294. *The Stereochemistry of Catalytic Hydrogenation. Part X. The Hydrogenation of* trans-as-*Octahydrophenanthrene Derivatives. A New Form of the Perhydrophenanthrene Ring and a Model for the Inversion of the 6-Keto-steroids.*

By R. P. Linstead and Richard R. Whetstone.

The hydrogenation, over platinum, of *trans-as*-9-keto-octahydrophenanthrene and of the two alcohols derived from it has been studied. There is formed a mixture of 60% of *cis-syn-trans-* and 40% of *cis-anti-trans*-perhydro-9-phenanthrol. The *cis-syn-trans*-alcohol on oxidation with chromic acid yields the corresponding *cis-syn-trans*-ketone, and on dehydration followed by ozonisation gives *cis-syn-trans*-perhydrodiphenic acid. As the corresponding *trans-syn-cis*-compounds are known, the new substances must belong to the *cis-syn-trans*-series.

The *cis-anti-trans*-alcohol on chromic acid oxidation gives the corresponding *cis-anti-trans*-ketone, readily inverted to the known *trans-anti-trans*-ketone, thus proving the structure and configuration.

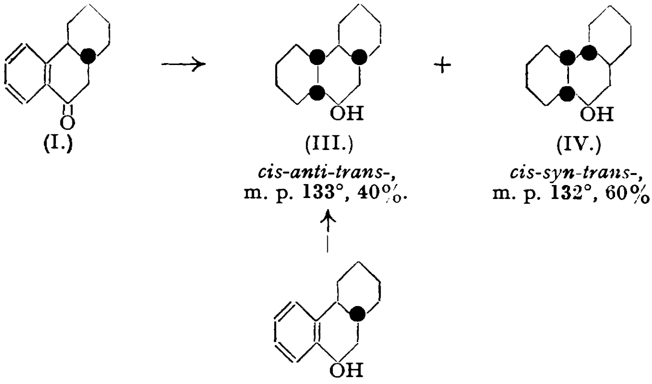
It is shown that the results conform to the principles of one-sided addition and of catalyst hindrance already enunciated.

Derivatives of four out of six of the possible forms of the perhydrophenanthrene ring are therefore now known. Five of the possible eight C$_{(9)}$ ketones and nine of the possible sixteen C$_{(9)}$ alcohols have been isolated.

In a previous paper (Linstead, Whetstone, and Levine, *J. Amer. Chem. Soc.*, 1942, **64**, 2014) it was shown that classical stereochemistry allowed for the existence of six perhydrophenanthrenes, eight inactive ketones with a carbonyl group on C$_{(9)}$, and sixteen inactive alcohols derived from them. Three of the possible ketones and four of the alcohols were described and the configurations of these ketones and of all but one of the alcohols were proved.

In the present paper the further investigation of this group is described and the isolation of two more stereoisomeric ketones and of five more alcohols is reported, together with the proof of their configurations.

Our earlier work had involved the hydrogenation of 9-phenanthrol, of *cis*-9-keto-*as*-octahydrophenanthrene, and of derived alcohols. We have now taken up the study of the corresponding octahydro-compounds of the *trans*-series. The parent ketone (I) (Cook *et al.*, *J.*, 1936, 71; 1939, 168; Linstead, Whetstone, and Levine, *loc. cit.*) undoubtedly contains a *trans*-locking of the rings, the *cis*-configuration of its stereoisomeride having been proved conclusively in our earlier work. It will be noted, moreover, that the further hydrogenation of the *trans*-octahydro-ketone invariably produces material for which one *trans*-junction can be independently established. The substances hydrogenated were the *trans*-octahydro-ketone, m. p. 96°, and the two derived epimeric secondary alcohols (II), m. p.s 91° and 101°, described in our previous paper. Hydrogenations, which were carried out with Adams's platinum oxide, were more difficult than in the *cis*-series. No reaction occurred in alcohol alone but in the presence of a little acetic acid reduction was smooth and there was little formation of hydrocarbon. The same product was obtained from all three starting materials. It was a mixture of two *per-*



(I.)

(III.) *cis-anti-trans-*, m. p. 133°, 40%.

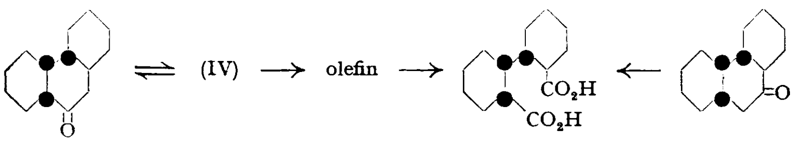
(IV.) *cis-syn-trans-*, m. p. 132°, 60%.

(II.) Two epimers.

hydro-9-phenanthrols, which have been proved to have the *cis-anti-trans-* (III) and *cis-syn-trans*-configurations (IV).*

The two alcohols had practically the same melting point but a mixture melted some 25° lower. Their separation was not easy (see Experimental section) but prior oxidation to the corresponding ketones was helpful as a convenient separation of the two series through the oximes was possible.

Oxidation of the *cis-syn-trans*-alcohol † (IV) gave cis-syn-trans-9-*ketoperhydrophenanthrene* (V), m. p. 72° (*oxime*, m. p. 206°). Reduction of this ketone with sodium in moist ether re-formed the *cis-syn-trans*-alcohol, m. p. 132°, whereas catalytic hydrogenation slowly yielded an *epimer*, m. p. 77°. The determination of configuration of these materials was difficult. No perhydrodiphenic acid could be isolated by nitric acid oxidation and attempts to convert the ketone into a 9 : 10-quinone by means of selenium dioxide or *iso*amyl nitrite were abortive. However the perhydro-alcohol, m. p. 132°, was dehydrated to an olefin which on ozonisation yielded the *cis-syn-trans*-perhydrodiphenic acid (VI) of Linstead and Doering (*J. Amer. Chem. Soc.*, 1942, **64**, 1991). This means that the new ketone and alcohol must belong to either the *cis-syn-trans-* (V) or the *trans-syn-cis*-series (VII). (The first prefix is by convention assigned to the configuration of the ring locking *adjacent* to the functional group.) But Linstead, Whetstone, and Levine (*loc. cit.*) have already isolated the *trans-syn-cis*-ketone (VII). Its structure is certain because (*a*) it yields the acid (VI) on oxidation and (*b*) it is formed by the inversion at the bridgehead next to $C_{(9)}$ of a ketone known to have the *cis-syn-cis*-configuration. Hence the new compounds belong to the *cis-syn-trans*-series (V).



(V.), m. p. 72° (VI.) (VII.), m. p. 57°

It is an interesting fact that the new ketone (V) is not inverted in configuration under the conditions which customarily convert *cyclo*hexane ketones with a carbonyl group next to a *cis*-bridgehead into their *trans*-isomerides, for example *cis-* into *trans*-α-decalone and *cis-syn-cis*-9-ketoperhydrophenanthrene into the *trans-syn-cis*-isomeride (VII). However, it would appear from Stuart models that the *trans-syn-trans*-ring system [which would be formed by the inversion of (V)] may be less stable than the *cis-syn-trans*-system. This illustrates the danger of argument by analogy in this field, and the need for the determination of configuration by unequivocal methods.

The second substance formed in the catalytic hydrogenation of *trans*-9-keto-*as*-octahydrophenanthrene and its derived alcohols was a *perhydro-9-phenanthrol* of m. p. 133°. Oxidation of this substance with chromic acid yielded a new 9-*ketoperhydrophenanthrene* of m. p. 54°, hydrogenation of which re-formed the parent alcohol. The ketone yielded an unstable *oxime*, m. p. 140°, which on acid hydrolysis yielded an isomeric, stable ketone, m. p. 47° (oxime, m. p. 233°). Isomerisation of the ketone of m. p. 54° into that of m. p. 47° could also be effected with alcoholic alkali. The inverted ketone, m. p. 47°, was identified by mixed melting point determinations of both ketone and oxime with the 9-ketoperhydrophenanthrene (" Form 3 ") made by Linstead and Walpole (*loc. cit.*) from Rapson and Robinson's unsaturated ketone (*J.*, 1935, 1285). This substance undoubtedly has the *trans-anti-trans*-configuration (VIII) : it can be oxidised to *trans-anti-trans*-perhydrodiphenic acid (Linstead and Walpole, *J.*, 1939, 850; Linstead and Doering, *J. Amer. Chem. Soc.*, 1942, **64**, 2003; Linstead, Davis, and Whetstone, *ibid.*, p. 2009). It follows with certainty that the new ketone, m. p. 54°, has the *cis-anti-trans*-configuration (IX) and so does the parent alcohol (III). They are the first derivatives of this form of the perhydrophenanthrene ring to have been made. Derivatives of four (*cis-syn-cis*, *cis-syn-trans*, *cis-anti-trans*, *trans-anti-trans*) of the six basic types are now known.

Catalytic hydrogenation of the ketone, m. p. 47°, gave a new trans-anti-trans-*perhydro-9-phenanthrol*, m. p. 80°, whereas alkaline reduction gave the epimer, m. p. 119°, already reported by Linstead and Walpole (*loc. cit.*).

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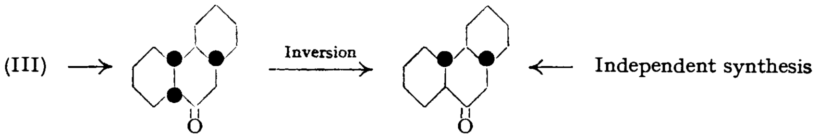
* For nomenclature see Linstead, *Chem. and Ind.*, 1937, **56**, 510; Linstead and Walpole, *J.*, 1939, 842.

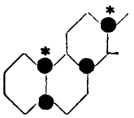
† The correct configurations are anticipated at this point for the sake of clarity.

The preparation and inversion of the *cis-anti-trans*-ketone (IX) is noteworthy for three reasons. First, the inversion of *cis-trans-* to *trans-trans*-form occurs in the *anti-* but not in the *syn*-series. Secondly, the *cis-anti-trans*-arrangement of the perhydrophenanthrene ring is that which is present in the normal series of steroids, *i.e.*, that including 5-*iso*androstane, pregnane, cholanic acid, coprostane, and their derivatives (X). Thirdly, the inversion of the *cis-anti-trans-* to the *trans-anti-trans*-configuration, now established (IX ⟶ VIII), is parallel to those observed in analogous steroid structures, for example, the change of 3 : 6-diketocholanic acid (from hyodeoxycholic acid) into 3 : 6-diketo*allo*cholanic acid (Windaus, *Annalen*, 1926, **447**, 253). The inversion of *cis-anti-trans-* to *trans-anti-trans*-9-ketoperhydrophenanthrene provides a much safer model for the changes of 6-keto-steroids than does that (*cis-* to *trans*-α-decalone) previously used.



(IX.) *cis-anti-trans*, m. p. 54°

(VIII.) *trans-anti-trans*, m. p. 47°



(X.)

* These dots represent methyl groups above the rings.

It has also been possible to study one other aspect of the *syn*-perhydrophenanthrol series. In our previous work we had identified with certainty one *cis-syn-cis*-alcohol, m. p. 111°, and one *trans-syn-cis*-alcohol, m. p. 89°. There was in addition an alcohol of m. p. 67°, prepared by Marvel and White (*J. Amer. Chem. Soc.*, 1940, **62**, 2739) by the reduction of 9-phenanthrol over nickel. Oxidation of this alcohol with hot chromic acid had given a 9-ketoperhydrophenanthrene, m. p. 57°, doubtless identical with the *trans-syn-cis*-ketone of the same melting point which we had prepared by another method. This means that the alcohol of m. p. 67° is an epimer of either the known *cis-syn-cis-* or the *trans-syn-cis*-alcohol. If it is a *cis-syn-cis*-compound the oxidation to the ketone must have been accompanied by inversion. This is quite feasible; we have observed the same thing in the oxidation of the *cis-syn-cis*-alcohol, m. p. 111°, with hot chromic acid.

We have now reduced our *trans-syn-cis*-9-ketoperhydrophenanthrene with sodium in alcohol to a new 9-*perhydrophenanthrol*, m. p. 100°. This must be the missing epimer of the *trans-syn-cis*-series. Hence we can provisionally say that Marvel and White's alcohol (m. p. 67°) is the missing epimer of the *cis-syn-cis*-series; its direct oxidation to a perhydrodiphenic acid is desirable.

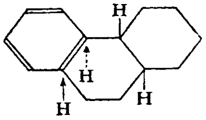
The present state of knowledge of the 9-substituted perhydrophenanthrenes is summarised in the table, which gives the melting points of the known compounds.

syn-Series :	Ketones.	Alcohols.		*anti*-Series :	Ketones.	Alcohols.	
cis-cis	44°[1]	111°[1],	67°[4]	*cis-cis*	—	—	—
trans-cis	57°[1,4]	100°[2],	89°[1]	*trans-cis*	—	—	—
cis-trans	72°[2]	132°[2],	77°[2]	*cis-trans*	54°[2]	133°[2]	—
trans-trans	—	—	—	*trans-trans*	49°[2,3]	119°[2,3]	80°[2]

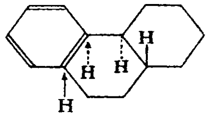
[1] Linstead, Whetstone, and Levine, *loc. cit.* [2] Present paper. [3] Linstead and Walpole, *loc. cit.* [4] Marvel and White, *loc. cit.*

With the exception of the *trans-syn-cis*-compounds, which are intermediate in type, the perhydro-alcohols fall into two classes. Four alcohols are high-melting (111° to 133°), moderately soluble and crystallise well. The other three resemble the related ketones in their physical properties, being lower-melting, more soluble, and much harder to crystallise. Each epimeric pair has one member of each type. The higher-melting epimer was always isolated readily from the hydrogenation of octahydrophenanthrene compounds. This is probably deceptive; the low-melting epimers were fairly certainly present in the mother-liquors, which by oxidation usually yielded some 10—30% of perhydro-ketones. Reduction of the perhydro-ketones to alcohols gave less uniform results. Two ketones (*cis-syn-trans*, *trans-anti-trans*) yielded the lower-melting alcohol by catalytic hydrogenation and the epimers by reduction with sodium. Two other ketones (*cis-syn-cis, cis-anti-trans*) were catalytically hydrogenated to the higher-melting alcohols and a low-melting isomeride could not be isolated. The distinction in physical properties of the two series must correspond with the packing of the molecules in the crystal lattice, which is affected by the relation in space of the hydroxyl group to the rest of the structure.

We must now review the new results in their bearing on the stereochemistry of hydrogenation of aromatic rings. The first point is that over Adams's platinum at room temperature the aromatic ring of *trans-as*-octahydrophenanthrene is hydrogenated to give *cis*-compounds, in accordance with the principle of one-sided addition (Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985). The second point is that hydrogenations go both *syn*- (60%) and *anti*- (40%) in the *trans*-series, whereas the corresponding *cis*-compounds are hydrogenated only to *syn*-products. At first sight this appears anomalous but consideration shows that it is to be expected on the hypothesis of catalyst hindrance (Linstead *et al.*, *loc. cit.*, p. 1989). According to this, hindrance between the catalyst and substrate will effect adsorption selectively so that one particular spatial arrangement may be expected to be favoured and the alternative inhibited. Hydrogenation will follow correspondingly, the hydrogen entering the molecule to give the configuration consequential on the preferred adsorption. This readily explains why *cis-as*-octahydrophenanthrene derivatives give *cis-syn-cis*-perhydro-compounds.



(XI*a*.)
Sorption leading
to *anti*-configuration.



(XI*b*.)
Sorption leading
to *syn*-configuration.

The case of *trans-as*-octahydrophenanthrene is different. The *trans*-decalin part of the molecule is approximately planar and the hindrance anticipated between the catalyst and one arrangement of the substrate (XI*a*) should not differ greatly from that with the alternate arrangement (XI*b*). There is no *prima facie* reason why adsorption should not occur in both ways. Hence we should expect both *cis-anti-trans*- and *cis-syn-trans*-materials to be produced, which is precisely what occurs. It would be premature to regard the hypothesis of catalyst hindrance as proved but it is interesting to find results such as these in line with its requirements. It may also be significant that in the *trans*-series, where both positions of sorption are somewhat hindered, hydrogenation is less ready than in the *cis*-series where one position of sorption is free from hindrance.

In addition to the above results, we have made some progress towards obtaining the various parent hydrocarbons, the perhydrophenanthrenes, in stereochemically homogeneous forms of known configuration. This is being further investigated and it is hoped to describe it later.

EXPERIMENTAL.

Hydrogenation of trans-9-*Keto*-as-*octahydrophenanthrene* (I).—A solution of the ketone, m. p. 95—96° (6·2 g.), prepared by the method of Linstead, Whetstone, and Levine (*loc. cit.*) in absolute alcohol (75 c.c.) containing 3 drops of acetic acid over Adams's platinum oxide (0·6 g.) took up 3·6 moles of hydrogen at atmospheric pressure in 4 days. After removal of the catalyst and solvent, the residual oil was diluted with hexane (30 c.c.) and set aside. There was deposited a solid (A.) (2·3 g.), m. p. 105—115°, which was dissolved in hexane (20 c.c.) and benzene (8 c.c.). The solution on being allowed to cool slowly deposited fine needles (B) (0·95 g.), m. p. 126—130°. Crystallisation of this from ether gave long prisms of cis-syn-trans-*perhydro*-9-*phenanthrol* (IV), m. p. 131·5—132° (Found: C, 80·8; H, 11·4. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%). The filtrate from (*B*), when kept overnight, deposited a solid (C) (0·25 g.), m. p. 129—132°, which on crystallisation from hexane yielded rosettes of fine, silky fibres of cis-anti-trans-*perhydro*-9-*phenanthrol* (III), m. p. 133—133·5° (Found: C, 81·0; H, 11·7%). A mixture of the two alcohols melted at 105—115°. Evaporation of the filtrate from (*C*) gave a mixture (*D*) of the two alcohols in approximately equal amounts. The m. p. of this was raised by admixture with either of the components. Some separation could be effected by slow evaporation of ethereal solutions, but the best technique for both this mixture and the mother-liquor from the original solid hydrogenation product (*A*) was through oxidation to the ketones (see below).

The two pure *trans-as*-octahydro-9-phenanthrols (m. p.s 90° and 100°; Linstead, Whetstone, and Levine, *loc. cit.*) were similarly hydrogenated. Each gave the same two perhydro-phenanthrols in about the same proportions.

cis-syn-trans-9-*Ketoperhydrophenanthrene* (V).—The *cis-syn-trans*-alcohol, m. p. 129—132° (0·50 g.), was oxidised with chromic oxide in acetic acid, and the ketone (0·42 g.; m. p. 69—71°) isolated in the usual way. Two crystallisations from light petroleum yielded long needles of pure cis-syn-trans-9-*ketoperhydrophenanthrene*, m. p. 71·5—72° (Found : C, 80·7; H, 10·9. $C_{14}H_{22}O$ requires C, 81·5; H, 10·8%). The *oxime*, which was formed readily in the cold, crystallised from alcohol in fine needles, m. p. 205—206° (Found : C, 76·2; H, 10·4. $C_{14}H_{23}ON$ requires C, 76·0; H, 10·5%). Hydrolysis of the oxime with boiling 5% sulphuric acid regenerated the parent ketone. The ketone was not inverted by heating (i) in hot alcoholic sodium ethoxide for 90 minutes, (ii) with hydrochloric acid in boiling ether for 9 hours, or (iii) alone at 200° for 2 hours.

Reduction of the ketone (0·20 g.) with sodium (0·25 g.) in moist ether (20 c.c.) gave 0·17 g. of the *cis-syn-trans*-alcohol (0·17 g.), m. p. 132°, already reported. The ketone (320 mg.) was hydrogenated over Adams's catalyst in alcohol (20 c.c.) containing acetic acid (2 c.c.). (In pure alcohol the hydrogenation was very slow.) The epimeric cis-syn-trans-*perhydro*-9-*phenanthrol* formed (230 mg.; m.p. 73—75°) was very soluble in organic solvents. Two recrystallisations raised the m. p. to 76—77° (Found : C, 80·95; H, 11·75. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%).

No solid acid could be isolated after oxidation, by nitric acid, of the *cis-syn-trans*-ketone or either of the derived alcohols. The technique used by Linstead and Doering (*loc. cit.*) for the isolation and purification of perhydrodiphenic acids was applied to the products without success. Reaction of the ketone with *iso*amyl nitrite (Litvan and Robinson, *J.*, 1938, 1977) or with selenium dioxide in dioxan or in acetic anhydride (cf. Evans, Ridgion, and Simonsen, *J.*, 1934, 137) failed to yield any 9 : 10-quinone.

The *cis-syn-trans*-perhydrophenanthrol, m. p. 132° (450 mg.), was dehydrated with potassium hydrogen sulphate (600 mg.) at 200° for 3 hours. The resulting liquid olefin was ozonised and the ozonide decomposed by evaporation with 3% hydrogen peroxide. The acid product in aqueous sodium carbonate was fractionally acidified. The third treatment yielded a crystalline solid (25 mg.; m. p. 190—195°) which after crystallisation from acetic acid melted at 196—198° alone or in admixture with authentic *cis-syn-trans*-perhydrodiphenic acid (Linstead and Doering, *loc. cit.*).

cis-anti-trans- *and* trans-anti-trans-*Series*. *cis-anti-trans*-Perhydro-9-phenanthrol (III), m. p. 133° (200 mg.), was oxidised in the cold with chromic and acetic acids. The ketone, isolated in the usual way, melted at 52—54° (110 mg.).

cis-anti-trans-9-*Ketoperhydrophenanthrene* forms needles (from light petroleum), m. p. 53—54° (Found : C, 81·2; H, 10·75. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%). The oxime was formed rapidly at room temperature. Crystallisation from alcohol, in which it was freely soluble, lowered its initial m. p. of 145—148° to 140—143°, presumably because inversion had commenced. Hydrolysis of the oxime with boiling 5% sulphuric acid yielded the *trans-anti-trans*-ketone (see below).

Catalytic hydrogenation of the *cis-anti-trans*-ketone (100 mg.) in alcohol containing a few drops of acetic acid (Adams's catalyst) yielded 80 mg. of the *cis-anti-trans*-alcohol, m. p. 132—133°, already reported.

The *cis-anti-trans*-ketone (80 mg.) was boiled for 105 minutes with sodium ethoxide (from 0·3 g. of sodium and 5 c.c. of alcohol). The product was poured into water and isolated by means of ether. After crystallisation of the residue from light petroleum, 10 mg. of *trans-anti-trans*-ketone were obtained, having m. p. and mixed m. p. 44—46°. The oxime had m. p. and mixed m. p. 230—233°.

The *trans-anti-trans*-ketone (240 mg.) (Linstead and Walpole, *loc. cit.*) rapidly took up one mole of hydrogen over Adams's catalyst, in alcoholic solution. Crystallisation of the product from light petroleum gave 120 mg. of a new trans-anti-trans-*perhydro*-9-*phenanthrol* (m. p., crude, 76—78°). Two recrystallisations from light petroleum, followed by sublimation at 90°/5 mm., gave the analytical sample, m. p. 80—80·5° (Found : C, 81·0; H, 11·8. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%). The epimeric alcohol was prepared in good yield by the reduction of the ketone with sodium in moist ether. It had m. p. 116—118°, in agreement with Linstead and Walpole.

Separation of cis-syn-trans- *and* cis-anti-trans-*Material*.—It has been said that the solid product (*A*; p. 1431) from the hydrogenation of *trans*-9-keto-*as*-octahydrophanthrene was separated by crystallisation into the *cis-syn-trans*- and *cis-anti-trans*-alcohols and a mixture (*D*; p. 1431). This mixture (900 mg.) was oxidised with chromic oxide in the usual way. Crystallisation of the product from light petroleum gave 210 mg. of *cis-syn-trans*-ketone (m. p. 67—69°). The residue from this, which could not be further crystallised, was converted into oximes (490 mg.), separated by fractional crystallisation from alcohol into *cis-syn-trans*- (120 mg.; m. p. 195—198°) and *cis-anti-trans*-oxime (350 mg.; m. p. 135—145°). (*D*) thus contains alcohols of the two series in about equal amounts.

The mother-liquor from the original solid hydrogenation product (*A*) was also examined. Some 9 g. of this were accumulated. Vacuum-distillation yielded 4·0 g. of non-viscous liquid, boiling below 125°/5 mm. and mainly composed of hydrocarbons, together with 5·1 g. of a viscous oil, b. p. 125—140°/5 mm. Oxidation of the high-boiling fraction with chromic acid yielded a mixture of ketones which was converted into oximes at room temperature. The following crops were removed separately : (i) after 5 minutes, m. p. 190—220°, 1·8 g., (ii) after another 30 minutes, m. p. 192—195°, 1·3 g., (iii) after storage overnight, m. p. 180—185°, 0·3 g. Crop (i) was separated into *trans-anti-trans*-, m. p. 230—232° (1·6 g.), and *cis-syn-trans*-oxime, m. p. 195—200° (0·2 g.). Crops (ii) and (iii) yielded 1·0 g. of *cis-syn-trans*-oxime, m. p. 200—202°. The *trans-anti-trans*-material was presumably formed by inversion at the stages of oxidation and oximation, but we cannot exclude the possibility that some was present in the original hydrogenation product.

From a review of the constituents of the various products, it is concluded that the hydrogenation of the *trans*-octahydro-ketone yielded about 60% of perhydrophenanthrols, of which 60% had the *cis-syn-trans*- and 40% the *cis-anti-trans*-configurations.

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HARVARD UNIVERSITY, CAMBRIDGE, MASS.
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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