

The half methyl ester of this acid should be capable of resolution but we have been unable as yet to find a suitable salt. The cinchonidine, cinchonine, ephedrine, brucine, quinine and strychnine salts could not be obtained crystalline (experiments by Miss E. J. Cook, Radcliffe College).

anti-Series

cis-anti-cis Acid (198°).—To a solution of 454.1 mg. of the acid and 1.051 g. of cinchonidine in 10 cc. of methanol there was added at the boiling point, 2.5 cc. of water. The solution deposited 1.03 g. of light needles, m. p. 194–200°, on cooling (A). The mother liquor was evaporated to dryness, the residue treated with acid and extracted with ether. The residue from the ether was crystallized from acetic acid. This yielded 100 mg. of the *dextro*-acid in heavy prisms, m. p. 235–239°. Recrystallization to constant rotation yielded material with m. p. 238.5–240.5°, $[\alpha]^{20D} + 43 \pm 1^\circ$ (1% in 95% alcohol).

The salt (A) was recrystallized from 15 cc. of methanol and 2 cc. of water. This yielded 670 mg. of well-formed needles, m. p. 204.5–205.5°. Regeneration of the acid in the usual way gave the *levo*-acid which after two crystallizations from acetic acid formed prisms, m. p. 239–241° (132.8 mg.). This material was submitted to a second treatment with cinchonidine but its properties were unaltered (m. p. 238.5–240.5°). The specific rotation $[\alpha]^{20D}$ of a 1% solution in 95% alcohol was $-45 \pm 1^\circ$.

The *dextro-cis-anti-cis* acid was esterified in the usual manner with diazomethane, yield 75.1 mg. from 84.5 mg. The *d*-dimethyl ester crystallizes from light petroleum at -70° in large prisms, m. p. 26–28°. $[\alpha]^{25D} + 69 \pm 1^\circ$ (1% in 95% alcohol).

trans-anti-trans Acid (247°).—The above *d*-dimethyl ester (140 mg.) of the *cis-anti-cis* acid was refluxed for 112 hours with 0.5 g. of potassium hydroxide in 2 cc. of methanol. A little water was added from time to time. The acidic product was isolated by means of ether in the usual way. After two crystallizations from dilute acetic acid, the *levo-trans-anti-trans* acid was isolated with m. p. 257–258.5°, $[\alpha]^{25D} - 79.5 \pm 5^\circ$ (1% in 95% alcohol).

Resolution of the 247° Acid (Experiments by Dr. Slinger).—The acid (3.0 g.) and ephedrine (1.98 g.) were

dissolved in 60 cc. of alcohol, 90 cc. of water was added and the mixture heated to effect solution. Slow cooling precipitated needles of a salt from which 950 mg. of a crude dextrorotatory acid was regenerated. This material was submitted to a second resolution with ephedrine. The product melted at 257.5–259° and had $[\alpha]^{20D} + 77.5^\circ$ (1% in alcohol). A further resolution failed to alter the m. p. or specific rotation.

An equal mixture of the *d*- and *l*-acids (4 mg. of each) was dissolved in dilute acetic acid. The solution deposited needles, m. p. 237–239°, of the *dl-trans-anti-trans* acid. After resolidifying, these melted at 245–247° and did not depress a sample of authentic *dl*-acid, m. p. 245–247°.

Summary

The perhydrodiphenic acid of m. p. 289° gives an acid methyl ester which can be resolved into *d*- and *l*-forms. Conversion of these into the acid or the dimethyl ester gives inactive material. The acid therefore has a symmetrical molecule and must belong to the *syn*-series.

The perhydrodiphenic acid of m. p. 198° (*cis-anti-cis*) can be resolved by means of cinchonidine. The dimethyl ester of the active ester on hydrolysis and double inversion with alcoholic alkali gives the *levo*-enantiomorph of the *trans-anti-trans* acid (m. p. 247°). The latter acid has been resolved to give the other enantiomorph. As two acids in this series can be resolved, it must be the *anti*-series.

The three acids of m. p.'s 289, 200 and 223°, therefore, constitute the *syn*-series and the acids of m. p.'s 198, 206 and 247°, the *anti*-series.

The acids of m. p.'s 200 and 206° are proved to be *cis-syn-trans* and *cis-anti-trans*, respectively.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Stereochemistry of Catalytic Hydrogenation. IV. Hexahydrodiphenic Acids

BY R. P. LINSTEAD AND SELBY B. DAVIS

Vocke¹ reported that the hydrogenation of diphenic ester over Raney nickel yielded a mixture of perhydro- and hexahydro-diphenic esters. From the hydrolysis product of this he isolated two hexahydrodiphenic acids of m. p. 242 and 220°. It was shown that the 242° acid could be converted into the 220° isomer, and the acids were assigned the structures of *cis*- and *trans*- modifications of the hexahydrodiphenic acid with one intact aromatic ring.

(1) Vocke, *Ann.*, **508**, 1 (1934).

We have investigated the partial hydrogenation of diphenic acid in acetic acid solution over a platinum catalyst. If hydrogenation is stopped arbitrarily at the half-way stage, there is obtained a mixture consisting substantially of *cis-syn-cis*-perhydrodiphenic acid, m. p. 289°,² a hexahydrodiphenic acid and unchanged diphenic acid. The hexahydro acid melts at 242° and has other properties which show its identity with Vocke's acid of similar m. p. The presence of an

(2) Linstead and Doering, *This Journal*, **64**, 1991 (1942).

aromatic ring is shown by the absence of reactivity with potassium permanganate and by the formation of a mono-nitro derivative, m. p. 219°. The latter can be reduced to an amine which can be diazotized and coupled with β -naphthol.

The proportions of the three compounds in the hydrogenation product are approximately: *c.s.c.*-perhydro acid, 25%; hexahydro acid, 25%; unchanged diphenic acid, 40%. The indications are therefore that the half hydrogenated compound is hydrogenated rather more readily than the original diphenic acid. When the hexahydrodiphenic acid, m. p. 242°, is further hydrogenated over platinum it yields *cis-syn-cis*-perhydrodiphenic acid, m. p. 289°. The yield of the pure *cis-syn-cis* acid is 77% and no isomers have as yet been isolated. Both the first and the second stages of the hydrogenation of diphenic acid under these conditions thus follow a substantially homogeneous steric course.

It is shown in the next paper that the 242° acid has the *cis*-configuration.

Treatment of the *cis*-hexahydro acid with acetic anhydride yielded a liquid anhydride from which the parent acid could be regenerated. If the *cis*-acid was kept at its melting point for an hour, it was converted into an isomeric acid which melts at 221°. The conversion is reversible with an equilibrium well on the side of the new acid. Catalytic hydrogenation of the new acid over platinum gave rise to *cis-syn-trans*-perhydrodiphenic acid (IV), m. p. 200°, identical with the material described in Part II.² The orientation of this perhydro acid has been completely proved.³ The yield of the perhydro acid was at least 84% and a careful search failed to show the presence of any of the *cis-anti-trans*-isomer. A

small amount of a decahydrodiphenic acid, m. p. 212°, was, however, isolated. It follows from these results that the new hexahydro acid, m. p. 221°, is the *trans*-isomer (III) of the 242° acid.

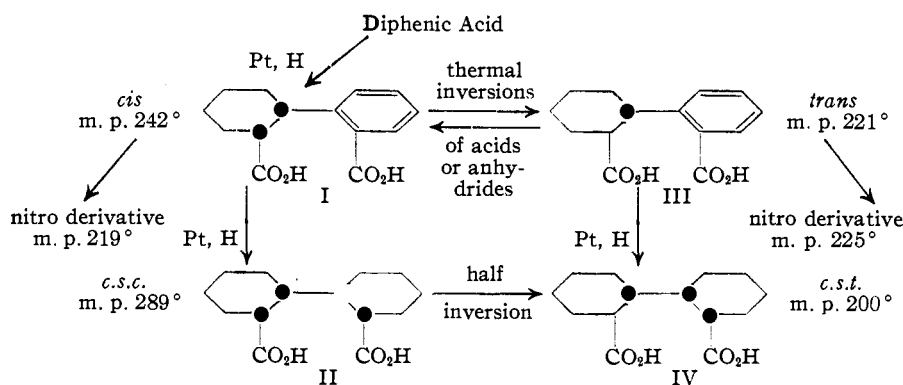
The presence of an intact aromatic ring in the *trans*-acid was shown by its nitration to a mono-

nitro derivative, not identical with that obtained from the *cis*-isomer.

When the *cis*-hexahydro acid was inverted by heat and the crude *trans*-acid treated with acetic anhydride, there was formed the beautifully crystalline *trans*-anhydride, which on hydrolysis yielded the parent acid, m. p. 221°. There can be no doubt that our *trans*-acid is identical with Vocke's second hexahydro acid of m. p. 220° which he obtained by heating the 242° acid to about 300°.¹ He reported the anhydride as melting at 120°, whereas the m. p. of our material could not be raised above 116°. When the *trans*-anhydride was heated for some time, and the product hydrolyzed, a mixture of *cis*- and *trans*-hexahydro acids was obtained, which contained about 70% of the *trans*-isomer.

An important general result from this work is that in the further hydrogenation of our hexahydro acids over platinum at room temperature, the integrity of the configuration already established is preserved, and the further hydrogenation goes almost entirely *cis*- and *syn*-. This presents an instructive contrast to Vocke's observation on the perhydrogenation of the same acids over nickel at high temperatures. He observed the formation of two perhydro acids (*trans-anti-trans* and probably *trans-syn-trans*) from each of the hexahydro acids. Clearly, the use of nickel at high temperatures may lead to inversions of configuration.

The results are summarized in the scheme



Experimental⁴

***cis*-Hexahydrodiphenic Acid.**—A solution of 10 g. of diphenic acid in 200 cc. of glacial acetic acid was hydrogenated in a Parr apparatus by means of 1 g. of Adams catalyst. After six and one-half hours, hydrogen equivalent to 3.0 moles had been taken up. The solution was then

(4) All melting points corrected. Analyses by Miss Eleanor Werble.

(3) Linstead and Doering, THIS JOURNAL, 64, 2003 (1942).

filtered. Extraction of the catalyst and insoluble material with alkali and reprecipitation with hydrochloric acid yielded 1.24 g. of *cis-syn-cis*-perhydrodiphenic acid, m. p. 275–280°, identified by mixed m. p. The acetic acid filtrate was freed from solvent by vacuum evaporation and the solid residue dissolved in 100 cc. of 10% aqueous sodium carbonate. A second run on the same amount of material required eight and one-half hours for the absorption of 3.0 moles of hydrogen and yielded 1.48 g. of the *cis-syn-cis* acid, m. p. 278–286°. The filtrate was treated as above. The combined carbonate solution was then submitted to the process of fractional acidification with 10% hydrochloric acid which has been described in Part II.² The hydrochloric acid was added to the boiling solution to incipient cloudiness. No precipitate appeared on cooling. After this successive 10-cc. portions of 10% hydrochloric acid were added to the boiling solution, and the solution allowed to stand for twelve to twenty-four hours after each addition, with the following results:

Fraction	HCl added, cc.	Acid pptd., g.	M. p. (crude), °C.	Main component
1	10.0	2.08	204–262	<i>c.s.c.</i> perhydro
2	10.0	0.70	80–95
3	10.0	5.39	212–227	<i>cis</i> -hexahydro
4	10.0	3.30	199–214	Diphenic acid
5	10.0	3.98	211–216	Diphenic acid

The total amount of acid isolated at this stage, including the *cis-syn-cis* acid which separated from the solution originally, was 18.17 g. Evaporation of the final mother liquor gave no useful material.

Recrystallization of fraction 3 from acetic acid containing about 20% water at the boiling point, yielded 3.90 g. of practically pure *cis*-hexahydrodiphenic acid, m. p. 238–240°. Another crystallization gave the pure acid, m. p. 241–242° (bath preheated to 235°). The acid was identical with that obtained as a by-product in perhydrogenations (see Part II²). Fractions 4 and 5, after crystallization from acetic acid, yielded diphenic acid, m. p. and mixed m. p. 229–231°.

The subsequent preparations were done in a similar manner. In some cases the *cis*-hexahydro acid appeared in the second fraction. Completion of the precipitation of perhydro acid was marked by a drop in the pH of the solution from 8 to 5. In one run a very small amount of material identified as the *trans*-hexahydro acid was obtained after the diphenic acid had been precipitated. The average yield of crude material from 20 g. of diphenic acid was *cis-syn-cis*-perhydrodiphenic acid, 4.8 g.; *cis*-hexahydrodiphenic acid, 5.0 g.; recovered diphenic acid, 7.7 g.

***cis*-Anhydride.**—The *cis*-acid (400 mg.) was refluxed for five hours with 4 cc. of acetic anhydride. The anhydride failed to solidify on standing *in vacuo* at 3° or on attempted crystallization from hexane. The oily anhydride on boiling with dilute hydrochloric acid regenerated the *cis*-acid, m. p. and mixed m. p. 238–240°.

Mono-nitro Derivative.—The *cis*-acid (100 mg.) was stirred into a mixture of 1 cc. of concentrated sulfuric acid with 1 cc. of concentrated nitric acid. The solution was heated to 60°, allowed to stand for thirty minutes, and then poured into 10 cc. of ice and water to give 104 mg. of crude nitro compound, m. p. 184–190°. From 90 mg. there was obtained 56 mg. of irregular prisms, m. p. 201–

202°, after two recrystallizations from acetone-benzene. Recrystallization from water, under such conditions that the substance separated as an oil and subsequently crystallized, gave identical material. By slow crystallization of a dilute aqueous solution the nitro compound is obtained in a stable higher melting form, needles, m. p. 218–219°. The mixed m. p. with the low-melting material was 218–219°.

Anal. Calcd. for C₁₄H₁₅O₃N: C, 57.34; H, 5.16. Found: C, 57.53; H, 5.02.

The high-melting form of the nitro derivative (5 mg.) was dissolved in 15 cc. of distilled water and shaken with hydrogen in the presence of 5 mg. of Adams catalyst. The theoretical amount of hydrogen for reduction to the amine was absorbed in fifteen minutes. Removal of the catalyst and solvent left the product as a clear, glassy film. On diazotization and coupling with alkaline β-naphthol in the usual manner, an immediate orange color was produced and a brown precipitate separated on standing.

Hydrogenation.—The *cis*-acid (2 g.) was hydrogenated in 200 cc. of acetic acid over 750 mg. of Adams catalyst. The theoretical quantity (3 moles) of hydrogen was taken up in thirty-five minutes and no further absorption was observed in another half hour. This is a remarkably quick hydrogenation of an aromatic ring. The reaction product was worked up in the usual manner. The precipitate yielded 1.32 g. (64%) of pure *cis-syn-cis*-perhydrodiphenic acid, m. p. 286–288°. Evaporation of the mother liquor yielded a solid residue, melting above 245°. Fractional crystallization of the latter yielded two successive crops of the *cis-syn-cis* acid and brought the total yield of this up to 77%. The small residue was not further examined.

***trans*-Hexahydrodiphenic Acid.**—The *cis*-acid (4 g.) was heated at 242 ± 3° for one hour. The residue set to a pale yellow glass. Crystallization from glacial acetic acid yielded 2.48 g. of nearly pure *trans*-acid, m. p. 215–218°. This substance was more easily purified through the anhydride. The *cis*-acid (1.5 g.) was heated as before and the residue was refluxed with 5 cc. of acetic anhydride for four hours. The reagent was removed and the sirup stirred with a few cc. of light petroleum in which it was practically insoluble. The solid *trans*-anhydride (1.2 g.) was so obtained. The yield corresponds with one of 87% of *trans*-acid in the thermal inversion. After three crystallizations from benzene the beautifully crystalline anhydride of the *trans*-acid was obtained, m. p. 115–116°. The m. p. could not be raised by further crystallization (compare Vocke¹).

Anal. Calcd. for C₁₄H₁₄O₃: C, 73.02; H, 6.13. Found: C, 73.28; H, 6.19.

A small portion of the anhydride was converted into the corresponding acid by means of alkali. The *trans*-acid so obtained melted at 220–221.5° and failed to depress the m. p. (218–220°) of that isolated by crystallization. The mixed m. p. with the *cis*-isomer was 197–210°. This is a good method for the final purification of the *trans*-acid, for repeated crystallization of the acid, which had not been taken through the anhydride, failed to raise the m. p. above 220°.

*Anal.*⁵ Calcd. for C₁₄H₁₄O₄: C, 67.72; H, 6.50. Found: C, 67.89; H, 6.65.

(5) Analysis by W. E. Doering.

Mono-nitro Derivative.—The *trans*-acid (96 mg.) was nitrated in the same manner as the *cis*- (*vide supra*) to obtain 116 mg. of the crude product, m. p. 212–217°. Two recrystallizations from acetone–benzene gave 65 mg. of irregular prisms, m. p. 218–219°. Further recrystallization from water, under such conditions that the substance separated as an oil and subsequently crystallized, gave material of similar appearance and m. p. Crystallization of 40 mg. from water, with slow cooling, gave 32 mg. of needles, m. p. 224–225°. The mixed m. p. with the low-melting material was 224–225°. The mixed m. p.'s of both forms with either form of the nitro derivative from the *cis*-acid showed depressions to about 185°.

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 57.34; H, 5.16. Found: C, 57.43; H, 5.12.

Hydrogenation.—The *trans*-acid (2 g.) in 200 cc. of acetic acid was hydrogenated over 550 mg. of Adams catalyst. The theoretical uptake of hydrogen (3 moles) occurred in one hundred minutes, after which there was no appreciable reaction. No precipitate separated. The catalyst was filtered and the solvent removed. The granular residue was crystallized from acetic acid, a seed of *cis-syn-trans*-perhydrodiphenic acid being introduced. The first crop, 1.60 g. (78%), melted at 190–194° alone, at 192–197° in admixture with *cis-syn-trans*-perhydrodiphenic acid (m. p. 198–200°) and at 192–196° after a further crystallization. As the m. p. of the *cis-syn-trans* acid is sensitive to traces of impurities, this material may be taken to be the nearly pure isomer. The mother liquor from this acid was submitted to an exhaustive fractional crystallization. It yielded three products: (a) more of the *cis-syn-trans* perhydro acid, bringing the total yield up to 84%; (b) about 10 mg. of an unsaturated acid, m. p. 210–211.5°, identical with material already isolated by Mr. Doering; (c) about 3 mg. of what was apparently another unsaturated acid. This formed soft needles of m. p. 261–264°, depressed the m. p. of the *cis-syn-cis* perhydro acid and readily reduced 0.5% potassium permanganate in aqueous

sodium bicarbonate solution. (Under the same conditions the hexahydro- and perhydrodiphenic acids require from eight to twenty-four hours for a discharge of the color of one drop of 0.5% permanganate.) During this fractional crystallization, the solution was frequently seeded with *cis-anti-trans* perhydrodiphenic acid (m. p. 206°), but none of this substance separated, and it can safely be concluded that it is either wholly or almost completely absent.

The pure *trans*-anhydride (150 mg.) was heated for one hour at 243 ± 3°. A little carbon dioxide was evolved, indicating the formation of some pyroketone. The acidic portion of the product was isolated by means of alkali and was crystallized from acetic acid. Seeding with the *cis*-hexahydro acid yielded three crops of this material (total, 20 mg.) and further seeding gave no more of it. The solution was accordingly seeded with the *trans*-hexahydro acid, which yielded five crops of *trans*-acid, totalling 45 mg. The acids were identified by m. p. and mixed m. p.

Summary

Half-hydrogenation of diphenic acid over platinum yields *cis*-hexahydrodiphenic acid. Thermal inversion of this acid yields the *trans*-isomer. Both the acids and their anhydrides yield mixtures rich in the *trans*-isomer when heated. The two acids yield distinct mono-nitro derivatives.

Further catalytic hydrogenation of the *cis*-hexahydro acid yields *cis-syn-cis*-perhydrodiphenic acid, and hydrogenation of the *trans*-hexahydro acid yields *cis-syn-trans*-perhydrodiphenic acid. The integrity of the configuration already established is therefore preserved, and further hydrogenation goes *cis*- and *syn*-.

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The Stereochemistry of Catalytic Hydrogenation. V. The Assignment of *cis*- and *trans*-Configurations

BY R. P. LINSTEAD, SELBY B. DAVIS AND RICHARD R. WHETSTONE

The stereochemical problem connected with the perhydrodiphenic acids which is left unsolved in the preceding papers is the allocation of *cis*- and *trans*-configurations to the terminal acids.¹ It has been shown that the 289 and 223° acids between them constitute the *cis-syn-cis* and *trans-syn-trans* acids, and the 198 and 247° acids share the *cis-anti-cis* and *trans-anti-trans*-configurations. There are many indications that the 289° and the 198° acids are the *cis*-members of the two series.

(1) Linstead and Doering, *THIS JOURNAL*, **64**, 2003 (1942).

The work described in the present paper proves this to be true.

The 289° perhydro acid has two similar arrangements of the carboxyl groups with respect to the backbone. It is made by the hydrogenation of the hexahydro acid of m. p. 242° by a method not involving an inversion.² Hence the configuration of the 242° acid is repeated twice in the 289° acid.

We therefore examined the configuration of

(2) Linstead and Davis, *ibid.*, **64**, 2006 (1942).