: C, 60·2; H, 8·5. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6%).

2-*Ethylcyclohexanone, etc.*—The ketone was made by oxidation of commercial 2-ethylcyclohexanol with potassium dichromate and dilute sulphuric acid and had b. p. 184—186°. It was converted by the usual methods into trans-2-*ethylcyclohexane*-1-*spiro*-5′-*hydantoin* (97%), plates (from ethanol), m. p. 237—240° (Found: C, 61·7; H, 8·4; N, 14·0. $C_{10}H_{16}N_2O_2$ requires C, 61·4; H, 8·2; N, 14·0%), and 1-*amino*-trans-2-*ethylcyclohexanecarboxylic acid* (by 60% sulphuric acid), plates (from water), m. p. 320° (sublime) (Found: C, 63·3; H, 10·0; N, 8·2. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%).

1-*Amino*-cis-2-*ethylcyclohexanecarboxylic Acid.*—2-Ethylcyclohexanone (20·0 g.), potassium cyanide (30·0 g.), ammonium chloride (25·0 g.) in water (150 ml.) and ethanol (75 ml.) were set

[14] Connors and Ross, *J.*, 1960, 2130.

aside for 60 hr. The dark solution was diluted with water (200 ml.) and saturated with hydrogen chloride. The solution was evaporated and the residue extracted with ethanol–ether (400 ml.; 9 : 1). From the extract, the crude amino-nitrile hydrochloride was obtained on removal of the solvent, and was hydrolysed with 70% sulphuric acid in 20 hr. to the *amino-acid*, plates (from 50% aqueous acetic acid), m. p. 340° (sinter) (Found: C, 62·7; H, 9·6; N, 8·5. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%).

trans-2-*Propylcyclohexane*-1-*spiro*-5′-*hydantoin* was prepared from the commercially available ketone in 65% yield; it formed plates (from ethanol), m. p. 200—202° (Found: C, 62·8; H, 8·9; N, 13·5. $C_{11}H_{18}N_2O_2$ requires C, 62·9; H, 8·6; N, 13·3%).

1-*Amino*-trans-2-*propylcyclohexanecarboxylic Acid*.—The previous hydantoin was converted by 60% sulphuric acid into the *amino-acid*, needles (from aqueous ethanol), m. p. 301—303° (Found: C, 60·7; H, 10·4; N, 7·7. $C_{10}H_{19}NO_2,\frac{1}{2}H_2O$ requires C, 61·8; H, 10·4; N, 7·2%). The *hydrochloride* formed needles, m. p. 321—323° (sublime), from hydrochloric acid–ethanol (Found: C, 54·4; H, 9·9; N, 6·4; Cl, 17·1. $C_{10}H_{10}ClNO_2$ requires C, 54·2; H, 9·1; N, 6·3; Cl, 16·1%).

trans-2-*Isopropyl*-5-*methylcyclohexane*-1-*spiro*-5′-*hydantoin*.—Prepared in 37% yield from natural (−)-menthone, this *spiran* formed needles (from ethanol), m. p. 228—231·5° (Found: C, 63·0; H, 8·8; N, 11·6. $C_{12}H_{20}N_2O_2,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 63·1; H, 9·4; N, 11·3%).

1-*Amino*-trans-2-*isopropyl*-5-*methylcyclohexanecarboxylic Acid*.—The previous hydantoin was hydrolysed by 60% sulphuric acid to the *amino-acid*, needles [from water–acetic acid (1 : 1)], m. p. 330° (Found: C, 62·9; H, 10·0; N, 6·1. $C_{11}H_{21}NO_2,\frac{1}{2}C_2H_4O_2$ requires C, 62·9; H, 10·0; N, 6·1%).

trans-2-*Butylcyclohexane*-1-*spiro*-5′-*hydantoin*.—Commercial 2-butylcyclohexanone was converted in 50% yield into the *hydantoin*, plates (from ethanol), m. p. 182—184·5° (Found: C, 63·5; H, 9·5; N, 11·7. $C_{12}H_{20}N_2O_2,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 63·1; H, 9·4; N, 11·3%).

1-*Amino*-trans-2-*butylcyclohexanecarboxylic Acid*.—The previous hydantoin was hydrolysed to the *amino-acid*, prisms (from aqueous ethanol), m. p. 295—297° (sublime) (Found: C, 66·1; H, 11·1; N, 6·7. $C_{11}H_{21}NO_2$ requires C, 66·3; H, 10·6; N, 7·0%).

Determinations of pK_1' and pK_2' at 20° were made for aqueous solutions of constant ionic strength 0·1. 50 or 25 ml. of 0·01M-solutions of the amino-acids were half-neutralised with 0·01M-hydrochloric acid or 0·05M-sodium hydroxide, and the calculated quantity of " AnalaR " sodium chloride was added. Pure nitrogen was passed through the solution and the pH determined with glass and a calomel electrode in conjunction with a Cambridge pH meter. The value of the pH for the half-neutralisation by hydrochloric acid was corrected for dilution effects by applying the equation,[15] $pK_1' = pH + \log [(\frac{1}{2}c - H^+)/(\frac{1}{2}c + H^+)]$, where c = initial concentration of the base and the values of pH and H^+ are those at the calculated half-neutralisation point. A similar correction for pK_2' was not applied since it was negligible in all cases.

Solubilities at 25° were measured by dissolving a known weight of the amino-acid in distilled water, adding the equivalent amount of sodium hydroxide or hydrochloric acid where necessary, and leaving the whole in a thermostat-bath for 48 hr. The undissolved material was then filtered off and weighed. The results are in Table 3.

TABLE 3.

Solubilities at 25° (g. per 100 ml.).

1-Amino-carboxylic acid	Strecker product	Bucherer product
Cyclohexane-	6·60	
4-Methylcyclohexane-	0·283	0·173
,, ,, Na salt	9·2	8·1
,, ,, hydrochloride	8·7	9·9
4-t-Butylcyclohexane-	0·0023	0·0047
,, ,, Na salt	0·075	0·057
,, ,, hydrochloride	0·035	0·285
2-Methylcyclohexane-	1·20	1·79

Paper chromatograms of the amino-acids were obtained by ascending elution with butan-1-ol–acetic acid (4 : 1) saturated with water as solvent, and sprays of 0·1% ninhydrin in butan-1-ol. No spots were detected for the 1-amino-2-methylcyclohexanecarboxylic acids except by using *s*-collidine as solvent.

[15] Morley and Simpson, *J.*, 1949, 1014.

In a typical experiment involving partition chromatography of the hydantoins, crude 3-methylcyclohexane-1-spiro-5'-hydantoin (8·27 g.), made by the Bucherer procedure, was passed in hot ethanol (100 ml.) on to a powdered cellulose column (57 cm.) saturated with water. Elution was with butan-1-ol–acetic acid (4 : 1) saturated with water; 480 ml. of the solvent were required to elute the pure main product (8·12 g.; m. p. 270°). Immediately after this, 0·016 g. of a product, m. p. 235—240°, was obtained; this was undepressed in m. p. on admixture with the hydantoin produced from the Strecker amino-acid.

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