292. *The Stereochemistry of Catalytic Hydrogenation. Part VIII.** *Pyrolysis of the Six Perhydrodiphenic Acids. Limitations of the Blanc Rule.*

By Selby B. Davis, W. E. Doering, Philip Levine, and R. P. Linstead.

All six of the stereoisomeric perhydrodiphenic acids give pyroketones (perhydrofluorenones). The three acids of the *syn*-series give the same mixture of *syn*-ketones, and the three *anti*-acids give the same *anti*-ketone mixture. The bearing of this on work on steroid oxidation products is discussed.

When ring B of the steroid skeleton is opened, dibasic acids can be obtained which are of the perhydrodiphenic acid type. Although 1 : 6-dicarboxylic acids, some compounds of this class have failed to give pyroketones under Blanc's conditions (*Compt. rend.*, 1907, **144**, 1356) or under similar experimental treatment. This anomaly at one time led to the erroneous formulation of ring B as five-membered (Windaus and Dalmer, *Ber.*, 1919, **52**, 162; Wieland and Weyland, *Z. physiol. Chem.*, 1920, **110**, 123). Later, when it became clear for other reasons that the ring was six-membered, Wieland and Dane (*ibid.*, 1932, **210**, 268) suggested that the rule that adipic acids give pyroketones was limited to acyclic and monocyclic acids and failed with perhydrodiphenic acids. Ruzicka (*Helv. Chim. Acta*, 1933, **16**, 216) expressed the view that the steroid perhydrodiphenic acids failed to give ketones because they contained at least one *trans*-linkage.

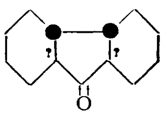
Investigations of the model compounds, the perhydrodiphenic acids themselves, have been made by Vocke (*Annalen*, 1934, **508**, 1), Hückel (addendum to Vocke's paper), and Linstead and Walpole (*J.*, 1939, 850).

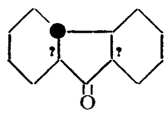
The interpretation of this early work was somewhat complicated by the incorrect assignment of the perhydrodiphenic structure to two acids. We refer to this matter later. However, the subject has been placed on a firm basis by the isolation and interrelation of all six stereoisomeric forms of perhydrodiphenic acid (Linstead and Doering, *J. Amer. Chem. Soc.*, 1942, **64**, 1991), and against this background it is possible to summarise the early results. Three isomeric acids are relevant, those of m. p. 244° (now 247°), 273° (now 289°), and 220° (now 223°), described by Vocke, Hückel, and Linstead and Walpole, respectively. We now know all these to be perhydrodiphenic acids with the configurations. *trans-anti-trans*, *cis-syn-cis*, and *trans-syn-trans* respectively. All give pyroketones.

The isolation of the remainder of the possible stereoisomeric forms of the acid and the proof of their configuration (Linstead and Doering, *loc. cit.*; Linstead, Davis, and Whetstone, *ibid.*, p. 2009; Davis and Linstead, following paper) have enabled us to complete the investigation.

We can now report that all six acids readily yield pyroketones. The same ketonic product is obtained from the three acids of the *syn*-series: *cis-syn-cis* (m. p. 289°), *cis-syn-trans* (m. p. 200°), and *trans-syn-trans* (m. p. 223°). It is, not unexpectedly, a mixture of two (perhaps three) of the possible *syn*-ketones (I), *i.e. cis-cis*, *cis-trans*, or *trans-trans*. It gives a mixture of oximes and a semicarbazone which is difficult to obtain homogeneous. The oximes are sensitive to light and heat. Careful crystallisation of the original mixture in a dark room gives a homogeneous *syn*-oxime, m. p. 173°, already isolated by Hückel (*loc. cit.*), but when this is heated or left in daylight, either in the solid state or in solution, the melting point falls and from the product a second *form*, m. p. 152—154°, can be isolated by crystallisation. This change is very likely caused by an inversion of configuration of the ring involving hydrogen migration from a bridgehead, but *cis-trans* isomerism about the carbon–nitrogen double bond cannot be excluded.

(I.)





(II.)

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* The experimental work described in this paper and the two succeeding Parts was carried out at Harvard University mainly in 1941. Publication has been greatly delayed from a variety of causes. The paper does not deal directly with the topic of catalytic hydrogenation. Nevertheless it seems best to add it to this series as it is concerned with the same compounds. R. P. L.

The three acids of the *anti*-series (*cis-anti-cis*, m. p. 198°; *cis-anti-trans*, m. p. 206°; *trans-anti-trans*, m. p. 247°) all give the same mixture of *anti*-perhydrofluorenones (II), characterised by the formation of the semicarbazone, already prepared by Vocke, and by Linstead and Walpole.

These ketonisations thus proceed in the expected way; there is an inversion of configuration at the α- but not at the β-carbon atom. The inversion may precede ketonisation for it has been shown that the acids of the *syn*-series are labile to heat. Thus the acid recovered (as anhydride) from the pyrolysis of both the *cis-syn-cis*- and the *cis-syn-trans*-isomerides was largely the *trans-syn-trans*-form. When either the *cis-syn-cis*- or the *trans-syn-trans*-acid was heated in an inert solvent at 243° there was formed a mixture mainly consisting of *trans-syn-trans*- with a small amount of *cis-syn-trans*-acid. The occurrence and the direction of these changes are fully as expected and fall into line with previous work on the relative stability of the *syn*-acids to reagents.

Although therefore the six authentic perhydrodiphenic acids all yield pyroketones, two other acids which have previously been assigned this constitution do not. These are the acid, m. p. 203°, of Linstead and Walpole (*loc. cit.*) and that, m. p. 213°, reported by Vocke (*loc. cit.*). Neither of these can be a perhydrodiphenic acid and their behaviour on pyrolysis is therefore not material to the present paper. Their probable constitutions have been discussed by Linstead and Doering (*loc. cit.*).

To revert to the central point of this work: As all the configurational forms of perhydrodiphenic acid give pyroketones, the abnormality of the steroid oxidation products is not caused by their being perhydrodiphenic acids, as suggested by Wieland, or by their having a *trans*-link, as proposed by Ruzicka. We think it probable that the difference between the perhydrodiphenic and the bilianic acids is one of degree and not of kind, and that the failure of the steroid acids to ketonise was caused by insufficiently drastic experimental conditions. It is well known that there is a good deal of variation in the conditions, particularly the temperature, under which different adipic acids yield ketones. For examples, it has been shown by Stange (*Z. physiol. Chem.*, 1933, **218**, 74) that an acid of this type which failed to cyclise under Blanc's conditions gave a pyroketone when its barium salt was heated to 390°.*

The conditions under which the perhydrodiphenic acids give ketones are described in the Experimental section. In no case was drastic treatment necessary, pyrolysis of the acid or anhydride at 310° or less being sufficient.

EXPERIMENTAL.

cis-syn-cis-*Acid* (compare Hückel, Linstead, and Walpole, *locc. cit.*).—The acid (m. p. 288—289°; 500 mg.) was heated for 2 hours at about 310° in a stream of dry nitrogen. The nearly colourless product was extracted with ether. From this solution aqueous sodium hydroxide extracted 50 mg. of a mixture of acids. The residue from the ether was then freed from anhydride by boiling 10% aqueous sodium hydroxide. This alkaline extract on fractional acidification (Linstead and Doering, *loc. cit.*) yielded 20 mg. of fairly pure *trans-syn-trans*-acid. The neutral ketonic fraction (150 mg.) was converted into the oxime (120 mg.) in the usual way. In a larger preparative experiment, the yield of mixed oxime was 5·01 g. from 8·65 g. of acid (78%).

The ketone was also prepared by heating the dry sodium salt of the *cis-syn-cis*-acid with acetic anhydride (Perkin and Thorpe, *J.*, 1904, **85**, 128). The carbon dioxide was swept out with dry nitrogen and weighed. Most was evolved between 130° and 140°. The yield of oxime was 1·36 g. from 5·43 g. of sodium salt. A similar mixture of oximes was obtained by both methods, melting mainly in the range 145—150°.

To obtain the pure oxime (needles, m. p. 172·5—174°) described by Hückel 8 crystallisations from 95% alcohol in a darkened room were necessary. The m. p. of this material fell when it was kept dry or in solution, particularly in light. A similar change was effected more quickly by heating the oxime or by treating it with sodium ethoxide. Crystallisations had to be carried out rapidly.

Oxime melting in the range 160—170° was kept for some weeks and then hydrolysed and the ketone reconverted into the oxime. Careful crystallisation from light petroleum yielded a second *syn*-perhydrofluorenone oxime, m. p. 152·5—154·5°, which appeared to be nearly homogeneous.

rac.-cis-syn-trans-*Acid*.—This acid (m. p. 198—200°; 250 mg.) was heated in nitrogen for 1 hour at 310°. The product was separated as described above into free acid (15 mg.), anhydride (yielding 10 mg. of an acid (mainly *trans-syn-trans*), and ketone (120 mg.). The ketone gave 100 mg. of a mixture of oximes, m. p. (crude) about 140—150°. Two crystallisations from methanol gave fine needles, m. p. 159—164°, which did not depress the m. p. of the oxime of similar m. p. prepared from the *cis-syn-cis*-acid. It was also indistinguishable from oxime prepared from *lævo-cis-syn-trans*-acid (see following paper).

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* Aliphatic acids not containing an α-hydrogen atom fail to yield a pyroketone. This seems a fundamental property, connected with the mechanism of the reaction (see Neunhoeffer and Paschke, *Ber.*, 1939, **72**, 919).

The semicarbazone of the *syn*-series (m. p. 200—202°) is less easily formed than the oxime.

Thermal Inversion of syn-*Acids*.—(i) *cis-syn-cis*-Perhydrodiphenic acid (1 g.) was boiled under reflux for 2 hours in 1-methylnaphthalene (5 c.c.). The product was freed from a little unchanged *cis-cis*-acid by extraction with ether and dissolved in alkali. It was then submitted to the usual process of fractional acidification and crystallisation from acetic acid. Pure *trans-syn-trans*- and impure *cis-syn-trans*-acids were isolated.

(ii) *trans-syn-trans*-Acid (300 mg.) was treated similarly for 10 hours. Again, pure *trans-syn-trans*- (m. p. 222—223°) and impure *cis-syn-trans*-acids (m. p. 189—193°) were isolated from the product. The proportion of *cis-trans*-material in these mixtures is of the order of 20%.

cis-anti-cis-*Acid*.—The acid (m. p. 198°) was converted into its anhydride (m. p. 100°; Linstead and Doering, *loc. cit.*). This (89·3 mg. was pyrolysed for 3 hours at 270° under carbon dioxide, and the product separated into anhydride and ketone. The anhydride yielded a mixture of *anti*-acids, m. p. 175—195° (32·6 mg.). The crude semicarbazone of the *anti*-perhydrofluorenone (26·9 mg.) melted at 196—208°. Crystallisation from 96% alcohol yielded 16·2 mg., m. p. 218·5—224° (bath at 215°). A sample of *anti*-semicarbazone prepared from *trans-anti-trans*-perhydrodiphenic acid melted at 220—226° (bath at 215°) and a mixture at the same temperature.

cis-anti-trans-*Acid*.—This rare acid (42 mg.; m. p. 205—206°) was refluxed for 20 minutes at 310° in a stream of nitrogen. The product was worked up in the usual way. The semicarbazone melted at 214—218° after one crystallisation and at 217—220° in admixture with that described above.

The ketonisations of rac.-*trans-anti-trans*- (m. p. 247°) and of *trans-syn-trans*-perhydrodiphenic acid (m. p. 223°) have been described by Linstead and Walpole (*loc. cit.*). Those of the *lævo-cis-syn-trans*- and the *dextro-trans-anti-trans*-acid are recorded in the following paper.

A number of experiments have been made with the object of hydrogenating fluorenone or a hexahydrofluorenone to perhydrofluorenone which could be compared with the products obtained from the perhydrodiphenic acids. These have failed because of the easy elimination of the oxygen under the conditions necessary for perhydrogenation.

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