

1 : 2-Dicarboxylic Acids. Part III.* Nitrogenous Derivatives of the Isomeric Hexahydrophthalic Acids and of 3 : 4 : 5 : 6-Tetrahydrophthalic Acid.

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Imides, diamides, and dinitriles of these acids are described, together with certain other derivatives. It is shown that among derivatives of the geometrically isomeric saturated acids, the expected stereochemical relations hold and that the *trans*-forms of simple derivatives are more stable; whereas when an *ortho*-heterocyclic ring is present the *cis*-isomeride is the more stable.

THE discovery of the imidines (see, for example, Elvidge and Linstead, *J.*, 1952, 5000; 1954, 442) and the opening of a new route to azaporphins has prompted an investigation into the imidines derived from hexahydro- and 3 : 4 : 5 : 6-tetrahydro-phthalic acid. This has involved a preliminary study of the nitrogenous derivatives of these acids, which is described in the present paper.

Hexahydrophthalic Series.—The relative stabilities of the *cis*- and the *trans*-forms of cyclic and acyclic derivatives of the hexahydrophthalic acids have been of interest for over 60 years. It is well known from the work of von Baeyer and of Hüchel that the acids, esters, and anhydrides can be obtained in two forms; that in the acids and esters the *trans*-form is the more stable, but that of the two anhydrides the *cis* is the more stable. Hüchel and Müller (*Ber.*, 1931, **64**, 1981) found that the imide system behaved like the anhydride. Our work supports this and shows that, in general, the nitrogenous derivatives behave like their oxygen counterparts. Where there is no *ortho*-ring the *cis*-form is either the only isomer which can be isolated or the more stable of the pair.

cis-Hexahydrophthalimide (I) is most easily prepared by fusion of the corresponding anhydride with urea. The product, m. p. 137°, is identical with material prepared by catalytic hydrogenation of phthalimide (Willstätter and Jacquet, *Ber.*, 1918, **51**, 767; Vavon and Peignier, *Bull. Soc. chim.*, 1929, **45**, 296; Hüchel and Müller, *Ber.*, *loc. cit.*). The *cis*-configuration was postulated by Willstätter and proved by Hüchel. Sircar (*J.*, 1927, 1252) reported that distillation of the ammonium salt of *cis*- or *trans*-hexahydrophthalic acid gave a *trans*-imide of m. p. 164°. Hüchel and Müller pointed out the improbability of this observation and were unable to repeat it, their product being the *cis*-imide contaminated with a product of m. p. 167°. The constitution of the latter was not fully established but it was not a hexahydrophthalimide.

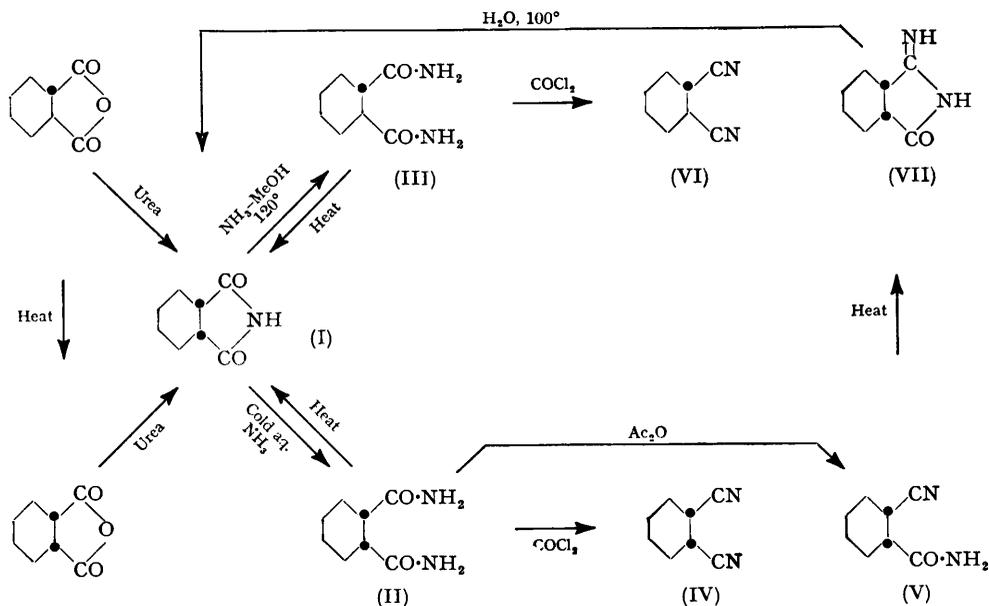
We find that the *cis*-imide is obtained alike by distillation of ammonium *trans*-hexahydrophthalate, the fusion of *trans*-hexahydrophthalic anhydride with urea, or by the action of heat on the diamide of either the *cis*- or the *trans*-acid. It is clear therefore that the *cis* is the thermally stable imide and that Sircar's observation is erroneous.

The *cis*-imide reacted slowly at room temperature with aqueous ammonia to give the *cis*-amide (II), m. p. 190—191°. At 120° with methanolic ammonia, however, an inversion

* Part II, preceding paper.

of configuration occurred, the *cis*-imide giving the *trans*-amide (III), m. p. 281—282°. Price and Schwarcz (*J. Amer. Chem. Soc.*, 1940, **62**, 2891) were unable to prepare these diamides from the corresponding diesters by the action of ethanolic ammonia at room temperature. We find, however, that dimethyl *trans*-hexahydrophthalate slowly reacts with aqueous ammonia at room temperature or with methanolic ammonia at 100°, to give the *trans*-diamide.

Dehydration of the *cis*-amide with acetic anhydride gave either *cis*-hexahydrophthalonitrile (IV) or the corresponding *cis*-cyano-amide (V) according to the length of treatment. The *cis*-dinitrile was better prepared, in almost quantitative yield, by dehydration of the *cis*-amide with carbonyl chloride. The same reagent dehydrated the *trans*-amide to the



trans-dinitrile (VI). The configurations and homogeneity of all these compounds were established by hydrolysis to the parent acids under non-inverting conditions. We have been unable to effect interconversion of the two dinitriles. Both dinitriles are crystalline and it is of interest that the usual relations between the melting points (*trans* > *cis*) which holds for example for the acids, amides, and anilides is reversed for the dinitriles, the *cis*-form of which melts at 64°, 12° above the *trans*. The same feature has been encountered among the derivatives of the $\alpha\alpha'$ -dimethylsuccinic acids (Linstead and Whalley, preceding paper).

Many years ago, hexahydrophthalonitrile had been prepared in these laboratories by Dr. K. Sams (Thesis, London, 1934) by another route: cyclohexanone cyanohydrin was dehydrated to 3 : 4 : 5 : 6-tetrahydrobenzonitrile which by the action of hydrogen cyanide yielded hexahydrophthalonitrile as a non-crystalline mass of m. p. about 42—46°. This material has been re-examined and is found to be a mixture of the two geometrical isomerides (IV and VI).

When *cis*-2-cyanohexahydrobenzamide was fused it changed into the isomeric octahydro-1-imino-3-oxoisindole (VII), the reaction being analogous to the thermal isomerisation of *o*-cyanobenzamide (Braun and Tcherniac, *Ber.*, 1907, **40**, 2709). The cyclic imino-imide (which forms a picrate and a monohydrochloride) has the *cis*-configuration and readily gives *cis*-hexahydrophthalimide on hydrolysis with boiling water. The corresponding di-imine (hexahydrophthalimidine) is also stable in the *cis*-configuration.

Four examples are thus known (anhydride, imide, imino-imide, and imidine) of cyclic

derivatives of hexahydrophthalic acid stable in the *cis*-form.* These results are discussed in the preceding paper.

3 : 4 : 5 : 6-Tetrahydrophthalic Series.—Most of the essential nitrogenous intermediates have already been described (Ficken and Linstead, *J.*, 1952, 4846). Their preparation has been improved in two respects. First, 3 : 4 : 5 : 6-tetrahydrophthalic anhydride can be readily obtained by the catalytic isomerisation of its 1 : 2 : 3 : 6-isomeride over palladium.† Secondly, for the dehydration of Δ^1 -diamide to Δ^1 -dinitrile, carbonyl chloride is to be preferred to the phosphoric oxide-triethylamine reagent used in our previous work.

The properties of the various derivatives of the three series are summarised in the Table, and the main reactions in the Chart.

TABLE. *Melting points of derivatives of cis- and trans-hexahydrophthalic and of 3 : 4 : 5 : 6-tetrahydrophthalic acid.*

	<i>cis</i> -Hexahydro	<i>trans</i> -Hexahydro	3 : 4 : 5 : 6-Tetrahydro
Diacids	192°	227—229°	120°
Diamides	190—191	281—282	220 *
Cyanoamides	143—145	—	169—170
Dinitriles	63—65	51—53	97
Anhydrides	32	144—145	72
Imides	136—137	Labile	172
Imino-imides	227—229 (picrate, 205)	—	200—202 (picrate, 190)

* Rapid heating in sealed tube.

EXPERIMENTAL

3 : 4 : 5 : 6-Tetrahydrophthalic Anhydride from *cis*-1 : 2 : 3 : 6-Tetrahydrophthalic Anhydride.—*cis*-1 : 2 : 3 : 6-Tetrahydrophthalic anhydride (200 g.) was heated to 200—210°, 20% palladium-charcoal (1.8 g.) was added, and heating at this temperature was continued for 3 hr. The product was boiled with water (500 ml.), the solution evaporated to dryness on the steam-bath, and the residue extracted repeatedly with light petroleum (b. p. 60—80°). The extracts yielded 3 : 4 : 5 : 6-tetrahydrophthalic anhydride (151 g., 76%), m. p. and mixed m. p. 70°.

3 : 4 : 5 : 6-Tetrahydrophthalonitrile.—Carbonyl chloride, dried by passage through concentrated sulphuric acid, was passed into a stirred suspension of 60 g. of 3 : 4 : 5 : 6-tetrahydrophthalamide (Ficken and Linstead, *loc. cit.*) in pyridine (500 ml.) in a flask fitted with a wide air-condenser and a thermometer dipping into the liquid. The flask was heated in a water-bath, which was removed as soon as the internal temperature reached 60°. A strongly exothermic reaction occurred; the temperature rose rapidly to 75—80° and was maintained in this range by adjusting the rate of flow of carbonyl chloride. Passage of gas was continued until the temperature began to fall, by which time an increase in weight of about 100 g. had occurred. The mixture was allowed to cool to room temperature, and the dark brown, viscous product was added cautiously to crushed ice (1 kg.), and the solution was neutralised (Congo-red) with hydrochloric acid and continuously extracted with ether for several days. The extract was washed with a little saturated salt solution, and dried (Na₂SO₄); the ether was removed, and the residue distilled at 204°/50 mm. The yield of tetrahydrophthalonitrile was 30 g. (64%) and after crystallisation from aqueous ethanol the m. p. and mixed m. p. were 97°.

***cis*-Hexahydrophthalimide (I).**—*cis*-Hexahydrophthalic anhydride, prepared in 94% yield by hydrogenation of *cis*-1 : 2 : 3 : 6-tetrahydrophthalic anhydride in the presence of a platinum catalyst (Jenkins and Costello, *J. Amer. Chem. Soc.*, 1946, 68, 2733), had m. p. 30°, and on hydrolysis yielded *cis*-hexahydrophthalic acid, m. p. 190—192° (decomp.).

The *cis*-anhydride (277 g.) and urea (60 g.) were heated together at 160° until a vigorous reaction occurred; then the heating-bath was removed. When the reaction slackened the mixture was reheated for a further 30 min., and poured with vigorous stirring into ice and water (1 kg.). The white *cis*-hexahydrophthalimide was filtered off and washed with water. The yield was 217 g. (78%) and the m. p. of the crude product was 134—136°, raised by crystallisation

* Since this was written, a further example—that of *cis*-hexahydro-*N*-methylphthalimide—has been reported (Bailey, Haworth, and McKenna, *J.*, 1954, 969). Compare also the *N*-phenylimides prepared by Stoermer and Steinbeck (*Ber.*, 1932, 65, 413).

† This unusual rearrangement is being further investigated by Mr. K. D. Whiting in this Department.

from water to 136—137° (Hückel and Müller, *loc. cit.*, give m. p. 137°) (Found : N, 9.2. Calc. for $C_8H_{11}O_2N$: N, 9.1%).

cis-Hexahydrophthalamide (II).—Finely powdered *cis*-hexahydrophthalamide (146 g.) was added to aqueous ammonia (450 ml.) saturated at 0°, and the mixture left at this temperature for 7 days. The white crystalline precipitate of *cis*-hexahydrophthalamide (125 g.) was filtered off; the m. p. was 190—191° (decomp.), unchanged by crystallisation from dilute aqueous ammonia (Found : C, 56.3; H, 8.4; N, 16.2. $C_8H_{14}O_2N_2$ requires C, 56.45; H, 8.3; N, 16.5%). The filtrate from the above preparation was evaporated to dryness and the residue was heated at 170° for 1 hr., to give *cis*-hexahydrophthalamide (24 g.). With allowance for this recovered imide, the yield of diamide was 92%. When the diamide was heated just above its m. p., ammonia was evolved; the product on crystallisation from acetone gave *cis*-hexahydrophthalamide, m. p. and mixed m. p. 135—136°. On hydrolysis with 2*N*-nitric acid for 15 hr. the diamide yielded almost pure *cis*-hexahydrophthalic acid, m. p. 184—187°, mixed m. p. 185—188°.

cis-2-Cyanohexahydrobenzamide (V).—*cis*-Hexahydrophthalamide (30.0 g.) and acetic anhydride (60 ml.) were refluxed together vigorously for 10 min., and the solution was cooled and poured into ether (500 ml.). The white precipitate of *cis*-2-cyanohexahydrobenzamide (9.7 g., 36%) was filtered off and washed with ether; after crystallisation from ethyl acetate the m. p. was 143—145° (Found : C, 63.1; H, 7.9; N, 18.3. $C_8H_{12}ON_2$ requires C, 63.1; H, 7.95; N, 18.4%).

cis-Hexahydrophthalonitrile.—(a) *Acetic anhydride*. *cis*-Hexahydrophthalamide (5.3 g.) and acetic anhydride (25 ml.) were refluxed for 4 hr. Most of the acetic acid and anhydride were distilled out and the residue was boiled with water (100 ml.) containing sufficient ammonia to neutralise the acid. The aqueous solution was decanted from a small amount of dark, viscous material and cooled in ice. The white solid was filtered off, washed with a little cold water, and dried. The yield of *cis*-hexahydrophthalonitrile (IV) was 970 mg. (21%) and the m. p. was 52—53°, raised to 63—65° by sublimation (Found : C, 71.8; H, 7.6; N, 20.65. $C_8H_{10}N_2$ requires C, 71.6; H, 7.5; N, 20.9%). The nitrile (440 mg.) on hydrolysis with boiling 2*N*-nitric acid yielded an acid (410 mg.), m. p. and mixed m. p. with *cis*-hexahydrophthalic acid, 186—189°. The dianilide (prepared according to Linstead, Davis, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 2013) had m. p. and mixed m. p. with *cis*-hexahydrophthalanilide, 237—238°.

(b) *Carbonyl chloride*. *cis*-Hexahydrophthalamide (81 g.) was dehydrated with carbonyl chloride, as described for the tetrahydrophthalamide, except that the temperature was kept at 60—65°. The product from the ether-extraction distilled at 130—131.5°/0.7 mm. The distillate had m. p. 63—65°, undepressed by admixture with the product obtained by acetic anhydride dehydration. The yield of *cis*-hexahydrophthalonitrile was 61 g. (95%). In another experiment, where the temperature was allowed to rise to 90°, the product did not solidify completely after distillation, indicating the presence of a certain amount of *trans*-dinitrile; hydrolysis yielded an acid, m. p. 171—184°.

trans-Hexahydrophthalamide.—(a) Dimethyl *trans*-hexahydrophthalate, prepared by isomerisation of the mixture of isomerides obtained by catalytic hydrogenation of dimethyl phthalate (Price and Schwarcz, *loc. cit.*; cf. Haggis and Owen, *J.*, 1953, 389), had b. p. 143°/28 mm., m. p. 28°; on hydrolysis with ethanolic potassium hydroxide it yielded *trans*-hexahydrophthalic acid, m. p. 225—227°. The *trans*-ester (9.8 g.) was mixed with aqueous ammonia (*d.* 0.880; 30 ml.) and sufficient methanol to form a homogeneous solution. This was left for 5 days at room temperature, then the precipitated solid was filtered off (690 mg.). *trans*-Hexahydrophthalamide (III) formed colourless needles from aqueous ethanol, m. p. 281—282° (decomp.) (Found : C, 56.3; H, 8.3; N, 16.7. $C_8H_{14}O_2N_2$ requires C, 56.45; H, 8.3; N, 16.5%). The filtrate from the above preparation slowly deposited further amounts of the diamide, and after 35 weeks a total of 4.0 g. (37%) had been obtained. On hydrolysis with 2*N*-nitric acid it yielded an acid, m. p. 221—225°, mixed m. p. 223—226° with *trans*-hexahydrophthalic acid. When heated above its m. p., the *trans*-diamide evolved ammonia, the product being the *cis*-imide, m. p. and mixed m. p. 133—136°. When the *trans*-ester was heated with methanolic ammonia at 120° for 18 hr., only 3% of the diamide and much unchanged ester were obtained.

(b) *cis*-Hexahydrophthalamide (16.6 g.) was heated for 24 hr. in an autoclave at 120° with methanol (100 ml.) containing ammonia (50 ml. of liquid). The solid was filtered off and washed with methanol, to yield *trans*-hexahydrophthalamide (16.3 g., 89%), m. p. and mixed m. p. 281—282° (decomp.).

trans-Hexahydrophthalonitrile.—*trans*-Hexahydrophthalamide (11.8 g.) was dehydrated with carbonyl chloride as for the *cis*-diamide. The product obtained by ether-extraction crystallised from light petroleum (b. p. 40—60°), to yield *trans*-hexahydrophthalonitrile (VI)

(8.4 g., 90%), m. p. 51—53° unchanged after sublimation (Found: C, 71.6; H, 7.5; N, 21.4. $C_8H_{10}N_2$ requires C, 71.6; H, 7.5; N, 20.9%). The mixed m. p. with the *cis*-dinitrile was 40—47°. The nitrile (540 mg.) on hydrolysis with 2N-nitric acid yielded an acid (660 mg.), m. p. 222—225°, mixed m. p. 224—227° with *trans*-hexahydrophthalic acid. The dianilide had m. p. and mixed m. p. with *trans*-hexahydrophthalanilide (Linstead, Davis, and Whetstone, *loc. cit.*), 314—315°.

Attempted Interconversion of the Dinitriles.—No isomerisation occurred when either *cis*- or *trans*-hexahydrophthalonitrile was subjected to the following conditions: (a) A mixture of the nitrile (500 mg.), pyridine (10 ml.) and acetyl chloride (0.5 ml.) was refluxed for 6 hr. (b) A mixture of the nitrile (250 mg.), acetic anhydride (5 ml.), and acetyl chloride (0.5 ml.) was refluxed for 16 hr. The identity of each recovered nitrile with the starting material was proved by hydrolysis in the usual manner to the corresponding acid.

Addition of Hydrogen Cyanide to 3 : 4 : 5 : 6-Tetrahydrobenzonitrile (with K. SAMS).—*cyclo*-Hexanone cyanohydrin was dehydrated with thionyl chloride in benzene (Ruzicka and Brugger, *Helv. Chim. Acta*, 1926, **9**, 399) to yield 3 : 4 : 5 : 6-tetrahydrobenzonitrile, b. p. 85—87°/18 mm., n_D^{19} 1.4821. Kidd, Robins, and Walker (*J.*, 1953, 3244) give b. p. 85—90°/17 mm., n_D^{19} 1.4864.

A solution of hydrogen cyanide was prepared by the addition of concentrated hydrochloric acid (20 ml.) to potassium cyanide (53 g.) in water (220 ml.), and was heated in a pressure bottle at 100° for 4 hr. with a solution of 3 : 4 : 5 : 6-tetrahydrobenzonitrile (22 g.) in ethanol (220 ml.). After removal of the alcohol, the aqueous solution was extracted with ether. The extract was washed with concentrated calcium chloride solution, dried ($CaCl_2$), and fractionated. A mixture of *cis*- and *trans*-hexahydrophthalonitrile was obtained, b. p. 184—188°/25 mm.; the distillate solidified almost completely, and after removal of oil on a porous tile melted at 42—46°.

No hexahydrophthalonitrile could be obtained by heating 3 : 4 : 5 : 6-tetrahydrobenzonitrile under reflux with liquid hydrogen cyanide and potassium cyanide as catalyst or by slow acidification of a boiling aqueous-ethanolic solution of the tetrahydronitrile and potassium cyanide.

cis-Octahydro-1-imino-3-oxoisindole.—*cis*-2-Cyano-hexahydrobenzamide (6.7 g.) was heated at 180—185° for 3 hr. The product was boiled with ethyl acetate, filtered off, and washed with ethyl acetate, to yield a brown solid (3.0 g.), m. p. 211—215° (decomp.). After crystallisation from 2-ethoxyethanol (charcoal), *cis-octahydro-1-imino-3-oxoisindole* (VII) was obtained colourless and had m. p. 227—229° (decomp.) (Found: C, 62.95; H, 7.9; N, 18.3. $C_8H_{12}ON_2$ requires C, 63.1; H, 7.95; N, 18.4%). The *picrate*, crystallised from 2-ethoxyethanol-ethanol, had m. p. 204—206° (decomp.) (Found: C, 44.2; H, 4.15; N, 18.1. $C_{14}H_{15}O_8N_5$ requires C, 44.1; H, 4.0; N, 18.4%). The *hydrochloride*, crystallised from ethanol-ethyl acetate, had m. p. 201—203° (decomp.) (Found: C, 51.0; H, 7.0; N, 14.9; Cl, 18.9. $C_8H_{13}ON_2Cl$ requires C, 50.9; H, 6.9; N, 14.85; Cl, 18.8%). The free base (250 mg.) was boiled with water (4.0 ml.) for 3 hr., and the solution was cooled in ice; the precipitate (126 mg.) had m. p. 134—136°; evaporation of the filtrate gave a further crop (98 mg.) of the same m. p. Both crops had mixed m. p. 135—137° with *cis*-hexahydrophthalimide.

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