[Contribution from the Department of Chemistry, University of Michigan]

THE RELATIVE STABILITIES OF *CIS-TRANS* ISOMERS OF FUSED RING SYSTEMS CONTAINING ANGULAR METHYL GROUPS[1]

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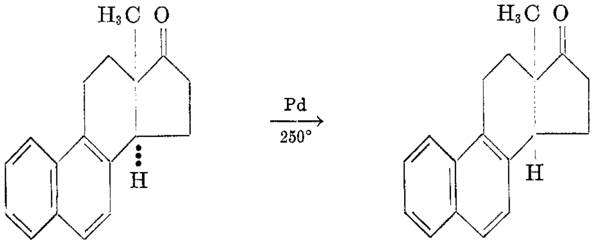
INTRODUCTION

Following the work in which he demonstrated that bicyclic systems of the decalin type are stable in both the *cis* and *trans* forms (1), Walter Hückel proceeded to study the relative stabilities of such structural isomers (2). Later R. P. Linstead and coworkers (3) extended these studies to other bicyclic systems. As a result, a fair amount of reliable data concerning the relative stabilities of *cis* and *trans* isomers of bicyclic ring systems has become available. This work is well summarized in reviews by Hückel and Linstead (4). They show that in all systems studied containing two fused six-membered rings (including systems with heterocyclic oxygen) equilibrium favors the *trans* form. In all systems studied where a five-membered ring is fused to a six-membered ring or to another five-membered ring (including systems with heterocyclic oxygen or nitrogen) the *cis* form is favored in the equilibrium.

From these results there has arisen the generalization that the fusion of two six-membered rings will always result in a system more stable in the *trans* form, whereas if one or both of the rings is five-membered, the resulting bicyclic system will be more stable in the *cis* form. These generalizations have been rather liberally used in studies of the stereochemistry of the steroids (5). It must be noted however that the steroid studies were made with compounds containing angular methyl groups, whereas the basic generalizations were derived from studies of unmethylated bicyclic systems.

In only one instance has one of these generalizations been systematically checked in a bicyclic system with an angular methyl group whose configuration



I

II

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[1] Abstracted from the doctoral dissertation of Alexander Ross, May, 1953. Presented at the W. E. Bachmann Memorial Session, Organic Chemistry Division, American Chemical Society, Chicago Meeting, September 8, 1953.

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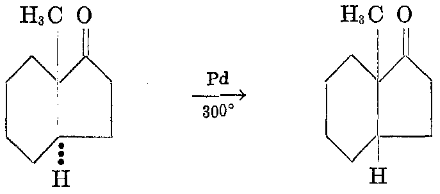
was authentically known. In the course of some studies on the stereochemistry of estrogens, Bachmann and Dreiding (6) successfully converted desoxyequilenin (I) and some of its analogs to the corresponding desoxyisoequilenin (II) compounds by heating with palladium catalyst. This was, in effect, an epimerization at the C/D ring junction from the *trans* to the more stable *cis* form, the catalyst probably acting on the hydrogen at carbon No. 14. When this method was applied to the oxime of *trans*-8-methyl-hydrindanone-1 (III), this epimer was converted into the *cis* form (IV) by the same catalyst at 300°.



III IV

It is therefore apparent that in bicyclic compounds in which a five-membered ring is involved, the relative stabilities are unaffected by the presence of an angular methyl group.

It was the object of this work to investigate the effect of an angular methyl group on the relative stability of bicyclic systems where both rings are six-membered.

METHOD

In this investigation the palladium-catalyzed epimerization was applied to a series of bicyclic imides in which both rings are six-membered. The imides were selected since they are stable, crystalline compounds which are readily prepared. Palladium was used as the catalyst for it can epimerize compounds in which there is no enolizable bridge hydrogen. The preparation of the imides in pure *cis* and *trans* forms from acids of previously authenticated configuration is described below. From the pure epimers thus obtained a series of standards was made up and, from the infrared spectra of the latter, working plots of concentration *vs.* optical density were obtained for each of the distinguishing frequencies. (Table I). Epimerization was accomplished by heating each of the pure epimers with the catalyst at the desired temperature and then determining the infrared spectra, from which the concentration of *cis* and *trans* isomers could be estimated. Equilibrium was considered achieved when both *cis* and *trans* epimers gave mixtures with practically identical spectra.

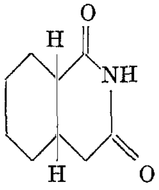
Preparation of imides. The *trans*-decahydroisoquinoline-1,3-dione (VI) was readily prepared by pyrolysis of the ammonium salt of *trans*-hexahydrohomophthalic acid (7). When treated in exactly the same manner, the ammonium salt of the *cis*-hexahydrohomophthalic acid also yielded the *trans* imide (VI). This ready epimerization can be attributed to the enolizable angular hydrogen. The *cis*-decahydroisoquinoline-1,3-dione (V) was finally prepared in the pure state only when care was taken to avoid contact with strong acids, bases, or high

TABLE I

PER CENT TRANSMISSION OF MIXTURES OF EPIMERIC PAIRS OF DECAHYDROISOQUINOLINE-1,3-DIONES (HEXAHYDROHOMOPHTHALIMIDES)

COMPOSITION		DECAHYDROISOQUINOLINE-1,3-DIONE		9-METHYLDECAHYDROISOQUINOLINE-1,3-DIONE		10-METHYLDECAHYDROISOQUINOLINE-1,3-DIONE
cis, %	*trans*, %	8.55μ	8.77μ	7.88μ	8.39μ	8.55μ
100	0	74.5	72.5	73.0	36.5	79.0
80	20	66.0	76.0	66.0	43.0	71.0
60	40	57.5	79.0	59.0	49.5	61.0
40	60	49.5	84.5	54.0	57.5	53.0
20	80	42.5	88.0	48.0	66.5	46.0
0	100	36.5	93.5	44.0	71.0	37.5

temperatures, all of which catalyze the epimerization to the *trans* form. This involved conversion of the *cis*-hexahydrohomophthalic acid (8) to its anhydride with acetic anhydride and opening the anhydride to the amidic acid (position of the amide group uncertain) with ammonia. The cyclodehydration of the amidic acid to the *cis* imide (V) was then accomplished with acetic anhydride. Since the configurations of the parent hexahydrohomophthalic acids are known (8, 9) the configuration of the imides may be considered established.



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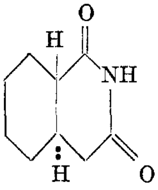
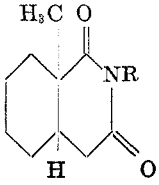
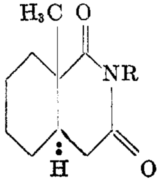


VI

To prepare the *cis*- and *trans*-9-methyldecahydroisoquinoline-1,3-dione (VII and VIII, R = H), the parent acids, *cis*- and *trans*-2-methyl-2-carboxycyclohexane-1-acetic acid were first prepared according to the methods described by Bachmann and Kushner (10). The correctness of the configurational assignments of these acids was eventually established by the work of Davis (11). Conversion to the respective imides was accomplished *via* the anhydrides and amidic acids, as before. In these compounds, however, there is no angular hydrogen adjacent to a carbonyl function, and the possibility of enolization is eliminated, permitting the imides to be sublimed without epimerization.



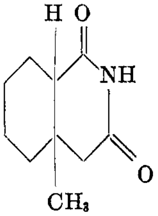
VII



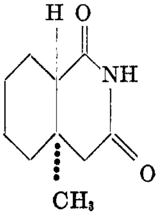
VIII

The *cis*-N-benzyl imide (VII R = $C_6H_5CH_2$—) and the *cis*-N-methyl imide (VII, R = CH_3—) were also prepared from the *cis* acid in the same manner, except that benzylamine and methylamine were used respectively in place of ammonia.

Using the same series of reactions, a third pair of imides, the *cis*- and *trans*-10-methyldecahydroisoquinoline-1,3-dione (IX and X), were prepared from *cis*- and *trans*-1-methyl-2-carboxycyclohexane-1-acetic acid.

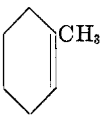


IX

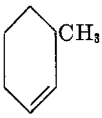


X

The parent acids were obtained from the sodium hypobromite oxidation of 10-methyldecalin-1,3-dione (XVI) (12). The preparation of this diketone, however, presented many difficulties, and it was obtained only in very poor yield. The original work of Ruzicka, Koolhaas, and Wind (13), which was followed here, involved the dehydration of 2-methylcyclohexanol to 1-methylcyclohexene (XI). It has recently been shown (14) that some isomeric 3-methylcyclohexene (XII) is also produced by this reaction.

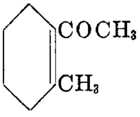


XI

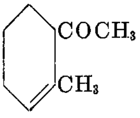


XII

The second step, the Friedel-Crafts acetylation of XI, has been the subject of several recent investigations (15), which have shown that the result is a mixture of 1-acetyl-2-methylcyclohexene (XIII) and 3-acetyl-2-methylcyclohexene (XIV).

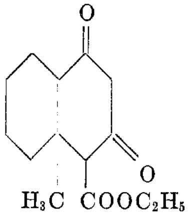


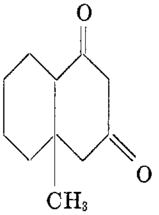
XIII



XIV

Having assumed that their acetylation product was pure XIII, Ruzicka, *et al.* (13) [and others who repeated their work, (9, 12, 16), including ourselves] encountered great difficulty in the condensation of the acetylation product with diethyl malonate. In the main, oily products were obtained. From these the desired diketo ester (XV) was isolated in low yield. Decarboxylation of XV yielded XVI as a glassy resin, very difficult to crystallize (9, 12, 13, and 16). In our hands, however, two small crystalline samples were obtained from different runs, one melting at 107–110°, and the other at 149–151°. Both gave the correct analysis for the diketone (XVI). It is possible that these are *cis-trans* isomers or else the keto and enol forms. The only previously reported melting point for this compound is 129–130° (16). At the present time these discrepancies cannot be explained.


XV


XVI

Strong arguments for the assignment of configurations to the 1-methyl-2-carboxycyclohexane-1-acetic acids[4] are given by Linstead and Millidge (12). To these we wish to add confirming evidence from the infrared spectra of the corresponding imides. The *trans* imide X shows a strong band at 8.55μ, (Fig. 5) in common with the other *trans* imides (Fig. 1 and Fig. 3) of known configuration discussed above. None of the *cis* imides show a band at this wave length.

From the dehydration of the intermediate *cis* amidic acid with acetic anhydride, two products were obtained. One was the desired imide (X), but the other was shown to be a nitrile acid by its analysis, infrared spectrum, and neutral equivalent. The position of the amide in the amidic acid and the nitrile in the nitrile acid was not definitely established.

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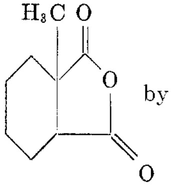
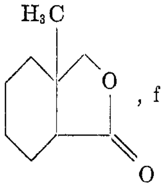
[4] These arguments are actually stronger than Linstead and Millidge themselves realized. They prepared the 172° acid from the known *cis* anhydride  by reduction to the *cis* lactone , followed by treatment with potassium cyanide at elevated temperatures to get a nitrile acid which was then hydrolyzed to the 172°-melting 1-methyl-2-carboxycyclohexane-1-acetic acid. The authors are somewhat doubtful of this evidence for assigning the *cis* configuration to the 172° acid because of the "high temperature—280°—required for the fission of the lactone ring". Their experimental data, however, shows that the 172° isomer is unstable with regard to the 132° isomer when heated to 200° with hydrochloric acid. If an isomerization had occurred during the reaction of the *cis* lactone with potassium cyanide, the resulting nitrile acid would have to be *trans*. Hydrolysis would then yield the corresponding *trans* diacid which upon isomerization would give the *cis* diacid. It is unlikely that the nitrile acid would be more stable in the *trans* form and the diacid more stable in the *cis* form as this argument would imply. It must therefore be concluded that the 172° acid is formed from the *cis* lactone with retention of configuration and that the only isomerization is that of the *cis* to the *trans* diacid under the catalytic influence of hydrochloric acid at 200°.

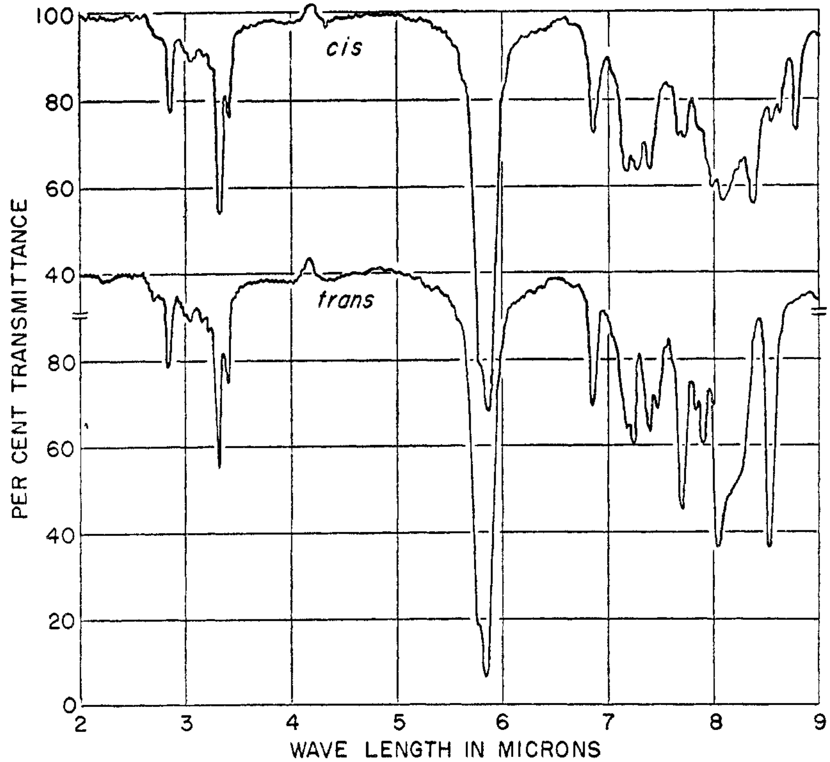


FIG. I – INFRARED SPECTRA OF THE DECAHYDROISOQUINOLINE-I, 3-DIONES

Epimerization results. The infrared spectra of the decahydroisoquinoline-1,3-diones (V and VI) showed a strong band at 8.55μ for the *trans* form, while a weak band at 8.77μ was characteristic of the *cis* isomer (Fig. 1). From these, independent graphical Beer's Law plots could be made.

When the palladium-catalyzed epimerizations of V and VI were run at 250°, extensive decomposition was observed. However, at 190° equilibrium was reached in about three hours when starting with the *cis* imide (V) (Table II, Run No. 11), and the product had an analysis of 33% *cis* and 67% *trans*. When starting with the *trans* imide (VI), equilibrium was reached in a run of 90 minutes (Table II, Run No. 8), and the analysis showed 31% *cis* and 69% *trans* (Fig. 2). Since enolization is possible in these imides, heat alone can effect the epimerization. Without a catalyst, it was found that equilibrium at 250° was reached at 40% *cis* and 60% *trans* in 90 minutes (Table II, Run No. 5). From the equilibrium constants at the two temperatures, the value for ΔH was estimated by use of the van't Hoff equation. For the reaction *cis* → *trans*, $\Delta H = -2.8$ K cal./mole. This value is comparable to the 2.1 K cal./mole difference in heat content between *cis* and *trans*-decalin that Davies and Gilbert (17) found from the heats of combustion.

TABLE II

EPIMERIZATIONS OF DECAHYDROISOQUINOLINE-1,3-DIONE

RUN NO.	STARTING CONFIGURATION	TEMP., °C.	DURATION, MIN.	RECOVERY, %	COMPOSITION OF PRODUCT, %		NORMALIZED RATIO	
					cis	*trans*	*cis*	*trans*
1	*trans*	250	30	57	34	23	60	40
2	*cis*	250	30	49	30	19	61	39
3*	*trans*	250	30	82	16	66	19	81
4*	*trans*	250	90	99	39	60	39	61
5*	*trans*	250	150	97	39	58	40	60
6	*trans*	190	45	81	17	64	21	79
7	*trans*	190	45	90	25	65	28	72
8	*trans*	190	90	98	30	68	31	69
9	*cis*	190	45	97	48	49	50	50
10	*cis*	190	120	97	36	61	37	63
11	*cis*	190	210	75	25	50	33	67

* No catalyst used.

For the 9-methyldecahydroisoquinoline-1,3-diones (VII and VIII, R = H) a sharp band for the *cis* isomer was found at 8.39μ, whereas the *trans* isomer showed a strong band at 7.88μ (Fig. 3). Starting with the *cis* epimer (VII), equilibrium was reached in 90 minutes at 71% *cis* and 29% *trans* (Table III, Run No. 8); while the *trans* form was equilibrated in the four-hour run (Table III, Run No. 13) to 70% *cis* and 30% *trans* (Fig. 4).

Attempts in preliminary experiments to epimerize the *cis*-2-benzyl-9-methyldecahydroisoquinoline-1,3-dione (VII, R = $C_6H_5CH_2$—) and the corresponding N-methyl compound (VII, R = CH_3—) were unsuccessful. However, it was discovered that 5% palladium-on-charcoal at 300° caused replacement of the benzyl group by hydrogen. This was not investigated further, but it is probably another example of the reductive cleavage which the benzyl group is known to undergo with ease.

With the 10-methyldecahydroisoquinoline-1,3-diones (IX and X), a distinctive infrared band was found only in the case of the *trans* isomer (at 8.55μ—Fig. 5). Fortunately, however, the epimerizations proceeded very cleanly and the *cis* epimer could be estimated by difference. Furthermore, when starting with the *cis* (Table IV, Run No. 3) or with the *trans* epimer (Table IV, Run No. 2), epimerization at 190° gave products whose spectra were identical in every way with that of the standard made up with the composition 60% *cis* and 40% *trans* (Fig. 6), thus establishing the point of equilibrium.

CONCLUSIONS

The foregoing results are summarized in Table V.

It is easily seen that the angular methyl group definitely alters the relative stabilities at equilibrium in favor of the *cis* isomer (at least in the temperature range used, *ca.* 200°). Furthermore this effect appears to operate whether the angular methyl group replaces the hydrogen adjacent to the carbonyl or the

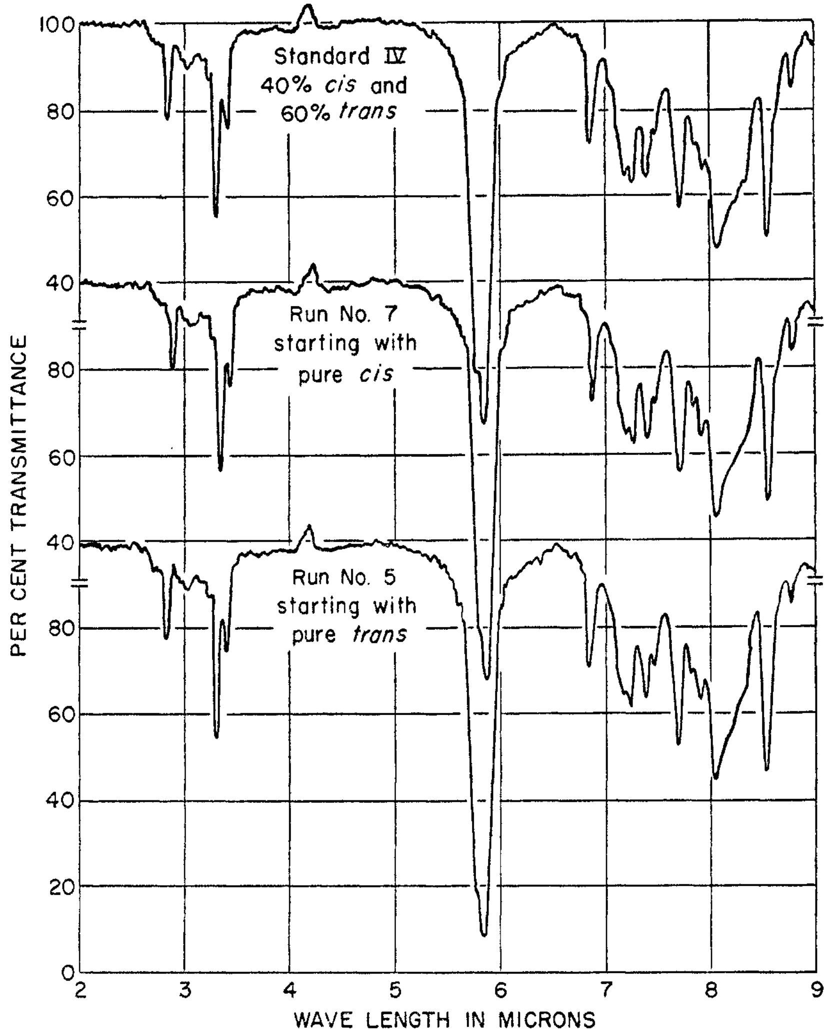


FIG. 2—INFRARED SPECTRA OF THE DECAHYDROISOQUINOLINE-1,3-DIONES

hydrogen at the other end of the ring fusion; this leads to the conclusion that the influence of the methyl group is steric in nature.

There is other evidence in the literature for this effect of the angular methyl group. Linstead and Millidge (12) found that the anhydrides of 1-methyl-2-carboxycyclohexane-1-acetic acid (XVII) were equilibrated to a 50–50 mixture of *cis* and *trans* in contrast to the 75% *trans* obtained with the corresponding desmethyl compounds. They concluded that "the angular methyl group tends to stabilize the *cis* forms of *o*-dicyclic systems."

Further evidence is found "in the tendency for the *cis* form of 10-methyl-

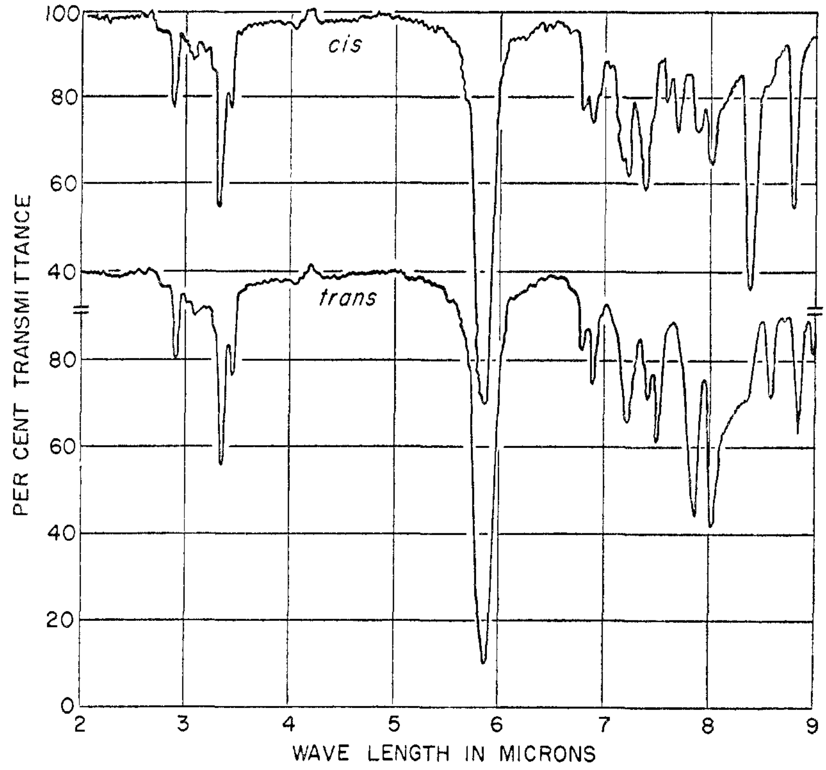


FIG. 3—INFRARED SPECTRA OF THE 9-METHYLDECAHYDROISOQUINOLINE-1,3-DIONES

TABLE III

EPIMERIZATIONS OF 9-METHYLDECAHYDROISOQUINOLINE-1,3-DIONE

RUN NO.	STARTING CONFIGURATION	TEMP., °C.	DURATION, MIN.	RECOVERY, %	COMPOSITION OF PRODUCT, %		NORMALIZED RATIO	
					cis	*trans*	*cis*	*trans*
1	*cis*	300	15	93	87	6	94	6
2	*cis*	300	30	66	53	13	80	20
3	*cis*	300	60	51	40	11	80	20
4	*cis*	300	90	37	32	5	86	14
5	*cis*	250	30	95	89	6	94	6
6	*cis*	250	60	100	78	22	78	22
7	*cis*	250	90	81	59	22	73	27
8	*cis*	250	90	87	62	13	71	29
9	*cis*	250	120	79	57	22	72	28
10	*cis*	250	240	80	59	21	74	26
11	*trans*	250	60	92	31	61	34	66
12	*trans*	250	180	100	67	34	67	33
13	*trans*	250	240	99	69	30	70	30
14*	*cis*	300	60	96	94	2	98	2

* This run was made without using any catalyst.

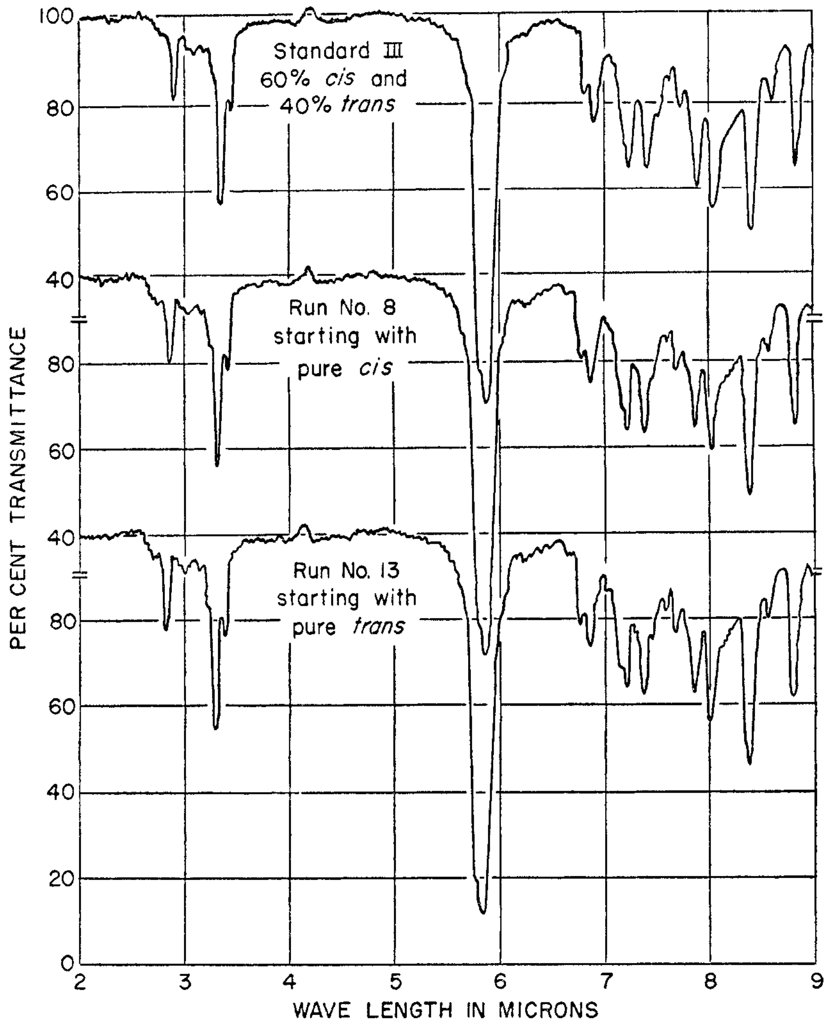
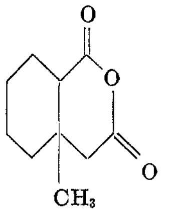
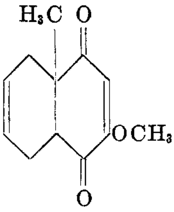


FIG. 4 - INFRARED SPECTRA OF THE 9-METHYLDECAHYDROISOQUINOLINE-1,3-DIONES

decalin-1,3-dione (XVI) to persist after alkaline hydrolysis of the keto ester (XV)" (12).



XVII



XVIII

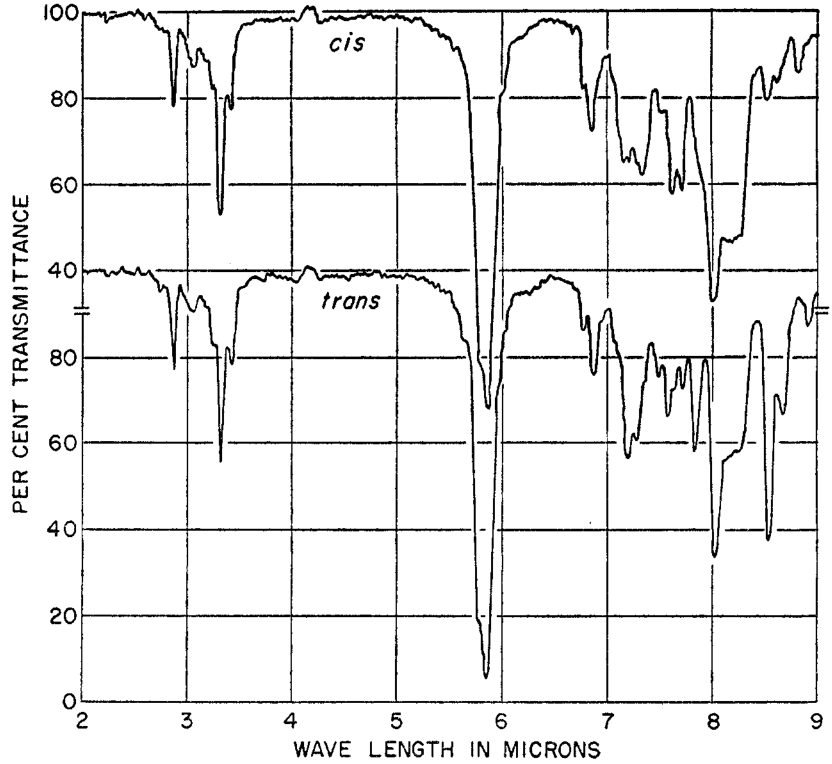


FIG. 5 — INFRARED SPECTRA OF THE 10-METHYLDECAHYDROISOQUINOLINE-1,3-DIONES

TABLE IV

EPIMERIZATIONS OF 10-METHYLDECAHYDROISOQUINOLINE-1,3-DIONE

RUN NO.	STARTING CONFIGURATION	TIME, HOURS	TEMP., °C.	RECOVERY, %	*cis*, % (BY DIFFERENCE)	*trans*, %
1	*trans*	1.5	190	82	58	42
2	*trans*	2.5	190	83	60	40
3	*cis*	1.5	190	85	60	40
4	*trans*	1.5	250	76	62	38
5*	*trans*	2	190	93	31	69

* Run without a catalyst.

Recently Woodward and co-workers (18) suggested that in compound XVIII "the *trans*-isomer does not predominate at equilibrium to the extent which obtains with simple saturated decalins, *e.g.* the pair *cis*-α-decalone/*trans*-α-decalone". While these authors attributed this effect to the presence in XVIII of trigonal carbon atoms and double bonds it is possible that the angular methyl group may also be responsible.

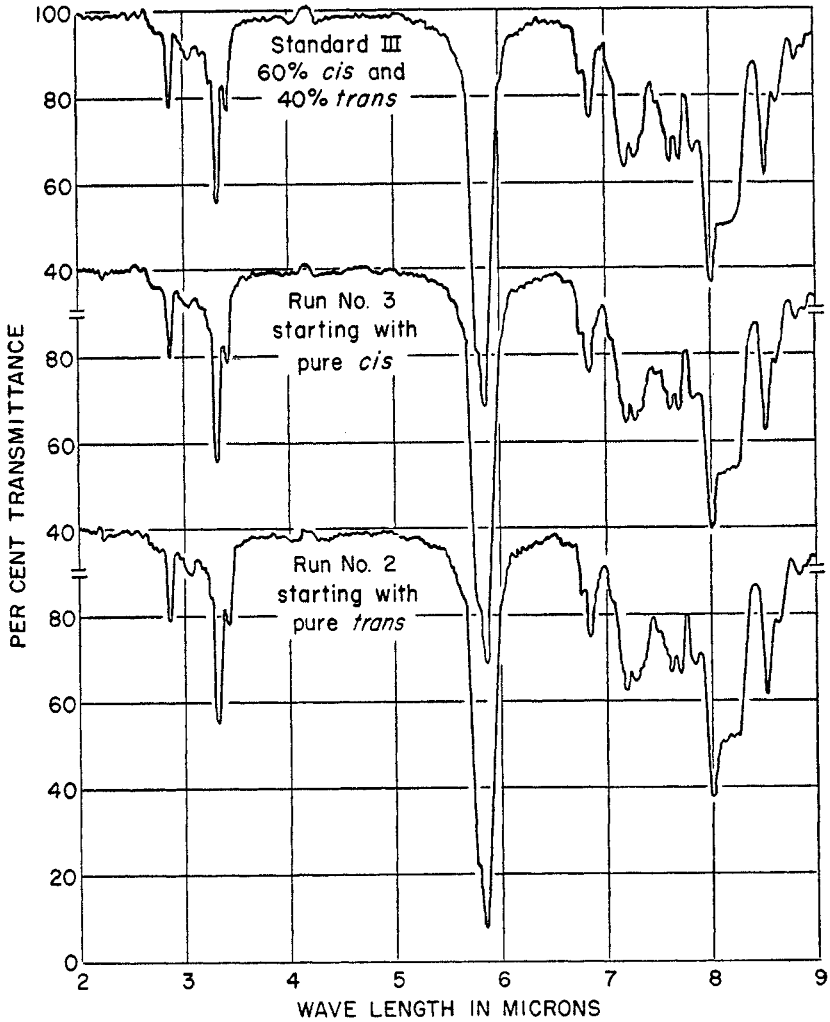


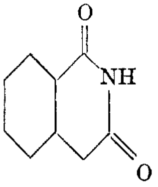
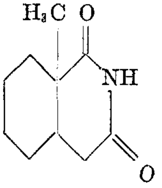
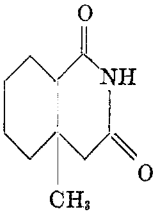
FIG. 6—INFRARED SPECTRA OF THE 10-METHYLDECAHYDROISOQUINOLINE-1, 3-DIONES

The effect of the angular methyl group can be rationalized partially in terms of steric hindrance as used in conformational analysis (19). It has been well established that cyclohexane exists preferentially in the chair form (19a). Substituents on the cyclohexane ring are more stable when in the equatorial position (19 a,c) which means for 1,2-disubstituted cyclohexane the *trans* configuration.

The two rings of the decalins have also been shown to exist preferentially in the chair form. Since the *trans* form allows all four of the C—C bonds at the bridgeheads to be equatorial, whereas in the *cis* form two of these bonds must

TABLE V

Composition of Epimeric Hexahydrohomophthalimides at Equilibrium

COMPOUND	EQUILIBRIUM	
	cis, %	*trans*, %
	32	68
	71	29
	60	40

be polar, it follows that the *trans* form of decalin is the more stable, as has been experimentally verified. The same analysis, when applied to six-membered, bicyclic compounds, containing hetero atoms, explains the greater stability of the *trans* form of hexahydrohomophthalic anhydride (8) and of the *trans* form of hexahydrohomophthalimide (VI) (this work). Further support for the applicability of the method of conformational analysis to some heterocyclic systems comes from studies with sugar pyranosides (20) and alkaloids (21).

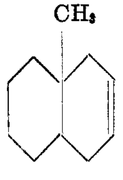
The application of this analysis to six-membered bicyclic systems with an angular methyl group shows that in the *trans*-form 4 C—C bonds may be equatorial and 2 have to be polar, while in the *cis*-isomer 3 C—C bonds may be equatorial and 3 have to be polar. Thus the ratio of equatorial to polar C—C bonds does not favor the *trans*-form (4:2) over the *cis*-form (3:3) as much in the case with the angular methyl group as it does in the case without the angular methyl group (*trans*, 4:0 and *cis*, 2:2). This shows that an angular methyl group (or other alkyl group) will act so as to decrease the energy difference between the *cis*- and the *trans*-forms.

On the basis of another approach, Turner (22) concluded that the energy difference between the *cis* and *trans* forms of decalin is decreased from 2.4 K cal to 0.8 K cal/mole by the introduction of an angular methyl group. This quantitative analysis assumes that the steric energy of the skew form as compared with the staggered constellation is the same (0.8 K cal/mole) whether the interactions involve a methyl group or only ring methylene groups. This, however, may not be the case. If it is assumed that the skew interactions involving a methyl group have a greater steric energy, it is possible that *cis*-9-methyldecalin may be calculated to have a lower energy than the *trans* isomer; for, while *cis*-9-methyldecalin has one more over-all skew interaction than the *trans*-isomer, the latter has 4 skew interactions involving a methyl group, while the former has only two of the same.

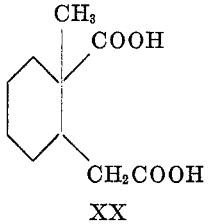
Although the experimental work in this paper has involved only heterocyclic imides, there are cogent reasons for believing that the angular methyl group will probably affect carbocyclic systems in the same way. As was pointed out above, two cases of carbocyclic compounds in the literature (12, 18) may be interpreted in this manner. Secondly the ΔH of isomerization for the hexahydrohomophthalimides is about the same as that reported for the decalins. Lastly the same rules of conformational analysis seem to apply to heterocyclic systems containing oxygen or nitrogen (20, 21) as to the carbocyclic systems. This is reasonable when one considers the similarity in bond lengths and angles involving carbon, oxygen, or nitrogen (23). It should be noted, however, that, while a ring methylene group has two hydrogens, a ring oxygen has no hydrogens, and a ring nitrogen only one hydrogen. The exact effect of this difference is not known.

There is only one report in the literature which conflicts with our conclusions. Hibbit and Linstead (24) reported the preparation of *cis*-9-methyldecalin and claimed to have isomerized it to the *trans* epimer with aluminum chloride. Their basis for configurational assignment is twofold:

1. The precursor to their *cis* compound, Δ^2-9-methyloctalin (XIX), was degraded through a series of supposedly *cis* intermediates to a 2-methyl-2-carboxycyclohexane-1-acetic acid (XX),



XIX



XX

m.p. 175°, which was considered to be the *cis* acid. A year later, Linstead, Millidge, and Walpole reversed this assignment (25), and the work of Davis (11) definitely proved that the 175° acid was actually *trans*.

2. The product of the aluminum chloride-epimerization had a lower density, lower boiling point, lower index of refraction, but higher molar refraction than the starting material. Since *trans*-decalin bears the same relationship of physical properties to *cis*-decalin, Hibbit and Linstead concluded that their epimerized product was also a *trans* compound. The danger of using physical properties in this manner to assign configurations is pointed out by Siegel (26).

An alternative explanation of the significance of some of these physical properties is, however, possible. The greater molar refraction is generally associated with a greater molecular volume. For stereoisomeric hydrocarbons this could mean less crowding within the molecule and hence greater stability. Thus it is possible that it is always the more stable epimeric hydrocarbon that will show the greater molar refraction independently of its configuration.

The product of Linstead's aluminum chloride-isomerization had the same properties as the 9-methyldecalin obtained by Ruzicka, Koolhaas, and Wind (13), to which these authors had assigned the *trans*-configuration. Since this hydrocarbon had been prepared by the Clemmensen reduction of 10-methyldecalin-1,3-dione (XVI), which was later shown by Linstead and Millidge (12) (see above) to consist primarily of the *cis*-isomer,[4] it can be inferred that Ruzicka's hydrocarbon is actually *cis*. One would then conclude that Hibbit and Linstead actually epimerized *trans*-9-methyldecalin to the *cis* form in complete agreement with our findings here.

Since the energy differences between *cis* and *trans* isomers of six-membered bicyclic systems are small, care must be taken not to extend the generalizations deduced from simple compounds too far. It is possible that small changes, such as the introduction of a side chain, other fused rings, unsaturation, etc., may affect the relative stabilities. This appears to be the situation in a number of steroids where the A, B ring fusion has been shown to be more stable in the *trans* configuration. Apparently such factors can even contribute to the greater stability of the *trans* configuration in the C—D ring fusion (hydrindan type) of steroids (27).

EXPERIMENTAL

General method for preparation of imides. The parent acid was refluxed with an excess of acetyl chloride (or acetic anhydride in cases where any hydrochloric acid produced might effect epimerization) with benzene as a solvent. After removal of the solvent and excess reagent under a vacuum, the resulting anhydride was refluxed with an excess of aqueous ammonia. The resulting product was then worked up by one of the two following procedures: (a) The ammoniacal solution was dried, pyrolyzed to the imide at 120° to 160°, and sublimed; (b) The solution was neutralized with hydrochloric acid (or acetic acid if mineral acid was undesirable), and the free amidic acid which precipitated was filtered, washed with water and dried. The amidic acid was then cyclized by pyrolysis and sublimed. Alternatively, it was refluxed in benzene with acetic anhydride, followed by removal of excess reagent and the solvent, and recrystallized.

trans-Decahydroisoquinoline-1,3-dione (VI) (7). The ammonium salt from 1.5 g. of *trans*-hexahydrohomophthalic acid (8) was thoroughly dried, powdered, and heated in a sublimation apparatus. Between 160° and 180°, water and ammonia were evolved and the product was partially sublimed, yielding 0.35 g. of the desired imide, m.p. 182–186°. The residue in the tube was dissolved in methanol, decolorized with Norit, and, after removal of the solvent, yielded another 1.03 g. of product, m.p. 176–180°. Recrystallization from dilute methanol gave colorless needles, m.p. 185.5–187°.

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.66; H, 7.84; N, 8.38.
Found: C, 64.75; H, 8.04; N, 8.50.

cis-Decahydroisoquinoline-1,3-dione (V). One gram of *cis*-hexahydrohomophthalic acid (8) was treated according to the general method, using procedure (*b*) and avoiding epimerizing conditions. The product was crystallized from dilute methanol, yielding 0.74 g. (78%)

of the desired *cis* imide, m.p. 110–124°. Several recrystallizations from dilute methanol gave a white product melting at 124–126°.

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.66; H, 7.84; N, 8.38.
Found: C, 64.53; H, 7.98; N, 8.50.

cis-9-Methyldecahydroisoquinoline-1,3-dione (VII, R = H). The general method was applied to 500 mg. of *cis*-2-methyl-2-carboxycyclohexane-1-acetic acid (10). Peroxide-free dioxane was used as solvent when the ammonia was added. Procedure (*a*) was followed and 396 mg. (87%) of the desired *cis* imide, m.p. 94–114°, was obtained after sublimation at 160°/14–20 mm. Recrystallization from ethanol or methanol yielded colorless needles, m.p. 120.5–121.5°.

Anal. Calc'd for $C_{10}H_{12}NO_2$: C, 66.23; H, 8.34; N, 7.73.
Found: C, 65.76; H, 8.21; N, 7.50.

trans-9-Methyldecahydroisoquinoline-1,3-dione (VIII, R = H). When the general method was applied to 786 mg. of *trans*-2-methyl-2-carboxycyclohexane-1-acetic acid (10), using procedure (*a*) in the final step, 508 mg. (71%) of the desired *trans* imide, m.p. 169–174° was obtained. Recrystallization from ether raised the melting point to 174–175.5°.

Anal. Calc'd for $C_{10}H_{15}NO_2$: C, 66.23; H, 8.34; N, 7.73.
Found: C, 66.21; H, 8.27; N, 7.70.

cis-2-Benzyl-9-methyldecahydroisoquinoline-1,3-dione (VII, R = $C_6H_5CH_2$—). This compound was also prepared by the general method using 300 mg. of *cis*-2-methyl-2-carboxycyclohexane-1-acetic acid. Instead of ammonia, however, benzylamine was used to open the anhydride. In this instance the intermediate amidic acid was isolated, yielding, after one recrystallization from dilute methanol, 336 mg. (89%) of fine white needles, m.p. 180–181.5°.

Anal. Calc'd for $C_{17}H_{23}NO_3$: C, 70.55; H, 8.01; N, 4.84.
Found: C, 70.03; H, 7.96; N, 4.75.

This amidic acid (260 mg.) was cyclized by procedure (*b*) to yield, after sublimation, 116 mg. (50%) of the desired *cis*-benzyl imide, m.p. 50–55°. Upon recrystallization from dilute alcohol, the melting point was 59.5–60°.

Anal. Calc'd for $C_{17}H_{21}NO_2$: C, 75.26; H, 7.80; N, 5.16.
Found: C, 75.07; H, 7.70; N, 5.02.

In the course of further work it was found that the melting point of this imide had changed to 72.5–73°. Repeated preparation of the imide yielded only the material melting at 73°. The analysis, however, remained unchanged. It was concluded that the 60°-material was a metastable crystalline modification.

cis-2,9-Dimethyldecahydroisoquinoline-1,3-dione (VII, R = CH_3—). The general method was applied to 1.153 g. of *cis*-2-methyl-2-carboxycyclohexane-1-acetic acid. In place of ammonia, however, a stream of methylamine vapor was passed through a solution of the anhydride in benzene. (Alternately a 25% aqueous methylamine solution was used.) Following procedure (*a*), 1.225 g. of sublimate was obtained. Two products were isolated by crystallization from dilute methanol. One was the intermediate amidic acid, m.p. 140–141°.

Anal. Calc'd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N. 6.57.
Found: C, 62.06; H, 9.02; N, 6.63.

The second product was the desired *cis*-methyl imide, m.p. 72.5–73.5°.

Anal. Calc'd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.18.
Found: C, 67.65; H, 8.87; N, 7.19.

When subjected to procedure (*b*), the amidic acid was readily converted to the imide.

4-Carbethoxy-10-methyldecalin-1,3-dione (XV). The procedures of Ruzicka, Koolhaas, and Wind (13) were followed in preparing 1-acetyl-2-methylcyclohexene (XIII).

To a solution of 9.2 g. of sodium in 150 ml. of absolute alcohol there was added 64 g. of diethyl malonate and 55 g. of 1-acetyl-2-methylcyclohexene (XIII). When worked up according to Ruzicka, *et al.* (13) only oily products were obtained. When this oil was extracted with 25-ml. portions of 10% sodium carbonate (16) and the extracts then carefully acidified with hydrochloric acid, there was obtained 5.0 g. of 4-carbethoxy-10-methyldecalin-1,3-

dione (XV), m.p. 121–127°. The residual oils could not be crystallized and did not give the desired product when put through the next step. After recrystallization of the solid from dilute alcohol or ether and petroleum ether the melting point was 127–129°.[5]

Anal. Calc'd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99.
Found: C, 66.46; H, 7.98.

10-Methyldecalin-1,3-dione (XVI). The diketo ester XV (4.9 g.) was decarboxylated with barium hydroxide (7), yielding 3.42 g. (98%) of a glassy resin, a small sample of which was crystallized from hot water, m.p. 107–110°.[6]

Anal. Calc'd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95.
Found: C, 73.22; H, 8.91.

In another run the diketone XVI was distilled through a simple short-path apparatus, consisting of a small distilling flask with a wide side-arm terminating in an air-cooled bulb, b.p. 130–150°/0.1–0.3 mm. Some of this glassy distillate was recrystallized several times from a benzene and petroleum ether mixture to a constant melting point of 149–151°.[6]

Anal. Calc'd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95.
Found: C, 73.10; H, 9.07.

cis and *trans-1-Methyl-2-carboxycyclohexane-1-acetic acid.* A hypobromite oxidation (12) was carried out on 3.42 g. of the glassy diketone XVI yielding, upon acidification, 1.70 g. of the desired *cis* acid, m.p. 165–171°. Another 0.3 g. was obtained after concentration of the filtrate. After treatment with Norit and recrystallizing from boiling water, the melting point was 172–174°.[7]

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06.
Found: C, 59.80; H, 8.07.

The filtrate was then continuously extracted with ether for 24 hours, yielding 0.43 g. of the *trans* acid, m.p. 126–140° for a total yield of 2.43 g. (64%).

When 2.15 g. of the *cis* acid was heated for 5½ hours in a sealed tube at 200° with 8 ml. of concentrated hydrochloric acid (12), 1.91 g. (89%) of crude *trans* acid, m.p. 128–138°, was obtained. Fractional recrystallization from water improved the melting point only slightly to 130–135°.[7] Since this corresponds to a mixture of 5% or less of the *cis* acid,[8] this material was considered pure enough for the next step.

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06.
Found: C, 60.14; H, 8.20.

cis-10-Methyldecahydroisoquinoline-1,3-dione (IX). The general method for imides was applied to 1.50 g. of the *cis* acid, using procedure (*b*) and avoiding epimerizing conditions. The crude oily product was crystallized from a chloroform and petroleum ether solvent to yield 0.27 g. (25%) of a product, m.p. 135–143°. Recrystallization from the same solvent raised the melting point to a constant 143–144.5°. This material was shown to be a nitrile acid by means of its infrared spectrum, which showed no N—H band at 2.85 μ but did show the weak C≡N band at 4.35 μ; by its neutral equivalent of 182 [required for $C_{10}H_{15}NO_2$ (monobasic), 181] and by its analysis:

Anal. Calc'd for $C_{10}H_{15}NO_2$: C, 66.23; H, 8.34; N, 7.73.
Found: C, 65.92; H, 8.27; N, 7.76.

The mother liquors were put on a short column of alumina and eluted with 5% ethanol in benzene yielding 0.298 g. (27%) of the desired imide (IX), m.p. 93–98°. After recrystal-

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[5] Ruzicka, *et al.* (13) could not isolate any solid. Clemo and Dickenson (16) report a solid, m.p. 127–129°; Linstead and Millidge (12) report a solid, m.p. 130–131°.

[6] Clemo and Dickenson (16) report 129–130°. All other investigators report only glassy resins.

[7] Linstead and Millidge (12) report the *cis* acid, m.p. 171.5°, and the *trans* acid, m.p. 131.2°.

[8] Linstead and Millidge (12) give a table of melting points of the mixed *cis* and *trans* acids. For 10% *cis* and 90% *trans*, the melting point is 140° as compared to 131.5° for the pure *trans* acid.

lization from a mixture of chloroform and petroleum-ether, the melting point was 99–100°. Confirmation of structure was provided by the infrared spectrum (Fig. 5).

Anal. Calc'd for $C_{10}H_{15}NO_2$: C, 66.23; H, 8.34; N, 7.73.

Found: C, 66.41; H, 8.30; N, 7.68.

trans-10-Methyldecahydroisoquinoline-1,3-dione (X). When the general procedure was applied to 1.21 g. of the *trans*-1-methyl-2-carboxycyclohexane-1-acetic acid, 253 mg. (36%; some loss was incurred) of the desired *trans* imide (X), m.p. 135–140°, was obtained. Recrystallization from mixed chloroform and petroleum ether raised the melting point to 144–144.5°.

Anal. Calc'd for $C_{10}H_{15}NO_2$: C, 66.23; H, 8.34; N, 7.73.

Found: C, 66.62; H, 8.30; N, 7.70.

Attempted epimerization of cis-2-benzyl-9-methyldecahydroisoquinoline-1,3-dione (VII, R = $C_6H_5CH_2$—). When 250 mg. of this imide was treated as described below for 10 minutes at 300°, 230 mg. (92%) of residue was recovered. Chromatography on an alumina column gave, by elution with benzene, 198 mg. of the starting imide, m.p. 71.5–73.5°. Elution with 5% methanol in ether yielded 21.5 mg. of the *cis*-9-methyldecahydroisoquinoline-1,3-dione (VII, R = H), m.p. 120.5–123°. Identification was made by means of its analysis, infrared spectrum, and mixture melting point with authentic imide.

General method for epimerization and infrared analysis of the products. A sample (near 45 or 100 mg.) of the imide to be epimerized, mixed with an equal amount of 5% palladium-on-charcoal catalyst (Wilkins Anderson Co.) was placed into a small stainless steel cylinder (7 cm. × 10 mm. O.D.) equipped with a pressure-tight cap. An equal amount of catalyst was added on top of the mixture, the cap was bolted on securely, and the tube was inserted into a Wood's Metal bath held at the desired temperature ±5°. After cooling, the mixture was removed with methanol. The catalyst was filtered and washed, and the solvent was then evaporated. The residue was redissolved in chloroform, filtered, and the chloroform was then evaporated. The infrared spectrum was then taken on a 25 mg./ml. solution of this residue in chloroform. The results are shown in Tables 2–5.

SUMMARY

A series of saturated homophthalimides (decahydroisoquinoline-1,3-diones) were prepared in epimeric *cis* and *trans* forms. Equilibrium between epimeric pairs was reached by heating either epimer with a palladium catalyst. The resulting epimeric mixtures were analyzed by means of their infrared spectra. In the compounds having two angular hydrogens, the equilibrium was in favor of the *trans* epimer. Wherever one of these hydrogens was replaced by an angular methyl group, the *cis* form was favored at equilibrium. These results show that the angular methyl group reverses the relative stabilities of these *cis-trans* isomers. Data in the literature have been reexamined to show that this generalization may also apply to some carbocyclic systems, including 9-methyldecalin.

A possible rationalization of this effect in terms of conformational analysis is suggested.

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