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STEREOCHEMISTRY OF THE PERHYDROINDENE SYSTEM

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I. INTRODUCTION

The development of the chemistry of steroids and the introduction of conformational analysis have given rise to interest in the stereochemistry of perhydroindene. The reviews published several years ago[1,2] examined together the properties of perhydroindene itself and more complex steroid systems. Recent advances in conformational analysis of cyclopentane have explained a number of important specific stereochemical properties of perhydroindene and have formed a basis for their quantitative estimate.

The information at present available on the stereochemistry of perhydroindene has been successfully applied in the investigation of steroid and related polycyclic systems. The bicyclic perhydroindene systems constitute a combination of cyclopentane and cyclohexane rings in which each acquires new properties due to the effect of the neighbouring ring, the changes in properties being associated exclusively with steric factors. The study of the stereochemistry of perhydroindene thus broadens our ideas about such mutual influences within a molecule. The study of the stereochemistry of perhydroindene was begun by Hückel[3] who in 1926 achieved a stereospecific synthesis of both perhydroindene-2-one stereoisomers and established that the *cis*-isomer is more energy-rich than the *trans*-isomer.

The present review deals with a wide variety of specific stereochemical properties of perhydroindene and fills the gap which has existed in this field in the Soviet literature. An attempt is made at a systematic presentation of the available literature data on the stereochemistry of perhydroindene derivatives, from the point of view of modern ideas about the conformations of ring systems.

II. STEREOCHEMISTRY OF THE RING FUSION IN THE PERHYDROINDENE SYSTEM

According to the numerous determinations[4-7] of the heats of combustion of *cis*-perhydroindene and *trans*-perhydroindene, the *cis*-isomer is richer in energy than the *trans*-isomer, although this difference is appreciably smaller than for the two isomeric decalins. The most exact measurement of ΔH gave 0.74 ± 0.5 kcal mole^{-1}.[7] When the pure isomers are heated with palladised charcoal below 193°, *trans*-perhydroindene predominates in the equilibrium mixture, whereas at an even slightly higher temperature the *cis*-isomer is predominant. The calculated enthalpy of isomerisation at 279° is -1.07 ± 0.09 kcal mole^{-1} and the entropy -2.30 e.u.[8] For the analogous process in the decalin series ΔH = -2.7 kcal mole^{-1} and ΔS = -0.55 e.u.[9] The isomerisation of *cis*-perhydroindene to *trans*-perhydroindene under the action of aluminium bromide, discovered

by Zelinskii [10], is probably associated with the higher thermodynamic stability of the *trans*-isomer.

Nevertheless it is widely known that *trans*-perhydroinden-1-ones and *trans*-perhydroinden-4-ones are readily converted into the corresponding *cis*-isomers under the action of acids, bases, high temperature, and light. Furthermore, it is known that in ring closure yielding a five-membered ring forming a 1,2-junction with a six-membered ring, *cis*--cyclisation takes place more readily than *trans*-cyclisation and the resulting *cis*-bicyclic systems are usually more stable than the corresponding *trans*-isomers. In order to resolve these contradictions, it is necessary to examine the conformations of the stereoisomeric perhydroindenes (Scheme I).

Two conformations (Ia) and (Ib) are theoretically possible for the *trans*-perhydroindene molecule, but the latter is energetically so unfavourable that it can be disregarded. In conformation (Ia) the six-membered ring is present in the chair form and the five-membered ring is in conformation C_2 ("half-chair") in which the bridging carbon atoms lie on different sides of the plane containing the $C_{(1)}$, $C_{(2)}$, and $C_{(3)}$ atoms. With such a conformation unsubstituted *trans*-perhydroindene as a whole has a diad symmetry axis [11].

Comparison of the infrared spectra of 1-chloro- and 1-bromo-*trans*-perhydroinden-2-one and the unsubstituted *trans*-perhydroinden-2-one shows that the five-membered ring is indeed present in conformation C_2. [12] The presence of the C_2 conformation of the D ring in steroids was demonstrated from a study of the infrared spectra and the rotatory dispersion curves of the stereoisomeric 16-bromo-3β--hydroxy-5α-androstan-17-ones and 17-bromo-3β-hydroxy--5α-androstan-16-ones [13].

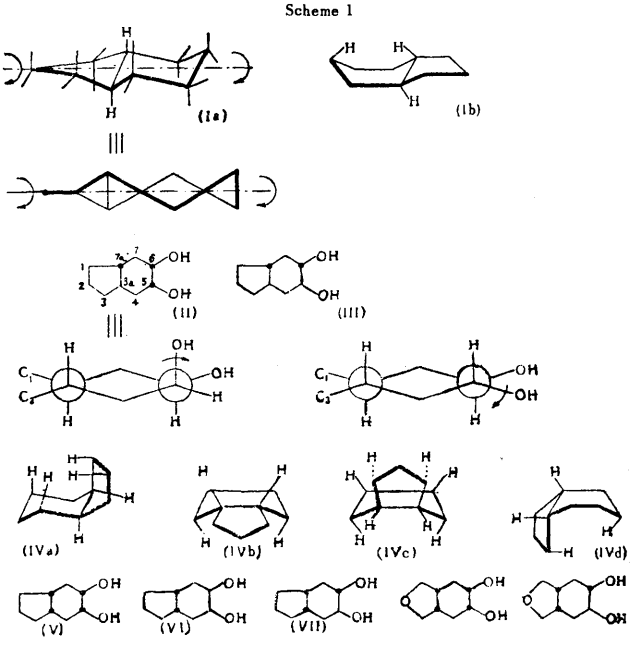
The chair conformation of the six-membered ring in the *trans*-perhydroindene system has been confirmed by the kinetic data for the oxidation of the stereoisomeric *trans*--perhydroindenediols [14]. The rate constant ratio $K^{25^\circ}_{cis}/K^{25^\circ}_{trans}$ for the two diols (II) and (III) is of the same order as for the *cis*- and *trans*-cyclohexane-1,2-diols (76 and 23 respectively). The *cis*-diol (II) is oxidised more rapidly and the *trans*-diol (III) more slowly than the corresponding cyclohexane-1,2-diols and therefore in the *trans*-perhydroindene system the projection angle between the *cis*-*ortho*--groups in the six-membered ring is less than 60°, whereas that between the equatorial *trans*-*ortho*-groups is greater than 60°. Examination of the projection formulae (Scheme I) shows that in both cases the change in the angle between the substituents is associated with repulsion of the axial groups at $C_{(5)}$ and $C_{(6)}$ from the angular hydrogen atoms. It is evident that in the *trans*-perhydroindene system the axial 1,3-substituents are closer together than in the unstrained cyclohexane or *trans*-decalin systems. Examination of the rotatory dispersion curves of *trans*-decalones and *trans*-perhydroindenones [15,16], which have similar structures, confirms the conclusion that the chair conformation of the six-membered ring in the *trans*-perhydroindene system is slightly deformed.

In the *cis*-perhydroindene molecule the six-membered ring can theoretically exist in four conformations (IVa–IVd); the number of possible conformations is even greater when substituted *cis*-perhydroindenes are considered [2]. Conformations (IVc) and (IVd) are improbable, being energetically unfavourable. The only unfavourable thermodynamic factor in conformation (IVb) is the boat form of the six-membered ring (here the five-membered ring is made up of equatorial bonds lying in the plane of the sides of the "boat"). Finally, in the chair conformation (IVa) there are three energetically unfavourable 1,3-diaxial interactions between the methylene groups. Thus both conformations (IVa) and (IVb) are probable for the *cis*-perhydroindene molecule.

The proof of the chair conformation of the six-membered ring in the *cis*-perhydroindene system was obtained in the same way as in the case of *trans*-perhydroindene (Scheme I). The rate constant ratio for the oxidation of the *cis*–*cis*--diols (V) and (VI) and the *cis*-*trans*-diol (VII) by lead tetraacetate is of the same order as for the two isomeric cyclohexane-1,2-diols. [17]. The absolute rate of oxidation of all the three diols (V–VII) is higher and the energy of activation lower than for both cyclohexane-1,2-diols. Hence it was concluded that in the *cis*-perhydroindene system the six-membered ring exists in the "flattened" chair conformation in which the distance between the axial 1,3-substituents is greater than in cyclohexane. The flattening of the chair conformation of the six-membered ring and the weakening of the 1,3-diaxial interaction in the *cis*-2-oxaperhydroindene system have been clearly demonstrated by Eliel and Pilar [18].

The chair conformation of the six-membered rings in the *cis*-perhydroindene system was also confirmed by an examination of the rotatory dispersion curves for certain *cis*-perhydroindenones [16,19] obtained in an investigation of the bromination kinetics of *cis*-perhydroinden-5-one, [20] and by the results of the study of the deamination of the epimeric 4- and 5-amino-*cis*-perhydroindenes and the saponification of the esters of the epimeric *cis*-4- and *cis*-5--decalols [21]. The greater distance between the axial substituents and the weakening of the 1,3-diaxial interaction in

Scheme 1



such a "flattened" six-membered ring behave as favourable thermodynamic factors, partly compensating the interaction between non-bonded methylene links in *cis*-perhydroindene.

Introduction of an angular methyl group in the perhydroindene framework alters the order of stability: the *cis*--isomer becomes somewhat more stable than the *trans*--isomer. This finding may be explained by the fact that although formally the number of interactions between non--bonded methylene links in 3a-methyl-*trans*-perhydroindene (VIII) is smaller than in the *cis*-isomer, which can exist in two conformations (IXa) and (IXb), the severity of these interactions will increase when the rings are joined in the *trans*-position and will decrease when they are joined in the *cis*-position, in consequence of the specific properties of the six-membered ring (described above) in the perhydroindene system.

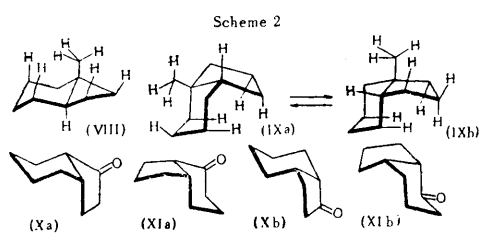
The oxime of 3a-methyl-*trans*-perhydroinden-1-one, which cannot be converted into the *cis*-isomer by an enolisation mechanism, is in fact converted into the *cis*-isomer in the presence of palladised charcoal[22]. The formation under the action of radiation of lumisteroids with rings C and D joined in the *cis*-position is also known[23].

Like *cis*-decalin, *cis*-perhydroindene can be converted from one conformation to another[24], probably *via* the boat conformation of the six-membered ring[3]. The results of the alkaline hydrolysis and epimerisation of the dimethyl esters of *cis-syn-cis*- and *cis-anti-cis*-perhydroindene--4,5-dicarboxylic acids confirm this conclusion[25]. The most favourable conformation for 3a-methyl-*cis*-perhydroindene is (IXb), where the methyl group is oriented equatorially in relation to the six-membered ring (Scheme 2). Investigation of the rotatory dispersion of 3a-methyl-*cis*--perhydroinden-6-one[16] confirms this conclusion.

The question of the relative stability of *cis*- and *trans*--perhydroindenones, with the oxo-group next to the angular hydrogen atom, which is thus capable of enolisation, is of interest. As a rule the *cis*-form is the more stable, *trans*-perhydroinden-1-ones and *trans*-perhydroinden-4--ones being converted into the *cis*-analogues by acids and bases, heat, ultraviolet irradiation, and sometimes spontaneously. This distinguishes the perhydroinden-1-ones from 1-decalones, whose *trans*-isomers are the more stable.

The stability of *cis*-perhydroinden-1-ones can be explained by the following two causes: (1) the preferential *cis*-ring junction due to thermodynamic factors[8]; (2) the 2-alkylketone and 3-alkylketone effects[3]. The first of these causes will be examined in the following section of the review and here we shall consider only the alkylketone effects.

Scheme 2



The angle between the equatorial methyl group and the carbonyl group in the 2-methylcyclohexanone molecule is only 15° and therefore their mutual repulsion is very powerful. With axial orientation of the methyl group in 2-methylcyclohexanone the angle between this group and the carbonyl group is 105° and there is no non-bonding interaction between them. According to Klyne's calculations[26], the elimination of interaction between the methyl and carbonyl groups reduces the energy of the molecule by 1 kcal mole^{-1} and as it were compensates for the energy of the diaxial 1,3-interaction between the methyl group and the methylene links in the ring. The interaction between the equatorial alkyl group and the carbonyl oxygen constitutes the 2-alkylketone destabilising effect.

In the axial conformation of 3-methylcyclohexane there is only one 1,3-diaxial interaction between the methyl group and the methylene link, since the carbonyl group in the other *meta*-position does not interact with the methyl group. Therefore 3-methylcyclohexanone is more stable than methylcyclohexane to the extent of one 1,3-diaxial methyl--methylene interaction (about 0.9 kcal mole^{-1}). Such relative stabilisation is called the 3-alkylketone stabilising effect.

A quantitative estimate of the 2-alkyl- and 3-alkyl--ketone effects for perhydroindenones containing the oxo--group in the five-membered ring is difficult at present. By a semiempirical procedure it has been estimated as 0.4 kcal mole^{-1}.[26] However the concept of these effects is extremely useful for a qualitative estimate of the stability of stereoisomeric perhydroindenones[3].

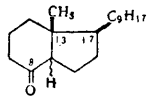
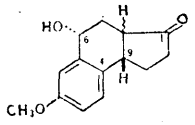
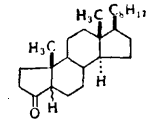
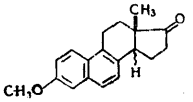
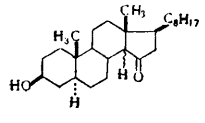
Although only one conformation is possible for *trans*--perhydroinden-1-one, *cis*-perhydroinden-1-ones can exist in two conformations, differing in the nature of the bond joining the carbonyl group with the bridging carbon atom (see Scheme 2). The latter can be either equatorial [*eq*-conformations (Xa) and (XIa)] or axial (*ax*-conformations (Xb) and (XIb)].

The importance of both alkylketone effects in the perhydroinden-1-one series is greater the lower the energy barrier between the *cis*- and *trans*-perhydroindene systems. The data in Table 1 demonstrate the validity of the alkylketone effects as criteria of the stability of the isomeric perhydroindenones.

Apart from the influence of the thermodynamic factor and the alkylketone effects, the equilibrium between the *cis*- and *trans*-forms of the more complex perhydroinden--1-ones greatly depends on fine steric effects acting over short, medium, and long distances[26,40-42]. The question of the stability of the *trans*-junction between the C and D rings in certain 15-oxosteroids is of interest. The evidence quoted by Barton and coworkers[39] in favour of the greater stability of the *trans*-ring fusion in such systems is consistent with the predictions based on an estimate of the alkylketone effects. However, many other 15-oxosteroids exist almost entirely as the *cis*-isomers in alkaline or acid media[26,43,45]. Conformational transmission has no effect on the equilibrium between steroid perhydroindenes[46].

Recently the unusual conversion of *cis*-Δ^5-hexahydroinden-1-one into *trans*-Δ^5-hexahydroindene has been observed in the Wolff–Kischner reduction[47], indicating the intermediate formation of *trans*-Δ^5-hexahydroinden-1-one

TABLE 1.

Perhydroindenone	Ketone effect: 2-alkyl	Ketone effect: 3-alkyl	Stable isomer: theoretical	Stable isomer: experimental	References
Perhydroinden-1-one *trans-* *cis-eq* *cis-ax*	O—C_1—C_8—C_7 — O—C_1—C_8—C_7	— — —	*cis-eq*	*cis*	5 27
Perhydroinden-4-one *trans-* *cis-eq* *cis-ax*	O—C_4—C_9—C_3 O—C_4—C_9—C_3 —	— —	***cis-ax***	***cis***	27–31
8-Methylperhydroinden-1-one *trans-* *cis-eq* *cis-ax*	O—C_1—C_8—C_7 O—C_1—C_8—CH_3 O—C_1—C_8—C_7	— —		*cis*	22
Degradation product of vitamin D  *trans-* *cis-eq* *cis-ax*	O—C_8—C_{14}—C_{15} O—C_8—$C_{14}C_{15}$	O—C_8/C_{13}—CH_3 O—C_8/C_{13}—C_{17} O—C_8/C_{13}—CH_3	*cis-ax*	*cis*	32–34
 *trans-* *cis-eq* (C_5-C_1) *cis-ax* (C_5-C_1)	O—C_1—C_8—C_7 O—C_4—C_9—C_3 O—C_1—C_8—CH_3 — O—C_1—C_8—C_7 O—C_4—C_9—C_3	O—C_4/C_8—CH_3 O—C_4/C_8—CH_3 —	*cis-eq*	*cis*	35, 36
 *trans-* *cis-eq* *cis-ax*	O—C_1—C_8—C_7 — O—C_1—C_8—C_7	— — —	*cis-eq*	*cis*	37
 *trans-* *cis-ax*	O—C_2—C_3—C_5 O—C_3—C_5—C_9	O—C_3/C_{10}—CH_3 O—C_3/C_{10}—C_9		*cis*	38
 *trans-* *cis-eq* *cis-ax*	O—C_{17}—C_{13}—C_{12} O—C_{17}—C_{13}—C_{12} O—C_{17}—C_{13}—CH_3	— —		*cis* (luminiequilenin or isoequilenin)	22, 23
 *trans-* *cis-*	O—C_{15}—C_{14}—C_8 O—C_{15}—C_{14}—C_8	O—C_{15}/C_{15}—CH_3 —	*trans*	*trans*	39

under alkaline conditions. In view of this finding it is necessary to treat with caution the alkylketone effects as stability criteria.

III. EFFECT OF THE THERMODYNAMIC FACTOR ON THE RELATIVE STABILITIES OF THE *cis*- AND *trans*--ISOMERS

From the point of view of the second law of thermodynamics, the fact that although *cis*-perhydroindene systems have higher heats of combustion *cis*-perhydroindene-1-ones are nevertheless the more stable[48] is not paradoxical. Since the free energy of a process is given by

$$\Delta F = \Delta H - T\Delta S,$$

it is not permissible to identify the difference in heat content with the free energy change determining the mode of isomerisation. In those systems where the role of the entropy factor is small (for example, in decalin) ΔF may be regarded as approximately equal to ΔH. If, however, the entropy factors of two isomers differ significantly from each other, the second term in the equation cannot be disregarded. In particular if the entropy of the *cis*-perhydroindene system is higher than that of the *trans*-perhydroindene system, the free energy of isomerisation at high temperatures will favour the formation of the *cis*-isomer although the latter has the higher heat content.

Thermochemical investigation of the equilibrium between *cis*- and *trans*-perhydroindene[8] confirms this hypothesis. The low value of ΔH (about -1 kcal mole^{-1}) is explained by the appreciable strain in *trans*-perhydroindene, unlike its homologue *trans*-decalin. The low value of the energy difference between *cis*- and *trans*-perhydroindenes is satisfactorily consistent with the fact that in the *trans*-perhydroindene system 1,3-diaxial interaction is more intense and in the *cis*-perhydroindene system less intense than in the unstrained chair conformation of the 6-membered ring.

The value $\Delta S = -2.3 \pm 0.1$ e.u. is of particular significance for the perhydroindene system. if the entropy is regarded as a function of the order of symmetry of the molecule (which ideally is two for *trans*-perhydroindene and one for *cis*-perhydroindene), the maximum value of ΔS can be only 1.4 e.u. The high value of the observed ΔS implies that in the *trans*-isomer the five-membered ring is more stretched and flattened than in the *cis*-isomer. Therefore *cis*-perhydroindene should show a greater capacity for pseudorotation of the five-membered ring. The presence of such an additional degree of freedom appears to be in fact responsible for the high entropy of the *cis*-isomer.

Allinger *et al.*[26] proposed an interesting empirical method for the calculation of the energy content of perhydroindene derivatives differing only in the type of ring junction. The properties of substituted perhydroindenes may be predicted provided that the properties of the corresponding pair of decalins and the "perturbation constant" (difference between the values of ΔF for the isomerisation of decalin and perhydroindene), which includes an entropy factor, are known. This method of calculation of the energy barrier between the *trans*- and *cis*-forms of perhydroindene, based on the "perturbation constant" (about 2.3 kcal mole^{-1}), gave satisfactory results for five pairs of steroid perhydroindenones. It must, however, be mentioned that in the calculation of the energy content of the isomers the 2-alkylketone effect for perhydroindenones was arbitrarily estimated as 0.4 kcal mole^{-1}.

There are many examples supporting the view that five-membered ring closure reactions of 1,2-disubstituted cyclohexanes and the analogous pyranoside systems occur readily with the *cis*-isomers but not with the *trans*-isomers. This also applies to reactions which while not forming cyclic products nevertheless take place *via* a transition state with a five-membered ring. Thus lead tetraacetate oxidises *cis*-cyclohexane-1,2-diol 22 times faster than the corresponding *trans*-isomer. This is because the five-membered transition complex forms more readily in the case of the *cis*-isomer[49]. The same phenomenon is observed in the oxidation of these diols by periodic acid[50]. Examination of the hydrogen-bond bands in the infrared spectra of stereoisomeric cyclohexane-1,2-diols[51] shows that the stability of the hydrogen bonded five-membered ring is greater with the *cis*-diol than with the *trans*-diol. Electron diffraction study of these diols[52] leads to the same finding.

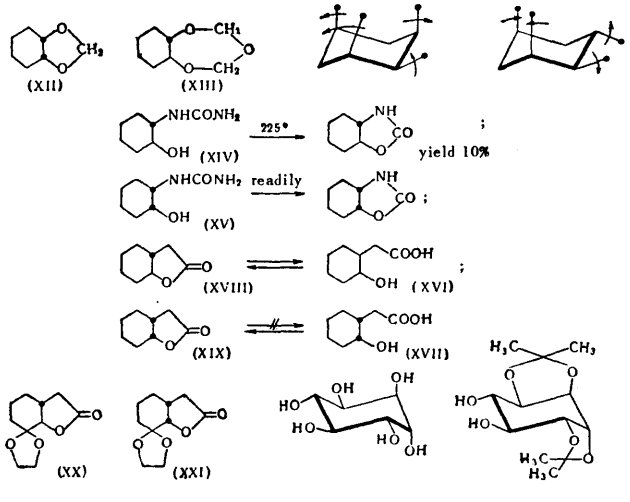
Reactions of the stereoisomeric cyclohexane-1,2-diols with carbonyl compounds are good examples of the preferential *cis*-cyclisation. Reaction of formaldehyde with the *cis*-diol yields *cis*-hexahydrobenzo-1,3-dioxolane (XII) in 74% yield, whereas the *trans*-diol is converted under analogous conditions into compound (XIII) in only 19% yield[53]. Mousseron *et al.*[54] noted differences in the ease of formation of cyclic sulphites from the isomeric cyclohexane-1,2-diols. They also showed that there are differences in the ease of cyclisation of the epimeric 2-hydroxycyclohexylureas (XIV) and (XV) into hexahydrobenzoxazole derivatives[55]. Investigation of the acyl rearrangement of the stereoisomeric *cis*- and *trans*-2-benzamidocyclohexanols, involving a five-membered transition complex, showed that the *cis*-isomer undergoes this reaction much more readily than does the *trans*-isomer[56].

Whereas *trans*-1-hydroxycyclohexane-2-acetic acid (XVI) is stable, its *cis*-isomer (XVII) does not exist in a free state because of spontaneous lactonisation. The *trans*-lactone (XVIII) undergoes ring-opening on hydrolysis, whereas the *cis*-lactone (XIX) resists hydrolysis[57]. Similar relations are observed in the hydrolysis of the γ-lactones (XX) and (XXI) where the hydroxy-acid corresponding to the *cis*-lactone (XXI) cannot be isolated from the alkaline solution due to relactonisation[58].

Angyal and Macdonald made an interesting study of the formation of the acetonides of inositol and epiinositol[59]. They showed that the acetone groups in the mono- and di-acetonides of these alcohols are combined only with the *cis*-hydroxy-groups, whereas the third acetone molecule is capable of binding also *trans*-*ortho*-groups. On the basis of this reaction, the hypothesis was put forward for the first time that *cis*-cyclisation takes place preferentially because in this process the axial *meta*-substitutents move away from one another and there is a decrease in 1,3-diaxial interactions. Conversely, in *trans*-cyclisation the axial *meta*-substituents approach one another due to "wrinkling" of the cyclohexane ring and such cyclisation is therefore unfavourable.

The above findings show that the formation under cyclisation conditions of a *cis*-junction between five- and six-membered rings is thermodynamically more favourable than the formation of a *trans*-linked system. Although this situation applies strictly only to systems where there are no appreciable repulsive forces between the links in the five-membered ring and the adjacent bridging atoms or axial hydrogen atoms in the six-membered ring [for example in dioxolane (XII)], it is reasonable to suppose that it does apply to the perhydroindene system.

Scheme 3



IV. STEREOCHEMISTRY OF PERHYDROINDENE DERIVATIVES

1. Solvolysis and Deamination

Solvolysis of esters has been throughly investigated only in the case of the *cis*-perhydroindenols. In the analysis of the results obtained account must be taken of the possibility

of a change in conformation of the *cis*-perhydroindene system. The results of the alkaline hydrolysis of hydrogen succinates and hydrogen phthalates of the isomeric *cis*-perhydroindenols[60], with corrections based on a reexamination of the configurations of the initial alcohols[24], are presented in Table 2. It is evident from a comparison of these data with the results of hydrolysis of the stereoisomeric *cis*-1-decalol and *cis*-2-decalol[60,61] that there is an analogy in the behaviour of the stereoisomeric *cis*-decalols and *cis*-perhydroindenols.

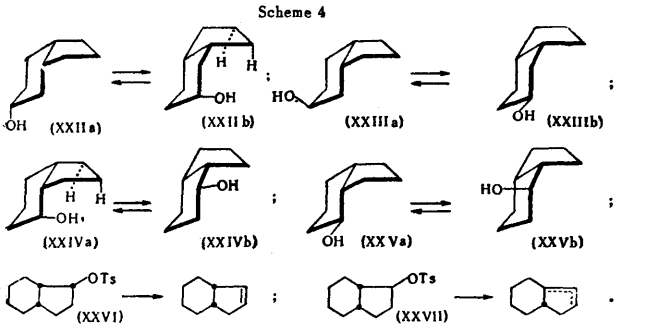
The hydrogen succinate of *cis*-*cis*-perhydroinden-5-ol (XXII) is hydrolysed appreciably more rapidly than the hydrogen succinate of the *cis*-*trans*-isomer (XXIII). This shows that the *cis*-perhydroindene system has the capacity for change in conformation similar to that observed for the *cis*-decalin system. The *cis*-*cis*-isomer exists preferentially in one (equatorial) conformation (XXIIa), whereas the energy barrier between the conformations of *cis*-*trans*-perhydroinden-5-ol (XXIIIa) and (XXIIIb) is much less. A characteristic feature is that weakening of 1,3-diaxial interactions reduces the differences in the rates of hydrolysis of the esters of *cis*-*cis*- and *cis*-*trans*-perhydroinden-5-ols compared with those of the corresponding decalols. It is reasonable to expect that *cis*-perhydroinden-4-ols will also exhibit a similar capacity for change in conformation. However, the relative behaviour of the isomers in this case is more complex. The rates of hydrolysis of the isomeric hydrogen succinates and hydrogen phthalates are similar, but among the former the hydrolysis of the *cis*-*trans*-isomer (XXV) takes place at a higher rate whereas among the latter that of the *cis*-*cis*-isomer (XXIV) is more rapid. Evidently the weakening of the 1,3-diaxial interactions in the perhydroindene system reduces in this case the energy difference between the pairs of conformers (XXVa ⇌ XXVb) and (XXVIa ⇌ XXVIb) and the slight predominance of one or other conformation in the mixture depends on the nature of the ester group.

Perhydroinden-1-yl toluene-*p*-sulphonate (XXVI) (m.p. 18°) hydrolyses so rapidly that the rate of hydrolysis cannot be measured, yielding *cis*-Δ^2-hexahydroindene. The epimeric toluene-*p*-sulphonate (XXVII) is hydrolysed at the same rate as the toluene-*p*-sulphonate of *trans*-2-methylcyclopentanol forming a mixture of olefins in more than 90% yield[62]. The exclusive formation of *cis*-Δ^2-hexahydroindene from the toluene-*p*-sulphonate (XXVI) confirms the *cis*-*cis*-configuration of the corresponding alcohol. Similar observations were made in the hydrolysis of the stereoisomeric *cis*-perhydroinden-4-ols. Here too the most stable is the toluene-*p*-sulphonate of the *cis*-*cis*-isomer in which the orientation of the toluene-*p*-sulphonyloxy-group (OTs) is favourable for scission according to Markovnikov's rule[63].

TABLE 2.

Initial alcohol	M.p., °C	Hydrolysis of hydrogen succinate, $K_{40°} \times 10^5$	Hydrolysis of hydrogen phthalate, $K_{50°} \times 10^5$
cis-cis-Perhydroinden-5-ol	43	1.172	—
cis-trans-Perhydroinden-5-ol	20	0.955	—
cis-cis-Perhydroinden-4-ol	16—31	0.5067	0.0349
cis-trans-Perhydroinden-4-ol	liq.	0.5264	0.0311
cis-cis-Perhydroinden-1-ol	liq.	0.768	0.0467
cis-trans-Perhydroinden-1-ol	18	0.943	0.0536
cis-cis-Perhydroinden-2-ol (?)	5	0.850	—
cis-trans-Perhydroinden-2-ol (?)	21	1.133	

Scheme 4



The action of nitrous acid on the amines of the *cis*-perhydroindene series was investigated by Hückel[21]. The results of deamination, allowing for corrections based on a reexamination of the configurations[24], are presented in Table 3.

Results for the deamination of 4-amino- and 5-amino-*cis*-perhydroindenes have been compared with those for the deamination of 1-amino- and 2-amino-*cis*-decalins[21,61]. An obvious analogy was found between the behaviour of aminoperhydroindenes with the amino-group in the six-membered ring and aminodecalins.

In all cases the main product of the deamination of amines with the *cis*-*cis*-configuration is the alcohol with the same configuration as the initial amine. This shows that the amino-group in these isomers behaves as an equatorial substituent, which in turn is satisfactorily consistent with the concept of the ease of conversion from one conformation to another in the *cis*-perhydroindene system, by a

TABLE 3.

Initial amine	Deamination products
cis-cis	>90% + traces
cis-trans	64% + 16% + 20%
cis-cis	80% + 20%
cis-trans	48% + 12% + 40%
cis-cis (?), benzoyl derivative, m.p. 180°	52% + 13% + 35%
cis-trans (?), benzoyl derivative, m.p. 135°	7% + 63% + 30%
cis-cis (?), benzoyl derivative, m.p. 144°	80% + ~20% + traces
trans-cis = *trans-trans*	=

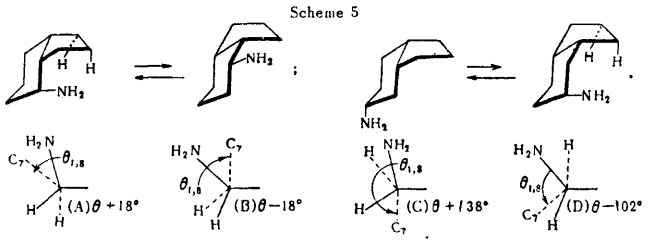
virtue of which the most bulky substituent tends to assume an equatorial orientation. However, depending on the configuration of the molecule, one of the conformers may predominate or both forms, with axial and equatorial orientation of the amino-group, may be present. In the case of the *cis*-*cis*-isomer one of the conformations predominates and the amine reacts almost entirely in this form (with the equatorial position of the amino-group) (see Scheme 5).

With *cis*-*trans*-isomers the difference in stability of the conformers is slight and therefore they behave as a mixture of equatorial and axial amines, *i.e.* their deamination yields together with the alcohol having the initial configuration an appreciable amount of the alcohol with the inverted configuration and an olefin.

In order to interpret the results of deamination of the stereoisomeric 1-amino-*cis*-perhydroindenes, it is necessary to bear in mind the following considerations[64]. If the projection formulae of 1-aminoperhydroindenes are considered from the side of their five-membered ring (see Scheme 5)†, then in the *cis*-*cis*-isomer steric compression will be the same in both conformations (A) and (B). In contrast to this, in the *cis*-*trans*-isomer smaller steric compression will be observed in conformation (C), as a result of which the substituent in the preferred conformation will possess quasi-axial character (the projection angle θ, which is 0° for the *cis*-isomer and 120° for the *trans*-isomer, can vary within ±18° in a planar model of the five-membered ring). In conformity with this finding, deamination of *cis*-*trans*-1-aminoperhydroindene yields 63% of the alcohol with the inverted configuration and 30% of olefins. In the case of the *cis*-*cis*-isomer the relative contribution of the "equatorial character" is reflected in a reduced yield of the alcohol with the inverted configuration. Thus 1-amino-*cis*-perhydroindenes react similarly to 1-amino-*cis*-decalins. The reactivity of the amino-group in 2-amino-*cis*-perhydroindenes is similar to that of aliphatic amines: deamination of the single known 2-amino-*cis*-perhydroindene results in formation only of alcohols with inverted and initial configurations.

The only amine of the *trans*-perhydroindene series investigated is 2-amino-*trans*-perhydroindene which on deamination is quantitatively converted into *trans*-perhydroinden-2-ol.[5] It appears[64] that here we have 100% inversion of configuration. The lack of data on deamination of *trans*-perhydroindene amines is partly compensated by the work of Shoppee[64,65] on deamination of norsteroid amines. It is known that reaction of nitrous acid with steroids having axial amino-groups does not yield alcohols with inverted configuration (in contrast to the amines of the cyclohexane and decalin series), only the corresponding axial alcohols and olefins being formed.

Scheme 5



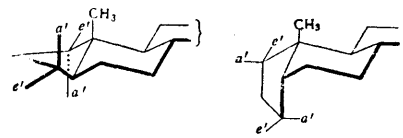
† Scheme 5 appears, however, to relate to 4- and 5-amino-perhydroindenes (Ed. of Translation).

In the presence of a fixed cyclopentane ring in the rigid norsteroid system the quasi-axial and quasi-equatorial character of the bonds at atoms adjoining bridge atoms should be very pronounced, unlike that of the bonds at the more distant fifth atom. The difference between the *cis*- and *trans*-ring fusion is now unimportant. It may be expected therefore that the quasi-axial norsteroid amines will behave like the truly axial steroid amines, *i.e.* will form either the alcohol with the same configuration or an olefin, whereas quasi-equatorial norsteroid amines will yield equatorial alcohols. In those cases where the amino-group is distant from the ring junction it will react like an aliphatic amino-group, *i.e.* will yield mainly the alcohol with the inverted configuration. The results of deamination of steroid amines confirm this hypothesis (see Table 4).

Table 4 shows that the amino-group in the rigidly fixed five-membered ring indeed exhibits more clearly its axial or equatorial properties (examples 2, 4, and 5 and to a lesser extent example 1). The amino-group distant from ring junction behaves as in aliphatic amines (example 3).

The relative stability of the epimeric alcohols or amines formed on reduction of perhydroindenones or their oximes may be estimated by determining with sodium in xylene. Hückel[21] compared the results obtained in the *cis*-perhydroindene and *cis*-decalin series. The results, allowing for later corrections to the configurations[24,61], are presented in Table 5.

TABLE 4.



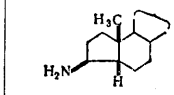
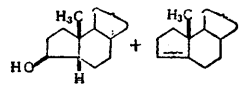
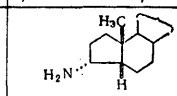
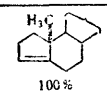
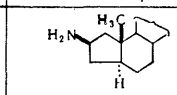
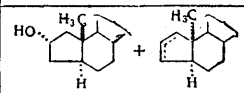
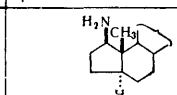
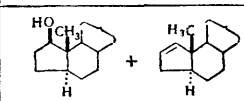
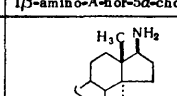
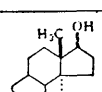
No. of example	Initial amine	Orientation of NH_2 group	Reaction products and their yield
1	 3β-amino-A-nor-5β-cholestane	e′	 40% 59%
2	 3α-amino-A-nor-5β-cholestane	a′	 100%
3	 2β-amino-A-nor-5α-cholestane	as in aliphatic amines	 93% 3%
4	 1β-amino-A-nor-5α-cholestane	e′	 80% 20%
5	 17β-amino-5α-androstane and 17β-amino-androst-6-en-3β-ol	e′	 100%

TABLE 5.

Initial ketone	Method of reduction and alcohol formed		Composition of mixture of alcohols after boiling with Na
	Na in alcohol	H_2/Pt in CH_3COOH	
cis-1-Decalone	*trans-trans*-1-decalol (epimerisation at $C_{(5a)}$)	*cis-cis*-1-decalol (~100%)	*trans-trans*-1-decalol
cis-Perhydroinden-4-one	*cis-trans*-perhydroinden-4-ol (~100%)	*cis-cis*-perhydroinden-4-ol (~100%)	*cis-trans* (80%) + + *cis-cis* (20%)
cis-Perhydroinden-1-one	*cis-cis*-perhydroinden-1-ol (~80%)	*cis-cis*-perhydroinden-1-ol (~100%)	*cis-cis* (50%) + + *cis-trans* (50%)
cis-2-Decalone	*cis-cis*-2-decalol (80%)	*cis-cis*-2-decalol (~100%)	*cis-cis* (80%) + + *cis-trans* (20%)
cis-Perhydroinden-5-one	*cis-trans*-perhydroinden-5-ol (80%)	*cis-cis*-perhydroinden-5-ol (~100%)	*cis-trans* (80%) + + *cis-cis* (20%)
cis-Perhydroinden-2-one	*cis-trans*-perhydroinden-2-ol (? 75%)	*cis-trans*-perhydroinden-2-ol (? 90%)	not established

As with perhydroinden-5-ol, in the case of perhydroinden-4-ol the most stable are the *cis-trans*-isomers (XXIII) and (XXV), where the interaction between the hydroxy--group and the methylene link is a minimum in any of the conformers, not exceeding that in cyclohexanol. However, the predominance of *cis-trans*-perhydroinden-5-ol in the equilibrium mixture has no analogy among the *cis*-2-decalols where the *cis-cis*-isomer is the most stable. This is probably due to different strengths of the 1,3-diaxial interactions in the *cis*-perhydroindene and *cis*-decalin systems.

Reduction of *trans*-perhydroinden-5-one with sodium in alcohol or with lithium aluminium hydride yields *trans--cis*-perhydroinden-5-ol with an equatorial hydroxy-group, whereas catalytic hydrogenation of this ketone results in the formation of only 25% of the *trans-trans*-isomer with an axial hydroxy-group. On heating with sodium, the latter is readily epimerised to the *trans-cis*-isomer[66].

Reduction of the oximes of the ketones yields amines whose configuration has been confirmed by means of the deamination reaction (see above). The results obtained[21] are presented in Table 6.

Tables 5 and 6 show that reduction of ketones and their oximes under similar conditions does not always give alcohols and amines with the same configuration. However, the configuration of the amines obtained under similar conditions from the oximes of *cis*-1- and *cis*-2-decalones and *cis*-perhydroinden-4-one and *cis*-perhydroinden--5-one are identical.

TABLE 6.

Initial ketone	Method of reduction of oxime and configuration of amines	
	Na in alcohol	H_2/Pt in CH_3COOH
cis-1-Decalone	*cis-trans*	*cis-cis*
cis-Perhydroinden-4-one	*cis-trans*	*cis-cis*
cis-Perhydroinden-1-one	m.p. of benzoyl derivative 135°	m.p. of benzoyl derivative 180°
cis-2-Decalone	*cis-cis*	mixture of *cis-cis* + + *cis-trans**
cis-Perhydroinden-5-one	*cis-cis*	*cis-trans*
cis-Perhydroinden-2-one	m.p. of benzoyl derivative 133°–139°	m.p. of benzoyl derivative 144°

* Yield of amine mixture 9%.

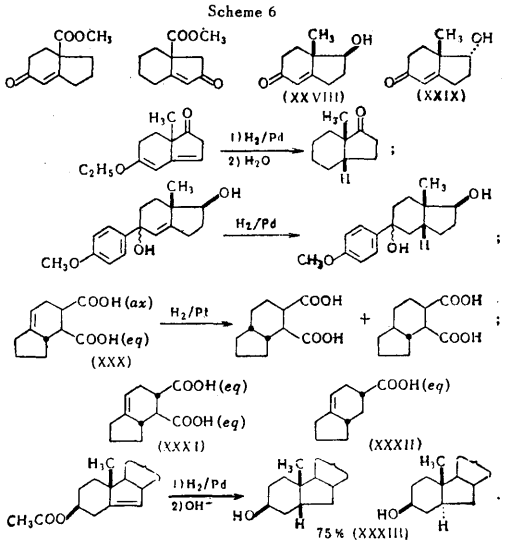
2. Catalytic Hydrogenation

Catalytic hydrogenation of systems such as $\Delta^{1(9)}$-octalin and Δ^4- and Δ^5-unsaturated steroids results mainly in isomers in which both six-membered rings are *trans*-linked. The main product of hydrogenation of 9-ethoxycarbonyl-Δ^4--3-octalone is 9-ethoxycarbonyl-*trans*-3-decalone[67]. Hydrogenation of 9-methyl-*cis*-$\Delta^{4(10),5}$-1-hexalinol and 5-ethoxy-9-methyl-$\Delta^{4(10),5}$-1-hexalinone also yields only *trans*-decalin derivatives[68]. In the catalytic hydrogenation of cholesterol in a neutral medium the yield of 5α-cholestanol exceeds 90%.[69] Similar results were obtained in the hydrogenation of numerous Δ^4- and Δ^5-steroids[70–73].

The situation is different in the case of perhydroindene compounds with the same structure. Here catalytic hydrogenation of the double bond at the ring junction results in preferential formation of the *cis*-perhydroindene system regardless of the reduction conditions. Reduction of $\Delta^{3a(4)}$-hexahydroinden-5-one over a palladium catalyst yields *cis*-perhydroinden-5-one.[74,75]. The *cis*-perhydroindene system is also formed on hydrogenation of 7a-methyl--$\Delta^{3a(4)}$-hexahydroinden-5-one [76] and 6-ethoxycarbonyl--$\Delta^{3a(4)}$-hexahydroinden-5-one [77]. It was shown recently that regardless of conditions hydrogenation of 7a-methoxycarbonyl-$\Delta^{3a(4)}$-hexahydroinden-5-one invariably yields only 7a-methoxycarbonyl-*cis*-perhydroinden-5-one. On catalytic hydrogenation of 7a-ethoxycarbonyl-$\Delta^{3(3a)}$-hexahydroinden-2-one in a neutral, acid, and alkaline medium, 7a-ethoxycarbonyl-*cis*-perhydroinden-2-one is invariably obtained[78]. Hydrogenation of the epimeric-1-hydroxy-7a--methyl-$\Delta^{3a(4)}$-hexahydroinden-5-ones (XXVIII) and (XXIX) forms only products with *cis*-linked rings whatever the mutual disposition of the methyl and hydroxy-groups[79].

Boyce and Whitehurst[80] studied the behaviour of $\Delta^{3a(4)}$--hexahydroindene-1,5-dione, 1-hydroxy-$\Delta^{3a(4)}$-hexahydroinden-5-one, $\Delta^{3a(4)}$-hexahydroindene-1,5-diol (two epimers), and certain other $\Delta^{3a(4)}$- and $\Delta^{3(3a)}$-hexahydroindenes under conditions of catalytic hydrogenation and reduction with lithium in liquid ammonia. In all cases *cis*-perhydroindene derivatives were the only reaction products (see Scheme 6).

Scheme 6



Hydrogenation of $\Delta^{3(3a)}$-hexahydroinden-3-carboxylic acid yields only *cis*-perhydroindene-1-carboxylic acid[81]. Despite the screening of the double bond by the axial carboxy-group in *cis*-*anti*-Δ^{7}-hexahydroindene-4,5-dicarboxylic acid (XXX) the principal product of hydrogenation is *cis*-*anti*-*cis*-perhydroindene-4,5-dicarboxylic acid, *i.e.* the *cis*-perhydroindene system is formed by addition of hydrogen from the sterically hindered side[25]. In those cases where the screening of the double bond is equal on either side, as for example in acids (XXXI) and (XXXII), hydrogenation results in the formation of only the *cis*-perhydroindene system[25,82].

The preferential formation of the isomer with *cis*-junction between rings A and B is also observed in the hydrogenation of B-norcholesterol acetate; the *trans*-A/B-configuration initially ascribed to the reaction product (XXXIII) was later corrected[83,84].

When an oxo-group adjoins the ring junction, it is reasonable to expect that hydrogenation of the double bond will result in the formation of *cis*-perhydroindenone under any conditions. Indeed catalytic hydrogenation of $\Delta^{3a(7a)}$-hexahydroinden-1-one and three of its higher analogues both in acid and alkaline media yields only isomers in which the rings are *cis*-linked[85].

The data discussed above show that in the reduction of systems of the type of $\Delta^{3a(4)}$- and $\Delta^{3(3a)}$-hexahydroindene addition of hydrogen can occur from the most screened side so that the main reaction product is the isomer with *cis*-linked rings. The general validity of this rule suggests that in the reduction of the above systems the entropy factor, favouring the formation of the *cis*-perhydroindene system, is decisive.

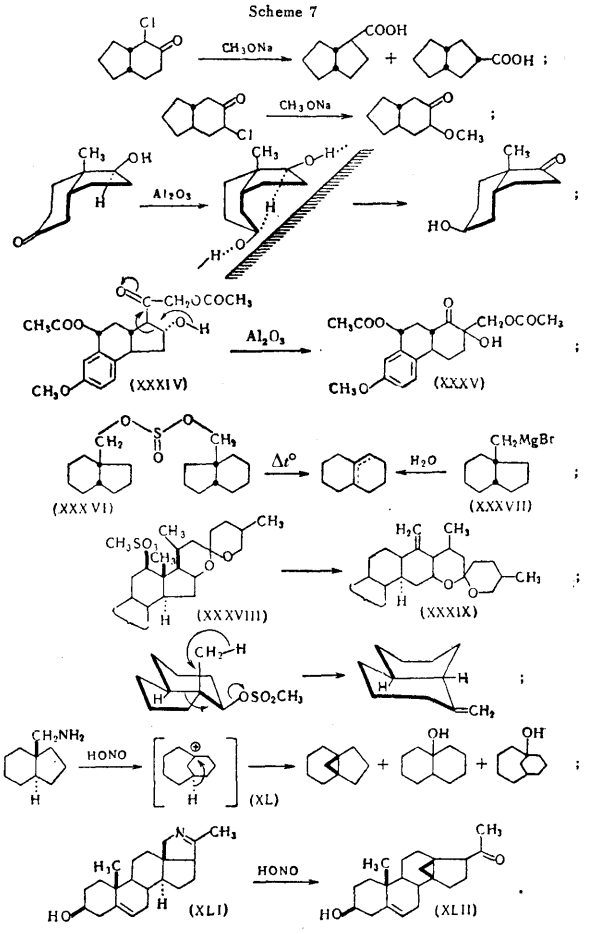
3. Rearrangement of Perhydroindene Derivatives

The influence of steric factors on the mode and nature of rearrangement of the perhydroindene system has been observed in only a few cases. Action of sodium methoxide on 4-chloro-*cis*-perhydroinden-5-one results in 78% yield of equal amounts of *cis*-*trans*-bicyclo[3,3,0]octane-2-carboxylic and *cis*-*cis*-bicyclo[3,3,0]octane-3-carboxylic acids[86]; the formation of both these products is consistent with the usual course of the Favorskii rearrangement. However, the action of sodium methoxide on 5-chloro-*trans*-perhydroinden-6-one does not result in reduction of ring size, since the *trans*-bicyclo[3,3,0]octane system would be very strained. The main reaction product is 5-methoxy-*trans*-perhydroinden-6-one.[87] 7a-Methyl-*cis*-*trans*-1-hydroxyperhydroinden-5-one (but not its *cis*-*cis*-isomer) readily undergoes, on activated alumina under mild conditions, an interesting rearrangement into 7a-methyl-*cis*-*trans*-5-hydroxyperhydroinden-1-one[79]. By virtue of the *cis*-junction between the rings the boat conformation arises on sorption, in which intramolecular and intermolecular shifts occur simultaneously (see Scheme 7); the *trans*-annular 1,5-transfer of hydrogen is in this case the same as in the cyclononane system. It is noteworthy that the isomerisation results in the formation of a system with a trigonal hydrogen atom in the five-membered ring and a tetrahedral atom in the six-membered ring. 3a-Methyl-*cis*-*trans*-1-hydroxy-6-decalone does not undergo a similar rearrangement. Another interesting rearrangement on alumina involves the expansion of the five-membered ring in compound (XXXIV) with formation of structure (XXXV).[37]

A rearrangement of the neopentyl type was observed on distillation of the sulphite (XXXVI) or in the hydrolysis of the organomagnesium compound (XXXVII); in both cases a mixture of $\Delta^{1(9)}$- and Δ^{9}-octalins was formed[88]. A very interesting rearrangement occurs during solvolysis of recogenine 12β-methylsulphonate (XXXVIII), resulting in the formation of C-nor-D-homosapogenin (XXXIX); this reaction is interesting from the point of view of the biosynthesis of certain steroid alkaloids[89]. It would be of interest to investigate the possibility of a similar rearrangement in the case of the simplest model — 8-methyl-*trans*-*trans*-perhydroinden-4-yl methylsulphonate (see Scheme 7).

The action of nitrous acid on 3a-aminomethyl-*trans*-perhydroindene results in a mixture of 74% of tricyclo[4,3,1,$0^{1,5}$]decane, 16% of 9-hydroxydecalin, and 6% of bicyclo[4,3,1]decane-1-ol instead of 7a-hydroxymethyl-*trans*-perhydroindene[90]; apparently the reaction proceeds *via* the intermediate formation of the ion (XL). This reaction also occurs in the steroid series. Thus action of nitrous acid on *N*-desmethylcona-5,*N*(20)-dien-3β-ol yields 14β,18-cycloprogesterone[90,91]. Deamination of 5-aminomethyl-*cis*-perhydroindene results in only one of the possible hydroxyazulenes. On deamination of 5-aminomethyl-6-methyl-*cis*-perhydroindene (the configurations at $C_{(5)}$ and $C_{(6)}$ are unknown), a mixture of both isomeric azulene alcohols is formed[92].

Scheme 7

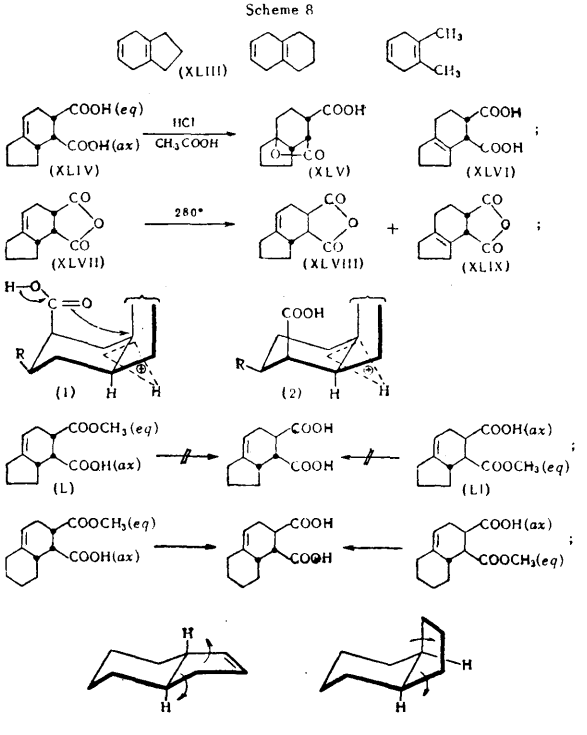


4. The Double Bond in the Perhydroindene System

The relation between the steric factors and the position and nature of the double bond in the perhydroindene system is of considerable interest. Comparison of the reactivity of cyclohexene (for which two half-chair conformations are possible) and *trans*-Δ^5-hexahydroindene (in which the six-membered ring is rigidly fixed by the five-membered ring in a single half-chair conformation) showed that the rate of epoxide formation is the same with both substances, but that hydrogenation of *trans*-Δ^5-hexahydroindene is slower[93]. There are data showing that the intercyclic $\Delta^{3a(7a)}$-double bond in the perhydroindene system is the most stable. Thus when indane is reduced with lithium in liquid ammonia the only reaction product is $\Delta^{3a(7a)5}$-tetrahydroindene (XLIII), virtually free of the possible byproduct of $\Delta^{4,7}$-tetrahydroindene[94]. Pyrolysis of the oxalate of *cis*-perhydroinden-7a-ol results in smooth formation of only $\Delta^{3a(7a)}$-hexahydroindene[95]. Earlier literature[96-98] quotes several instances in which the double bond in unsaturated perhydroindene derivatives was displaced to a "deeper" position (ultimately to the 3a,7a-position) by the action of both alkaline and acid reagents.

Lactonisation of *cis-cis*-Δ^7-hexahydroindene-4,5-dicarboxylic acid (XLIV) by hydrogen chloride in acetic acid yields γ-lactone acid (XLV) and, in addition, *cis*-$\Delta^{3a(7a)}$-hexahydroindene-4,5-dicarboxylic acid (XLVI). The orientation of the double bond in the last compound was demonstrated by a number of reactions. On heating with hydrogen chloride the γ-lactone acid (XLV) is itself slowly converted into the *cis*-carboxylic acid (XLVI), which is evidence of the stability of the latter[99]. Thermal isomerisation of the anhydride of *cis-cis*-Δ^7-hexahydroindene-4,5-dicarboxylic acid (XLVII) to the *cis-trans*-anhydride (XLVIII) is also accompanied by the formation of a very small amount of the *cis*-anhydride (XLIX) due to migration of the double bond[100].

Scheme 8



In order to account for the difference between the *cis-cis*-dicarboxylic acid (XLIV) and the analogous *cis-cis*-Δ^4-octalin-1,2-dicarboxylic acid (which is only lactonised by hydrogen chloride[101]), it was suggested that both the lactonisation and the double bond isomerisation take place *via* a common non-planar carbonium ion with a quasi-*cis*-junction between the rings (see Scheme 8). In the Δ^7-hexahydroindene series this reduces the probability of lactonisation [shift (1)] because of the increase in the distance between the axial *meta*-substituents which occurs in the *cis*-perhydroindene system. If lactonisation is excluded for steric reasons, the mode of reaction will be determined solely by shift (2), *i.e.* by the displacement of the double bond from the *exo*-position (in relation to the unsubstituted ring) to the intercyclic *endo*-position. A shift of this kind occurs more readily in the cyclopentane than in the cyclohexane system[102,103]. Therefore isomerisation involving displacement of the double bond across the ring junction is more probable in the perhydroindene than in the octalin series. Indeed, acids cause easy migration of the double bond from the Δ^7- to the $\Delta^{3a(7a)}$-position in perhydroindene[82,99,100]. It is noteworthy that the $\Delta^{3a(7a)}$-double bond in $\Delta^{3a(7a),5}$-tetrahydroindene (XLIII) is more reactive than the analogous bond in $\Delta^{2,8a}$-tetrahydronaphthalene or in 1,2-dimethylcyclohexa-1,4-diene.[104]

The influence of the Δ^7-double bond on the conformational flexibility of the monoesters of *cis-cis*-Δ^7-hexahydroindene-4,5-dicarboxylic (L) and *cis-trans*-Δ^7-hexahydroindene-4,5-dicarboxylic (LI) acids is interesting. Whereas the monoesters of the octalin series with a similar structure undergo epimerisation of the equatorial methoxycarbonyl group under the action of sodium methoxide[105], the monoesters (L) and (LI) are hydrolysed to the initial acids. This is interpreted as due to lack of conformational changes in the Δ^7-hexahydroindene series so that the equatorial methoxycarbonyl group cannot assume the axial orientation necessary for epimerisation[100]. It may be expected that as a result of the influence of the six-membered ring the strain in the cyclopentene ring in conformation C_s in the Δ^2-hexahydroindene system will be respectively somewhat greater and smaller than in cyclopentene itself when the rings are *trans*- and *cis*-linked. In the first case the $C_{(3)}$ and $C_{(7a)}$ atoms tend to come out of the plane of the double bond whereas in the second the influence of the six-membered ring favours their retention in this plane. As a result, the relative stabilisation on transition from *trans*-perhydroindene to *trans*-Δ^2-hexahydroindene is smaller and on transition from *cis*-perhydroindene to *cis*-Δ^2-hexahydroindene greater than on transition from cyclopentane to cyclopentene. Indirect support is lent to this conclusion by the low tendency of *trans*-perhydroinden-2-ol to dehydrate[5], the ease of isomerisation of *trans*-Δ^2-hexahydroindene-2-acetic acid to *trans*-2-carboxymethyleneperhydroindene[96], and the exclusive formation of *cis*-Δ^2-hexahydroindene on solvolysis of *cis-trans*-perhydroinden-1-yl toluene-*p*-sulphonate[62].

5. Other Reactions

The effect of the orientation of ring fusion on the reactivity of isomeric derivatives of perhydroindene is clearly

shown in the difference between *trans*- and *cis*-perhydroinden-2-ones. Thus the *trans*-isomer condenses with cyanoacetic ester in the presence of ammonia to yield more than 60% of the spirane (LII) whereas in the second case the yield of the analogous compound (LIII) does not exceed 5%. The same condensation in the presence of piperidine results in the formation of *trans*-2-(carboxycyanomethylene)perhydroindene (LIV) in more than 70% yield, whereas the yield of the corresponding *cis*-isomer (LV) is very low. Addition of hydrocyanic acid to the isomers (LVI) and (LV), involving the transition of the $C_{(2)}$ atom in the perhydroindene ring from the trigonal to the tetragonal configuration, takes place much more slowly in the case of the *cis*--isomer (LV). Finally, the Reformatskii reaction between perhydroinden-2-ones and ethyl bromoacetate proceeds much more readily with the *trans*-isomer than with the *cis*--isomer[104].

The relative reactivity of the isomeric *trans*- and *cis*--perhydroindene-2,2-diacetic acid towards Volhard–Zelinskii bromination is also of interest[105]. In the *trans*-isomer the two bromine atoms are equally distributed between both chains with formation of the acid (LVI), whereas in the *cis*-isomer both bromine atoms turn up in one side chain, and after hydrolysis compound (LVII) is formed.

These differences in the reactivities of *trans*- and *cis*--perhydroinden-2-ones and their derivatives can be readily explained on the basis of steric models of 2,2-disubstituted perhydroindenes (see Scheme 9). The transition of the $C_{(2)}$ atom from the trigonal to the tetrahedral configuration in the *trans*-isomer does not result in any appreciable interaction between the R_1 and R_2 substituents and the axial hydrogen atoms in the six-membered rings. However, in the *cis*-isomer such transition is inhibited because of the repulsion between the R_1 group and one of the axial hydrogen atoms in the six-membered ring. A similar effect operates when the size of R_1 is increased, as can be seen from the formation of (LVI) and (LVII), for example.

Several cases are known in which the five-membered and six-membered rings of the perhydroindene system behave independently and follow the same steric rules as those found for cyclopentanes and cyclohexanes. Thus in

Scheme 9

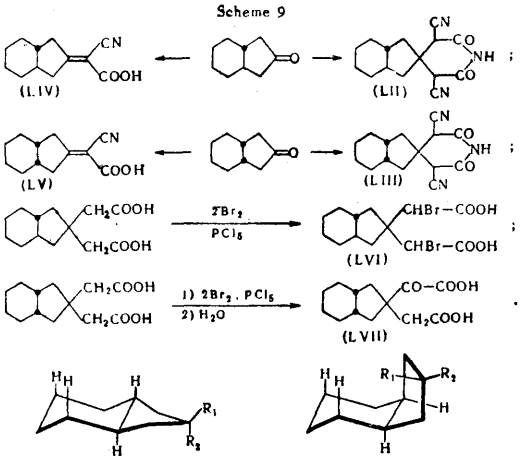


TABLE 7.

Electronegative substituent	Percentage of αβ-isomer in equilibrium mixture			
	CH_2X	CH_2X	CH_2X	CH_2X
—COOH	14	12	90	12
$—COOC_2H_5$	60	38	98	40
$—COCH_3$	77	23	100	35

their investigation of the percentage formation of a hemiketal in alcoholic medium, Djerassi and coworkers[15] established that whereas 7a-methyl-*trans*-*cis*-5-hydroxyperhydroinden-1-one is converted into the hemiketal only to the extent of 25%, 7a-methyl-*trans*-perhydroinden-5-one yields 74% of the hemiketal. These yields are close to those found for 3-methylcyclopentanone and 3-methylacyclohexanone. The rearrangement[79] of 7a-methyl-*cis*-*trans*--1-hydroxyperhydroinden-5-one to 8-methyl-*cis*-*trans*-5--hydroxyperhydroinden-1-one takes place according to the principle that the location of a trigonal carbon atom in the five-membered ring is more favourable than in the six--membered ring. In the Clemmensen reduction of 3a--methyl-*cis*-perhydroindene-1,4-dione under conditions designed for the reduction of only one oxo-group, the oxo--group in the six-membered ring is reduced exclusively and 7a-methyl-*cis*-perhydroinden-1-one is formed[35].

Comparison of the relative extents of three-carbon tautomerism of the similar α,β- and β,γ-unsaturated compounds of the cyclopentane, cyclohexane, *trans*-decalin, and *trans*-perhydroindene series[96] shows that in the *trans*--perhydroindene system the tendency of the double bond to occupy the exocyclic α,β-position is much more pronounced than in the remaining compounds (Table 7).

It is clear from the foregoing review that the concept of perhydroindene as a system containing a six-membered ring in the chair conformation (or half-chair conformation) and a non-planar five-membered ring is in good agreement with the available experimental data. The role of the thermodynamic (entropy) factor is more clearly shown in the reactivity of the perhydroindene system than in the related decalin system. The similarities and differences between these two systems can be briefly summarised as follows: (a) in both systems the conformations in which the six-membered ring has the chair form are preferred; (b) on the whole *trans*-fusion between the rings is the more stable in the decalin system, while in the perhydroindene series one may speak of either latent or explicit preference for the *cis*-fusion; (c) both *cis*-decalin and *cis*-perhydroindene possess conformational mobility (they are capable of undergoing changes in orientation of all the substituents); the conformational mobility of substituted Δ^7-hexahydroindenes appears to be less pronounced than that of substituted Δ^1-octalins; (d) when a trigonal carbon atom is present at the ring junction (enolic form of an α-ketone or an olefin), its conversion to the tetrahedral state (ketonisation or catalytic hydrogenation) results in the *trans*-fusion between the rings in the decalin system and the *cis*-fusion in the perhydroindene system; (e) the double bond in the perhydroindene system shows a greater tendency towards displacement to the intercyclic position than in the decalin system.

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PYRAZOLIDINE-3,5-DIONES, THEIR SYNTHESIS AND PHARMACOLOGICAL IMPORTANCE

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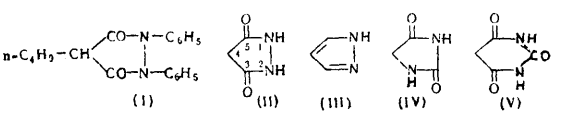
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I. INTRODUCTION

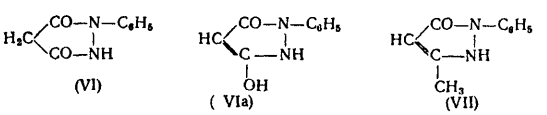
The discovery of the valuable therapeutic properties of 4-n-butyl-1,2-diphenylpyrazolidine-3,5-dione[1] (Butazolidine, Phenylbutazone, Butadione†) (I) promoted the development of the chemistry of this group of compounds. Thus, whereas a total of about 25 papers appeared in the 60 years after the synthesis of the first pyrazolidine-3,5-diones[2], in the last decade, and mainly during the last five years, no fewer than 300 papers and patents dealing with this group of substances have been published, not counting the hundreds of papers connected with the study of Butadione itself.

At the present time various methods of synthesising pyrazolidine-3,5-diones have been developed and many of their properties have been studied but these results are dispersed in numerous articles and it is difficult for the research worker to cover them. Much material present in dissertations (*e.g.* that of Têng[3]) is not accessible and the section on pyrazolidine-3,5-diones in Jacobs' article in the recently issued Volume V of the Collection "Heterocyclic Compounds"[4] is very short and to some extent out-of-date, because only references up to 1954 are included. The present review is an attempt to survey the published material on the chemistry of pyrazolidine-3,5-diones and their applications.



(I) (II) (III) (IV) (V)

Pyrazolidine-3,5-dione (II) is the 3,5-dioxo-derivative of completely hydrogenated pyrazole (III). It is isomeric with hydantoin (IV) and is structurally related to barbituric acid (V), and also to pyrazolones.



(VI) (VIa) (VII)

Thus, the enol form (VIa) of 1-phenylpyrazolidine-3,5-dione (VI) differs from 3-methyl-1-phenylpyrazol-5-one (VII)

† Trivial name used in USSR (Ed. of Translation).