781. *Some New Alicyclic α-Amino-acids.*

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Some new alicyclic α-amino-acids, including 1-amino-2-, 3-, and -4-methylcyclohexanecarboxylic acids, have been prepared, each in two stereoisomeric forms.

In 1958, when the work described here was complete, the stereoisomerism of the 1-amino-*x*-methylcyclohexanecarboxylic acids was unknown, and only one form (now thought to be 1-amino-*cis*-*x*-methylcyclohexanecarboxylic acid [1]) had been previously synthesised from the corresponding ketones by the Strecker synthesis.[2-4] The isomerism of the amino-acids is closely connected with that of the corresponding methylcyclohexane-1-spiro-5′-hydantoins from which the amino-acids can be obtained by alkaline hydrolysis (cf. Munday [1] who employed acid-hydrolysis). Brimelow *et al.*[5] showed that monosubstituted alicyclic ketones yield stereoisomeric hydantoins, depending on the method of reaction. For example, 3-methylcyclohexanone by the cyanate synthesis gave only one product, which they termed the β-isomer and is now thought to be the *cis*-3-methyl-1-spiro-5′-hydantoin.[1] * However, the Bucherer synthesis [6] yielded chiefly a different hydantoin, called by Brimelow *et al.*[5] the α-isomer, and this is probably the *trans*-3-methylcyclohexane-1-spiro-5′-hydantoin [1] (cf. Henze and Speer [7] who reported only one form).

In the present work, hydrolysis of the Bucherer hydantoins and those from the cyanate route gave, as expected, different amino-acids. Thus the purified Bucherer hydantoin, on alkaline hydrolysis, yielded the 1-amino-*trans*-3-methylcyclohexanecarboxylic acid,

* *cis* refers to the relation of the alkyl group to the 4-carbonyl group of the hydantoin or the carboxyl group of the acid.

[1] Munday, *J.*, 1961, 4372.
[2] Skita and Levi, *Ber.*, 1908, **41**, 2925.
[3] Zelinsky and Stadnikow, *Ber.*, 1906, **39**, 1729.
[4] Zelinsky and Stadnikow, *Z. phys. Chem.*, 1911, **75**, 350; Zelinsky, Annenkow, and Kulikow, *ibid.*, 1910, **73**, 465.
[5] Brimelow, Carrington, Vasey, and Waring, unpublished work.
[6] Bucherer and Lieb, *J. prakt. Chem.*, 1934, **141**, 5.
[7] Henze and Speer, *J. Amer. Chem. Soc.*, 1942, **64**, 522.

whereas alkaline hydrolysis of the cyanate hydantoin, or acid-hydrolysis of the amino-nitrile (obtained from the ketone by Strecker synthesis), gave the *cis*-3-methyl isomer. The latter method is that originally described [2-4] for preparation of these amino-acids.

The stereoisomeric 1-amino-3-methylcyclohexanecarboxylic acids were characterised by preparation of their *N*-acetyl and *N*-benzoyl derivatives and the ethyl esters. The esters, on reduction with lithium aluminium hydride, afforded the amino-alcohols. The other *cis*-substituted 1-aminocyclohexanecarboxylic acids described here were similarly synthesised by acid hydrolysis of the amino-nitriles. The *trans*-substituted 1-amino-cyclohexanecarboxylic acids were prepared by alkaline hydrolysis of the Bucherer hydantoin; this generally required 1 week's boiling with an excess of 3N-sodium hydroxide.

In this work it was evident that substituted 1-aminocyclohexanecarboxylic acids existed in two distinct stereoisomeric forms, though at the time no conclusions were drawn regarding their configurations. Recently, however, Munday [1] concluded that the Strecker amino-acid is the *cis*-substituted acid, and the product from hydrolysis of the Bucherer hydantoin the *trans*-substituted acid; this conclusion is based on the resistance to hydrolysis shown by 1-amino-4-t-butyl- and -4-isopropyl-cyclohexanenitrile hydrochloride,[8] which indicates that the cyano-group is in the axial position. Supporting evidence is provided by the infrared spectra and the dissociation constants of the amino-acids. This nomenclature has therefore been adopted here; however in Munday's paper [1] the terms *cis* and *trans* appear to have become interchanged in the case of the hydantoins and related amino-acids derived from 3-methylcyclohexanone, which has been corrected in this paper.

Other alicyclic 1-amino-carboxylic acids were also made. 1-Aminocyclopropane-carboxylic acid was prepared from diethyl malonate and ethylene dibromide as described by Burroughs.[9] Much difficulty was experienced with the initial condensation and the yields of diethyl cyclopropane-1,1-dicarboxylate reported by Dox and Yoder [10] could not be reproduced. 1-Aminocyclobutanecarboxylic acid was similarly synthesised from diethyl malonate and 1,3-dibromopropane; the initial condensation was as described by Perkin,[11] and the subsequent stages leading to cyclobutanespiro-5'-hydantoin followed Ingold's procedure.[12] 1-Aminocyclopentanecarboxylic acid,[4,13] 1-aminocycloheptanecarboxylic acid, and 2-aminodecahydronaphthalene-2-carboxylic acid were all prepared by acid-hydrolysis of the corresponding amino-nitriles.*

Experimental

The quoted R_F values are from paper chromatograms developed downwards with butan-1-ol–acetic acid–water (4 : 1 : 5) on Whatman No. 1 paper. The amino-acid spots were revealed by spraying with 0·1% buffered ethanolic ninhydrin and heating at 80° for 20 min. All m. p. determinations were performed in sealed capillary tubes.

1-*Aminocyclopropanecarboxylic Acid*.—When purified by sublimation at 180—200°/0·02 mm., this had m. p. 233—235° decomp. (lit.,[9] m. p. 234—236°), R_F 0·23 (Found: C, 47·4; H, 7·7; N, 13·5. Calc. for $C_4H_7NO_2$: C, 47·5; H, 7·0; N, 13·9%).

1-*Aminocyclobutanecarboxylic Acid*.—Cyclobutanespiro-5'-hydantoin [12] (3 g.) was boiled under reflux with 1N-sodium hydroxide (60 c.c.; 3 equiv.) for 24 hr. The solution was cooled, neutralised with hydrochloric acid, and evaporated *in vacuo*. The residue, after sublimation at 190—210°/0·03 mm., gave the amino-acid [14] (260 mg.; m. p. 270—272°; R_F 0·35) (Found: C, 51·5; H, 7·5; N, 11·7. Calc. for $C_5H_9NO_2$: C, 52·2; H, 7·8; N, 12·2%).

* These alicyclic amino-acids and their derivatives were synthesised as potential pesticides.

[8] Munday, *Chem. and Ind.*, 1960, 1057.
[9] Burroughs, *Nature*, 1957, **179**, 360.
[10] Dox and Yoder, *J. Amer. Chem. Soc.*, 1921, **43**, 2097.
[11] Perkin, *J.*, 1887, **51**, 2.
[12] Ingold, *J.*, 1922, **121**, 1177.
[13] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 3121.
[14] Demyanov and Telnov, *Bull. Acad. Sci. U.R.S.S.*, 1937. 529.

trans-3-*Methylcyclohexanespiro-5'-hydantoin*.—This was prepared from 3-methylcyclohexanone as described by Brimelow *et al.*[5] and had m. p. 270—272° (lit.,[1] m. p. 274°, lit.,[5] 268°, lit.,[7] 268·5—269°). The mother liquors gave a mixture, m. p. 220—234°, of both isomeric hydantoins.

Other substituted *trans*-cyclohexanespiro-5'-hydantoins were similarly prepared and had m. p.s in agreement with literature values. 2-*Methylcycloheptanespiro-5'-hydantoin* had m. p. 223—224° (Found: C, 61·0; H, 8·4; N, 13·9. $C_{10}H_{16}N_2O_2$ requires C, 61·2; H, 8·2; N, 14·3%).

1-*Amino*-trans-3-*methylcyclohexanecarboxylic Acid*.—*trans*-3-Methylcyclohexanespiro-5'-hydantoin (53 g., 1 mole) was boiled under reflux with 3N-sodium hydroxide (cf. ref. 1) (300 c.c., 3 moles) for 150 hr. The solution was filtered and neutralised by addition of concentrated hydrochloric acid. The precipitate was washed with water, dried, and sublimed at 180—210°/0·02 mm. to yield the *trans*-amino-acid (25 g.; m. p. 304—305°; R_F 0·60) (Found: C, 60·9; H, 9·4; N, 8·9. Calc. for $C_8H_{15}NO_2$: C, 61·15; H, 9·6; N, 9·0%). Brimelow *et al.*[5] report m. p. 316—317° for the semihydrate. The following derivatives were prepared: N-*acetyl* (acetic anhydride–water), needles (from methanol), m. p. 202—206° (Found: C, 59·6; H, 8·5; N, 7·2. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%); N-*benzoyl* (benzoyl chloride–aqueous sodium carbonate at 20° as described by Wild [15]), feathery needles, m. p. 148—151°, from aqueous methanol (Found: C, 68·3; H, 7·0; N, 4·9. $C_{15}H_{19}NO_3$ requires C, 68·9; H, 7·3; N, 5·4); N-*acetyl ethyl ester* (ethanol–hydrogen chloride, followed by acetylation), needles (from petroleum), m. p. 92—94° (Found: C, 63·3; H, 9·1; N, 6·1. $C_{12}H_{21}NO_3$ requires C, 63·4; H, 9·2; N, 6·2%); *methyl ester*, b. p. 60—66°/1 mm. (Found: C, 62·6; H, 9·6; N, 8·0. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%); and *isopropyl ester*, a liquid, b. p. 55—60°/0·05 mm. (Found: C, 66·3; H, 10·7; N, 6·6. $C_{11}H_{21}NO_2$ requires C, 66·3; H, 10·6; N, 7·0%).

The following *trans*-substituted 1-aminocyclohexanecarboxylic acids were similarly obtained from the corresponding Bucherer hydantoin by alkaline hydrolysis (in excess, 3 moles, of sodium hydroxide; and 120—170 hours' boiling); the products were purified by sublimation at 200°/0·02 mm.; 2-methyl-, m. p. 300—302° (decomp.) (lit.,[1] 300°, R_F 0·52. Found: C, 60·7; H, 9·6; N, 8·9. Calc. for $C_8H_{15}NO_2$: C, 61·15; H, 9·6; N, 9·0%); 4-methyl-, m. p. >300° (lit.,[1] 305—310°, R_F 0·63) (Found: C, 61·5; H, 9·4; N, 8·9. Calc. for $C_8H_{15}NO_2$: C, 61·15; H, 9·6; N, 9·0%); 3,4-*dimethyl*-, needles, m. p. 300—302° (decomp.) (R_F 0·70) (Found: C, 62·6; H, 10·3; N, 8·0. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%); 3,3,5-*trimethyl*-, m. p. 276—280°, R_F 0·80 (Found: C, 64·4; H, 10·0; N, 8·0. $C_{10}H_{19}NO_2$ requires C, 64·8; H, 10·4; N, 7·6%); and 2-*isopropyl*-5-*methyl*-, needles, m. p. 285—293° (decomp.), R_F 0·78 (Found: C, 66·0; H, 10·2; N, 6·7. $C_{11}H_{21}NO_2$ requires C, 66·3; H, 10·6; N, 7·0%).

1-*Amino*-cis-3-*methylcyclohexanenitrile hydrochloride* (Strecker synthesis).—3-Methylcyclohexanone (31 g., 1 mole) was stirred with ammonium chloride (15 g., 1 mole) and potassium cyanide (18 g., 1 mole) in 50% aqueous methanol (250 c.c.) for 24 hr. at room temperature. The mixture, after dilution with water, was extracted with ether (1·5 l.), and the extract washed with water, dried ($MgSO_4$), and concentrated to 300 c.c. Passage of dry hydrogen chloride and crystallisation of the precipitate from ethanol gave 1-*amino*-cis-3-*methylcyclohexanenitrile hydrochloride* as glistening plates [20 g.; m. p. 182° (decomp.) Found: C, 54·7; H, 8·9; N, 16·3; Cl, 20·9. $C_8H_{15}ClN_2$ requires C, 55·0; H, 8·6; N, 16·4; Cl, 20·3%]. The following 1-amino-nitrile hydrochlorides were similarly prepared: *cyclopentane*-, platelets, m. p. 179—180° (from methanol–ether) (Found: C, 49·6; H, 7·5; N, 18·6; Cl, 23·7. $C_6H_{11}ClN_2$ requires C, 49·2; H, 7·5; N, 19·1; Cl, 24·2%); *cis*-2-methylcyclohexane-, white powder (from ethanol), m. p. 182—185° (decomp.) (lit.,[1] 192—195°, lit.,[2] 182°) (Found: C, 54·3; H, 9·0; N, 15·7; Cl, 19·8. Calc. for $C_8H_{15}ClN_2$: C, 55·0; H, 8·6; N, 16·4; Cl, 20·3%); *cycloheptane*-, plates (from ethanol), m. p. 160—161° (Found: C, 54·4; H, 8·0; N, 16·4. $C_8H_{15}ClN_2$ requires C, 55·0; H, 8·6; N, 16·4%).

2-*Cyanodecahydro*-2-*naphthylammonium Chloride*.—This formed glistening platelets (from aqueous ethanol), m. p. 174—176° (Found: C, 60·8; H, 8·8; N, 13·3; Cl, 16·7. $C_{11}H_{19}ClN_2$ requires C, 61·5; H, 8·9; N, 13·05; Cl, 16·6%).

1-*Amino*-cis-3-*methylcyclohexanecarboxylic Acid* (Method 1).—1-Amino-*cis*-3-methylcyclohexanenitrile hydrochloride (15 g.) was treated at 0° with fuming hydrochloric acid (70 c.c.) and set aside overnight. The suspension was then diluted with water (50 c.c.), and boiled under reflux for 8 hr. Vacuum evaporation yielded a solid (17·5 g.), which was stirred with

[15] Wild, " Organic Compounds," Cambridge University Press, 1949, p. 167.

water (50 c.c.), and the mixture neutralised with ammonia solution (*d* 0·88; 45 c.c.). The precipitate was filtered off and dried (P_2O_5 at 120—150°/0·02 mm.), yielding 1-amino-*cis*-3-methylcyclohexanecarboxylic acid (6 g.), m. p. 318—320° (decomp.) (lit.,[1] 360—365°, lit.,[6] 330°) (Bucherer and Brandt,[16] by a different method of preparation, record m. p. 260°), R_F 0·73 (Found: C, 59·8; H, 9·7; 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 (from ethanol–ether), m. p. 198—199° (Found: C, 58·9; H, 8·4; N, 7·2. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%); the N-*benzoyl* clusters of needles (from aqueous ethanol), m. p. 166—170° (Found: C, 68·6; H, 7·3; N, 4·9. $C_{15}H_{19}NO_3$ requires C, 68·9; H, 7·3; N, 5·4%); and the N-*acetyl ethyl ester* was a liquid, b. p. 390° (Found: C, 62·9; H, 9·1; N, 5·9. $C_{12}H_{21}NO_3$ requires C, 63·4; H, 9·2; N, 6·2%).

The following 1-amino-carboxylic acids were similarly prepared: *cis*-2-methylcyclohexane-, m. p. >300° (lit.,[1] 355—360°, lit.,[2] >300°), R_F 0·66; *cis*-4-methylcyclohexane-, m. p. >300° (lit.,[1] 356—360°, lit.,[2] >300°), R_F 0·71; cyclopentane-, plates, m. p. 320—322° (lit.,[4] 320°, lit.,[13] 320—330°) after sublimation at 150—170°/0·02 mm. (Found: C, 55·7; H, 8·6; N, 11·4. Calc. for $C_6H_{11}NO_2$: C, 55·8; H, 8·5; N, 10·9%) [*methyl ester*, b. p. 85°/20 mm. (Found: C, 58·6; H, 9·2; N, 10·1. $C_7H_{13}NO_2$ requires C, 58·7; H, 9·15; N, 9·8%)], cycloheptane-, lustrous plates (from methanol), m. p. 310—312° (decomp.) (lit.,[3] 306—307°), R_F 0·58 (Found: C, 60·2; H, 9·6; N, 9·0. Calc. for $C_8H_{15}NO_2$: C, 61·15; H, 9·6; N, 9·0%); and 2-*amino-decahydronaphthalene-2-carboxylic acid*, m. p. 308—310° (after sublimation at 180—200°/0·01 mm.), R_F 0·76 (Found: C, 66·6; H, 9·5; N, 7·3. $C_{11}H_{19}NO_2$ requires C, 67·0; H, 9·6; N, 7·1%).

cis-3-*Methylcyclohexanespiro-5′-hydantoin* (Cyanate Synthesis).—This hydantoin was prepared from 1-amino-*cis*-3-methylcyclohexanenitrile hydrochloride, as described by Brimelow *et al.*[5]; it had m. p. 232—233° (from methanol; lit.,[1] m. p. 237—238°, lit.,[5] 238°).

1-*Amino*-cis-3-*methylcyclohexanecarboxylic Acid* (Method 2).—This was also obtained by alkaline hydrolysis of the corresponding hydantoin, as described by Brimelow *et al.*[5] The acid had m. p. 320—322° (after sublimation at 170—190°/0·01 mm.) (lit.,[5] m. p. 340—350°, lit.,[6] 330°, R_F 0·70). A mixture with the product from method 1 had the same m. p.

1-*Amino*-trans-3-*methylcyclohexylmethanol*.—Ethyl 1-amino-*trans*-3-methylcyclohexanecarboxylate (3·6 g.) in dry ether (60 c.c.) was added dropwise to a stirred suspension of finely powdered lithium aluminium hydride (1·6 g.; 3 equivs.) in ether (200 c.c.) at 0°. The mixture was kept at 0° for 1 hr., allowed to reach room temperature, and then boiled under reflux for 3 hr. Afterwards it was cooled (ice), excess of hydride was destroyed by addition of ice–water, and the complex was hydrolysed by alkaline Rochelle salt solution.[17] The mixture was extracted with ether (3 × 200 c.c.), and the extract washed with water, dried (Na_2SO_4), and evaporated to yield the trans-*amino-alcohol* as a pale yellow oil, b. p. 280—290° (Found: C, 67·5; H, 11·8; N, 10·2. $C_8H_{17}NO$ requires C, 67·1; H, 11·9; N, 9·8%).

1-*Amino*-cis-3-*methylcyclohexylmethanol*.—This was similarly prepared by reduction of ethyl 1-amino-*cis*-3-methylcyclohexanecarboxylate with lithium aluminium hydride. The cis-*amino-alcohol* separated as platelets (from petroleum), m. p. 58—60° (Found: C, 66·8; H, 11·8; N, 9·5. $C_8H_{17}NO$ requires C, 67·1; H, 11·9; N, 9·8%).

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[16] Bucherer and Brandt, *J. prakt. Chem.*, 1934, **140**, 129.
[17] Smith, Maienthal, and Tipton, *J. Org. Chem.*, 1952, **17**, 294.