[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Relative Stabilities of *cis* and *trans* Isomers. VIII.[1a] Optical Rotatory Dispersion Studies. XXXIV.[1b] Kinetic and Equilibrium Measurements on Some Steroidal Hydrindanones

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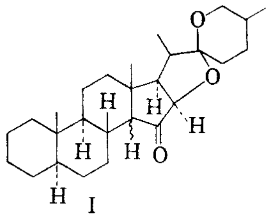
Utilizing optical rotation measurements in the ultraviolet region as a tool, the kinetics for the equilibration of a number of *cis*- and *trans*-hydrindanones in steroidal systems have been measured. The reactions are first order in ketone and first order in base. The equilibrium constants were also found. Approximate methods for predicting energy differences in hydrindane and hydrindanone systems are proposed and compared with experiment, and the agreement between theory and experiment is satisfactory.

INTRODUCTION

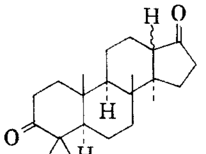
The relative stabilities of *cis* and *trans* hydrindanone systems when these are fused into more complicated structures have been studied by a number of workers.[3] For the most part the available data were obtained by product isolation, and are qualitative at best.

The present work is concerned with quantitative studies on the relative stabilities of a number of fused hydrindanone systems. Compounds I–V were selected for study and these comprise a fair cross section of known hydrindanone systems.

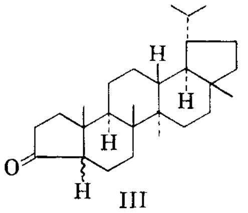
The ketones were obtained from various sources cited in the experimental section. Compound I was obtained by catalytic hydrogenation of the previously described[3d] Δ^2-5α,25α-spirosten-15β-ol followed by oxidation of the saturated alcohol.



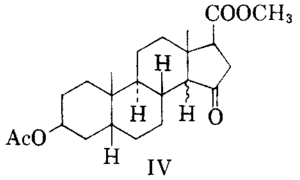
I



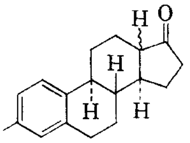
II



III



IV



V

The *cis* isomer of compound V is unexceptional, but the *trans* isomer requires comment. The latter was obtained[4] by retroaldolization of 18-hydroxyestrone. Although no stereochemistry was previously assigned to this compound at C-13, the rotatory dispersion curve (Fig. 3) is nearly identical with that of *trans* II and shows clearly that the compound has the 13β configuration (C/D *trans*). The equilibrium mixture of V contains essentially equal amounts of *cis* and *trans* isomers, but the material isolated here was a single compound and not the equilibrium mixture. It was obtained pure in a yield of only 15%, and was the only product isolated. This then is a case where the less stable product alone has been isolated under equilibration conditions, presumably because of some physical factor such as ease of crystallization.

The rotatory dispersion curves were first determined from both isomers in methanol solution except in the case of II, which was available in insufficient quantity. The curves for the *cis*- and *trans*-isomers of I and II have been reported[5] while those of III–V are reproduced in Figs. 1–3. From these curves the wave lengths were chosen which appeared to be best suited for analysis of mixtures of each pair.

It was desirable to use a wave length at which the difference between the rotations of the isomers was large, but other factors had to be considered

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(1) (a) Paper VII, N. L. Allinger, and J. L. Coke, *J. Am. Chem. Soc.*, in press. (b) Paper XXXIII, C. Djerassi, E. J. Warawa, R. E. Wolff, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

(2) Present address: Department of Chemistry, Stanford University, Stanford, California.

(3) (a) G. Quinkert, *Exper.*, **13**, 381 (1957). (b) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956). (c) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **78**, 4736 (1956). (d) C. Djerassi, T. T. Grossnickle, and L. B. High, *J. Am. Chem. Soc.*, **78**, 3166 (1956). (e) A. S. Dreiding, *Chem. and Ind.*, 992 (1954). (f) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, **52**, (1954). (g) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1949). (h) W. E. Bachmann and A. S. Dreiding, *J. Am. Chem. Soc.*, **72**, 1323 (1950). (i) R. P. Linstead, *Ann. Rep. Chem. Soc.* (London), 305 (1935). (j) A. Windaus, *Ann.*, **447**, 233 (1926).

(4) K. H. Loke, G. F. Marrian, W. S. Johnson, W. L. Meyer, and D. D. Cameron, *Biochem. et Biophys. Acta*, **28**, 214 (1958).

(5) C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw Hill, Inc., New York, New York, 1960, p. 59.

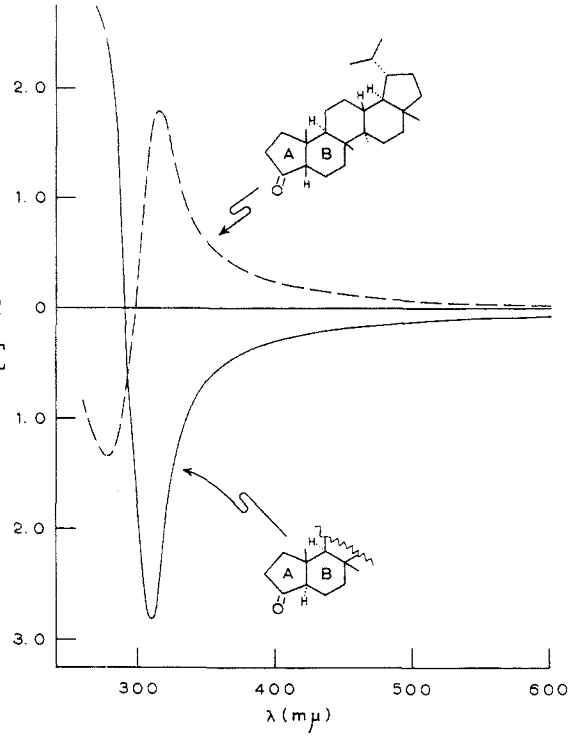

Fig. 1. Rotatory dispersion curves of A/B *cis* and *trans* III in methanol

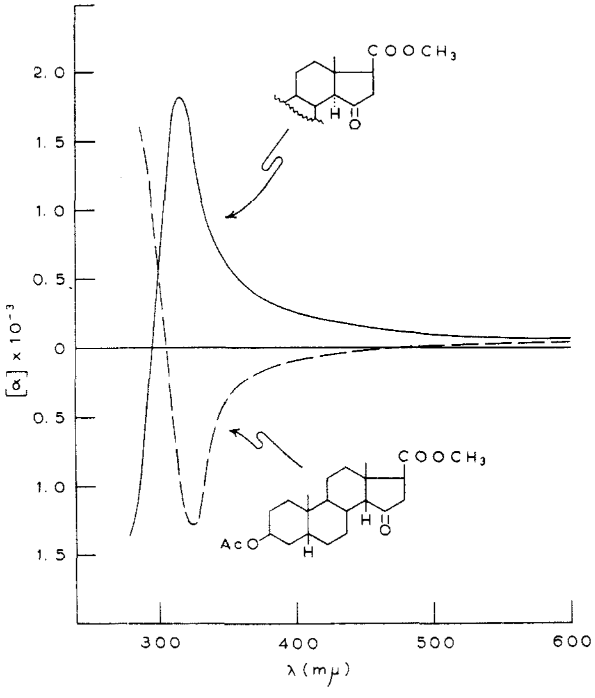

Fig. 2. Rotatory dispersion curves of C/D *cis* and *trans* IV in methanol

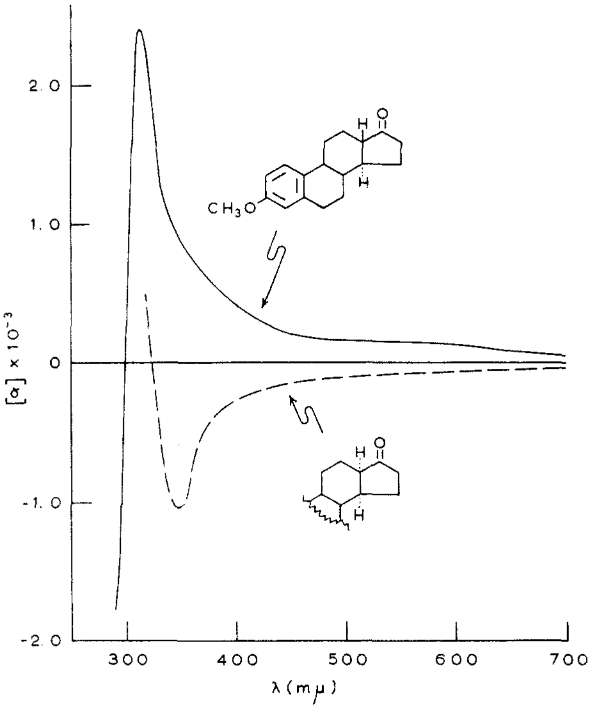

Fig. 3. Rotatory dispersion curves of C/D *cis* and *trans* V in methanol

also. It was not desirable to choose a wave length where either of the curves had a very steep slope as this would make the rotation difference very sensitive to errors in wave length setting, thereby increasing the error when different runs were compared. Also, the stability of the light source was better at wave lengths above 320mμ. By measuring the optical rotation of both pure epimers and the equilibrium mixture of the two at the wave length judged most suitable, the position of equilibrium was determined.

Optical rotation measurements in the ultraviolet region also appeared to be ideally suited for kinetic as well as equilibrium measurements.[5,6] Polarimetric rate constants obtained at the sodium D line have often been reported in the literature. As for most compounds the rotation in the ultraviolet is much larger than that at the D line, there are in general certain advantages in making the measurements at shorter wave length. In the present cases many of the compounds studied were available to the extent of only a few milligrams, and studies at the D line would have been impossible. Because of the enormous difference between the specific rotations for the isomers of a given hydrindanone at the proper wave length (on the order of 3000° near 315mμ), it was possible to carry out a kinetic run with approximately 1 mg. of compound. As the epimerization in base is a very fast reaction (observed second order rate constants are around 10^{+2} moles^{-1} l. sec.$^{-1}$), it was necessary to keep the concentrations rather low. Ordinarily the amount of hydroxide ion in the polarimeter tube was 10^{-5} to 10^{-6} moles. Special precautions therefore had to be taken to keep carbon dioxide out of the system efficiently. The rate and equilibrium constants ob-

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(6) C. Djerassi, *Rec. Chem. Progress*, **20**, 101 (1959).

TABLE I[a]

EQUILIBRIUM AND RATE DATA FOR EPIMERIZATION REACTIONS

		Rate Constants in Methanol (l., moles^{-1} sec.$^{-1}$) at t°K.		*Trans* ⇄ *Cis*				Rate Constants in Methanol (l., moles^{-1} sec.$^{-1}$) at t°K.		*Cis* ⇄ *Trans*			
Compound	Equilib., % *cis*[b]	293°	303°	$\Delta F_{293}^{\ddagger}$	$\Delta F_{303}^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	293°	303°	$\Delta F_{293}^{\ddagger}$	$\Delta F_{303}^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
I	>98	85.4	164.3	14.57	14.68	11.0	−12	—	—	—	—	—	—
II	61.4[c]	61.2	123.9	14.76	14.85	12.1	−9	(38.5)[d]	77.8[e]	15.03	15.13	12.1	−10
III	>99	457.2	939.9	13.59	13.63	12.3	−4	—	—	—	—	—	—
IV[f]	87	—	66.1	—	15.23	—	—	—	9.9[f]	—	16.37	—	—
V	55[g]	—	1160[f]	—	13.48[g]	—	—	—	930	—	13.62	—	—

[a] The values for $\Delta F^{\ddagger}$ and $\Delta H^{\ddagger}$ are in kcal./mole while those for $\Delta S^{\ddagger}$ are in cal./mole degree. Average probable errors in various quantities: $\Delta F^{\ddagger}$, 0.03 kcal./mole; $\Delta H^{\ddagger}$, 1 kcal./mole; $\Delta S^{\ddagger}$, 3 e.u.; ($T_{303} - T_{293}$), 0.1°. [b] The equilibrium constants were all measured at 303°K., and are assumed to be essentially independent of temperature over the range used. [c] The equilibrium composition of this compound has been found to be 58% *cis* in acetic acid-hydrochloric acid (private communication from Dr. G. Ourisson of the University of Strasbourgh). [d] This is a calculated value obtained from the data at 303° and the data for the *trans* isomer. [e] This is a calculated value obtained from the experimental equilibrium constant and the experimental rate of the *trans* isomer. An experimental value for the rate was found from the very small amount of *cis* compound available, and was 73 ± 10. The calculated value is believed to be more accurate. [f] This is a calculated value obtained from the data for the other isomer. [g] The *trans* isomer was available in such small amounts that the rotatory dispersion curve had to be determined at very low concentration. The accuracy of the curve is therefore probably less than usual, and the equilibrium constant and dependent quantities such as $\Delta F^{\ddagger}$ of expimerization of the *trans* (which was calculated from the data on the *cis*) may also be somewhat inaccurate.

tained are for the most part considered reliable to about ±2%. As the rates were measured at two temperatures in a few cases, the thermodynamic quantities for the epimerization could be found.

RESULTS

The equilibrium data, together with the rate constants for the epimerization reaction and the derivable thermodynamic quantities, are summarized in Table I.

For all of the hydrindanones studied in the present work, the equilibrium mixture contained predominantly the *cis* isomer, varying in amount from 55 to 99%. In the former case (V) the *cis* is more stable than the *trans* by only 0.1 kcal./mole, while in the latter (III), this difference is no less than 2.7 kcal./mole. This variation is far larger than has previously been generally recognized and is not accounted for by any of the previous theoretical discussions on the subject. One group of hydrindanones (cholestan-15-ones) is known in which the *trans* isomer appears to be the more stable.[3f,7]

The reactions were clearly second order under the conditions used, first order in ketone and first order in hydroxide ion. The rate constants were obtained from the data utilizing the standard methods for reversible or irreversible reactions as appropriate,[8] and the thermodynamic constants were found in the usual way.[9]

DISCUSSION

A priori it would seem that the epimerization reaction in basic solution must formally follow one (or both) of the following kinetic schemes[10,11]:

Mechanism A

$$(+)\text{R—H} + \overset{-}{\text{B}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (+)\text{R}^- + \text{H—B}$$

$$(+)\text{R}^- \xrightarrow{k_2} (\pm)\,\text{R}^-$$

$$(\pm)\text{R}^- + \text{H—B} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} (\pm)\,\text{R—H} + \text{B}$$

Mechanism B

$$(+)\,\text{R—H} + \text{B}^- \xrightarrow{k_1} (\pm)\text{R}^- + \text{H—B}$$

$$(\pm)\,\text{R}^- + \text{HB} \rightleftharpoons (\pm)\,\text{R—H} + \text{B}^-$$

In mechanism A the optically active carbanion exists as a discrete intermediate, and its epimerization is rate determining (k_2). In mechanism B the carbanion is epimerized as fast as it is formed. These appear to be the only reasonable alternatives consistent with the observed kinetics.

Earlier studies by Hsü, Wilson, and Ingold have shown that, at least in the particular case they studied, the rate of racemization of a ketone (optically active at the α-carbon) was the same as the rate at which the ketone took up deuterium from a deuteroxylated solvent, which would not be consistent with mechanism A.[10] Cases are known

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(7) The *cis* isomers are unknown.

(8) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley and Sons, New York, N. Y., 1953, p. 172.

(9) Ref. 8, p. 95.

(10) S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938).

(11) S. K. Hsü and C. L. Wilson, *J. Chem. Soc.*, 623 (1936).

in which reactions appear to proceed via a benzyl carbanion intermediate, and yet are stereospecific.[12]

One interpretation of these facts is that the carbanion is planar when adjacent to a carbonyl function, but pyramidal if adjacent to a group which can offer no better resonance stabilization than can a phenyl substituent. The isoelectronic situation of a nitrogen atom in place of the carbanion is informative, and appears to be quite analogous. Thus, an amide has a planar nitrogen atom[13] while aniline does not.[14]

The observed rate constants vary over a total factor of about 120, but $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ do not vary by significantly more than experimental error. The number of cases studied was too small to yield a discernible correlation between rate and structure.

The relative stabilities of *cis* and *trans* junctures in substituted hydrindanone systems present an apparently anomalous situation which had led to a considerable amount of speculation.[3] As little quantitative data have been available previously, the exact status of the problem has been unclear. One of the aims of the present work is to develop and apply to the available data a simple approximate theoretical treatment of the stabilities of these systems.

Conformational analysis has been applied extensively and with considerable success to six-membered rings,[15] but applications to rings of other sizes have been meager.[16,17] Studies carried out with the cyclopentane ring,[17] with which the present work is in part concerned, have served mainly to show how difficult the problem really is. Consequently, the approach used in this work has been what might be called a perturbation method. Instead of trying to deduce properties of the five-membered ring from basic principles, work is begun by comparing the parent decalin and hydrindane systems, for which data are available, and considering that the properties of the hydrindane are those of the decalin plus the perturbation. The perturbation is taken to be constant from one system to another and is then evaluated empirically. The properties of any substituted hydrindane can then be evaluated if the properties of the corresponding decalin are known (or can be predicted) by adding in the perturbation. Obviously such a simplified treatment is to be regarded as a first approximation, and whether it yields results of sufficient accuracy to be useful can only be judged empirically.

The available data for the decalins[18] show that for the reaction *cis*$\rightleftharpoons$*trans*, the thermodynamic quantities are $\Delta H^{586} = -2.72$ kcal./mole and $\Delta S^{586} = -0.55$ e.u.

The entropy effect appears small enough that in general when considering decalin systems it may be neglected[18] and ΔH can be equated with ΔF. This approximation is made for decalin systems throughout the remainder of this paper.

The thermodynamic quantities for the isomerization *cis*$\rightleftharpoons$*trans*-hydrindane are[19]: $\Delta H^{522} = -1070$ kcal./mole, $\Delta S^{522} = -2.3$ e.u. The entropy difference between the isomeric hydrindanes is therefore not negligible, and it should be taken into account. The value −440 kcal./mole at 273°K. is consequently used for ΔF. Part of the entropy effect may be a result of the symmetry of *trans*-hydrindane, but in the absence of more definite data a good approximation is to take $\Delta F = -0.4$ kcal./mole for isomerization of a *cis*- to a *trans*-juncture in a hydrindane in the vicinity of room temperature. If the corresponding value for the decalin juncture is taken as −2.7 kcal./mole, then the difference between these values (2.3 kcal.) can be regarded as a perturbation constant which includes entropy, and which can be used for free energy calculations in hydrindane systems.

Turning now to the structures I–V, it is possible to calculate by standard methods what the enthalpy of the epimerization of the ring juncture adjacent to the ketone would be if the ring were six-membered, using the energy 0.9 kcal. per *gauche* interaction. Adding the perturbation constant, the value for the actual system is obtained. The 2-alkyl and 3-alkyl ketone effects must be taken into account.[3a,20,21] In the cyclopentanone ring, the carbonyl angle is considerably compressed from the preferred value of 120°, even if the ring is planar. The planar form of cyclopentanone has the carbonyl oxygen placed favorably in a staggered position between the adjacent hydrogens, and it seems likely that the cyclopentanone ring will be

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[12] D. J. Cram, J. Allinger, and A. Langemann, *Chem. and Ind.*, 919 (1955).

[13] For a summary of available data, see W. J. Orville-Thomas, *Chem. Rev.*, **57**, 1179 (1957).

[14] C. A. Coulson, *Valence*, Oxford University Press, London, 1952, p. 244.

[15] For recent reviews see (a) W. G. Dauben and K. S. Pitzer in M. S. Newman's *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, N. Y., 1956, p. 1 (b) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

[16] (a) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959); N. L. Allinger and S. Greenberg, *J. Am. Chem. Soc.*, **81**, 5733 (1959); N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **81**, 5736 (1959); (b) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **25**, 262 (1960).

[17] (a) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959). (b) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959). (c) C. G. LeFevre and R. J. W. LeFevre, *J. Chem. Soc.*, 3549 (1956).

[18] (a) K. S. Pitzer and T. Miyazawa, *J. Am. Chem. Soc.*, **80**, 60 (1958). (b) J. P. McCullough, H. L. Finke, J. F. Messerly, S. S. Todd, T. C. Kincheloe, and G. Waddington, *J. Phys. Chem.*, **61**, 1105 (1957). (c) N. L. Allinger and J. Coke, *J. Am. Chem. Soc.*, **81**, 4080 (1959).

[19] N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, in press.

[20] W. Klyne, *Experientia*, **12**, 119 (1956).

[21] P. A. Robins and J. Walker, *J. Chem. Soc.*, 1789 (1955), *Chem. and Ind.*, 772 (1955).

TABLE II

$-\Delta F$ Kcal./mole for *trans* ⟶ *cis* FOR VARIOUS HYDRINDANONE SYSTEMS

	II		III		IV		V	
Compound	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
gauche	3	0	5	4	5	4	3	0
2-Alkyl ketone	1	1	1	1	1	1	1	1
3-Alkyl ketone	1	1	1	1	1	1	1	0
$-\Delta F$ (calcd.)	−0.4		1.4		1.4		0.0	
$-\Delta F$ (found)	0.4		2.7		1.0		0.1	

more nearly planar than the corresponding cyclopentane, and furthermore such puckering as does occur is expected to be brought about by having one (or both) of the β carbons move out of the plane.[17b] Thus, the 2-alkyl ketone effect will probably be less important here than in cyclohexanone systems. Similarly, a 3-alkyl ketone effect is of reduced importance in the five-membered ring. As numerical data are not yet available, the value 0.4 kcal./mole (approximately half that assigned in the cyclohexanone system) has been tentatively and somewhat arbitrarily assigned to each of these effects.

Effect of substituents. The above considerations apply as a first approximation to simple hydrindanones. Compound I, with the D/E *cis* fusion, is at present too complicated a system in which to predict relative stabilities. For the remaining systems (II–V), such predictions can be made as outlined, and the required data are summarized in Table II. In the *cis* isomer of IV there is a *gauche* interaction involving the B and D rings (between carbons 7 and 15) which is also present in the *trans* isomer, and in each compound there are various numbers of *gauche* interactions between the two rings of the hydrindanone systems, as listed in Table II. 2-Alkylketone interactions increase and 3-alkylketone interactions decrease the energy of the system.[20] Summarizing these energies and adding the perturbation constant gave the calculated values of $-\Delta F$, and these are compared with the experimental values in Table II.

For compound II the prediction is straight forward and in fair agreement with experiment. In compound III the *cis* isomer is predicted to predominate over the *trans* by about 10/1, and experimentally it predominates by 100/1. The abnormally large amount of *cis* isomer may be due to the 1,3-diaxial interaction between the methyl groups at carbon atoms 8 and 10. This interaction is known to distort the system considerably.[22] For structures IV and V, the agreement between prediction and experiment is good. The outstanding anomalies reported in the literature for hydrindanones are the 15-keto stanols.[3f] With these substances a *cis* C/D ring juncture forces the 18-methyl group to be very nearly eclipsed by the side chain. The *trans* compound in which ring D is less planar has this strain relieved to some extent, and it is probably the side chain which is displacing the equilibrium in this case. The carbomethoxy group in IV is flat and can apparently twist out of the way of the methyl substituent with the result that the carbomethoxy group is effectively too small to exert an energetically important eclipsing effect.

The simple perturbation method outlined in this paper offers a means of attempting to correlate the observed stabilities of the hydrindanone systems in so far as data are available. Some rather severe approximations were made in developing and applying the theory, and it is intended only as a starting point for the quantitative understanding of these systems. This treatment is only moderately consistent with the limited available data, and it may be too crude to be generally useful.

EXPERIMENTAL

Ketones. The *cis* and *trans* isomers of I were synthesized in the present work, while compounds II,[23] IV,[24] and V[4,25] have been reported in the literature, and were donated by the respective authors. The two isomers of III were furnished by Dr. T. G. Halsall of Oxford University.

5α,25a-Spirostan-15β-ol (I). Digitonin was converted to Δ^2-5α,25a-spirosten-15β-ol as described.[3d] The latter compound, 11.8 g., was reduced in 600 ml. of ethyl acetate using 1.0 g. of platinum oxide. The reaction was complete after 15 min. The solution was filtered and the solvent was evaporated. The residue, 11.4 g., m.p. 180–185°, was used directly in the next step. For analysis a sample was crystallized from acetone, m.p. 184–186°.

Anal. Calcd. for $C_{27}H_{14}O_3$: C, 77.83; H, 10.65. Found: C, 77.40; H, 10.65.

5α,25a-Spirostan-15-one. One and one-half grams of the alcohol (I) was dissolved in 300 ml. of acetone (purified by treatment with potassium permanganate) and oxidized at 19–21° by adding 1.6 ml. of 8*N* chromic acid reagent[26] dropwise during 45 min. The solution was allowed to stand for 3 hr., and then was poured into water. The precipitate was collected and taken up in chloroform. The chloroform layer was washed and dried, and the solvent was evaporated with the concurrent addition of methanol. The product crystallized, wt. 1.30 g., m.p. 183–191° (block) or 189–196° (capillary). It was found that the compound partially isomerized

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(22) Private Communication from Dr. G. Ourisson.

(23) J. Biellmann, P. Crabbé, and G. Ourisson, *Tetrahedron*, **3**, 303 (1958).

(24) A. Lardon, H. P. Sigg, and T. Reichstein, *Helv.*, **42**, 1457 (1959).

(25) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).

(26) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

at its melting point (by infrared spectra). The observed melting points of different samples were somewhat variable.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.46; H, 9.88.

22a,25a,14β-Spirostan-15-one. Epimerization of the 14α compound was carried out by dissolving 150 mg. in 10 ml. of methanol containing 127 mg. of potassium hydroxide, and refluxing the resulting solution for 15 min. The solution was diluted with water and extracted with chloroform. The chloroform extracts were washed to neutrality, dried, and the solvent was evaporated. The product, wt. 142 mg., m.p. 166–168°, was recrystallized from methanol, m.p. 166–169°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.02; H, 10.32.

General polarimetric procedure. A zirconium lamp was used for all of the 20° runs, and also for I at 30°. A xenon lamp was used at 30° for the other compounds. The wave length chosen for each compound was as follows: I, 345 mμ; II, 314 mμ; III, 314 mμ, IV, 327 mμ, and V, 330 mμ.

The polarimeter tube used was center filling, equipped with quartz windows and a water jacket. It had a length of 1 decimeter and a volume of slightly less than 1 ml. Water from a thermostated bath was circulated through the polarimeter jacket, and the temperature was measured as the water left the jacket. The polarimeter tube was first prepared by allowing it to stand for 4 hr. containing a solution of potassium hydroxide in methanol at the same concentration that was to be used in the kinetic run. The tube was then rinsed thoroughly with methanol, dried, and filled with nitrogen. A weighed sample of the ketone (about 5 mg.) was dissolved in 10 ml. of spectroscopic grade methanol at the desired temperature, and 1.00 ml. of standard potassium hydroxide (0.01 or 0.02*N* in methanol) at the desired temperature was added and the mixture was shaken. A 1-ml. aliquot was then transferred to the thermostated polarimeter tube and the rest of the solution was placed in a thermostated bath at the same temperature. Zero time was taken from when 0.5 ml. of the standard base had been added (about 10 seconds) to the solution of the compound. The first polarimetric reading was taken at about $t = 4$ min. Air was kept away from the solutions at all times by filling the pipettes, polarimeter tube, etc., with nitrogen, and storing and transferring the solutions under nitrogen. In all runs the polarimeter tube was emptied after about one-half life, and another aliquot of the solution in which the reaction had been proceeding in the thermostat was put in the tube, and the reaction was followed as before. If a plot of rotation *vs.* time for both samples could be fit by a single line, it was clear that no contamination of the reaction solution had occurred after the solution was prepared. This check was most important, as in the preliminary work the solution transfers were made in air in the ordinary way and the rate was inevitably much slower in the transferred solution. Any runs showing such contamination were discarded.

TABLE III

EPIMERIZATION OF COMPOUND I; A TYPICAL RATE RUN

t = 30.05° I = 0.001337 *M*, Time (Min.)	OH⁻ = 0.000822 M Solvent Methanol ("Spectra grade") α obs.°	t = 30.05° I = 0.001337 *M*, Time (Min.)	OH⁻ = 0.000822 M Solvent Methanol ("Spectra grade") α obs.°
0	—	121.8	0.116
4.5	0.353	129.5	0.102
9.3	0.345	145.0	0.072
11.8	0.336	160.0[a]	0.047
16.3	0.330	167.5	0.036
20.0	0.311	171.0	0.023
27.0	0.304	174.5	0.018
33.8	0.295	188.5	−0.009
40.0	0.288	191.3	−0.009
62.5	0.231	209.3	−0.036
72.0	0.205	220.2	−0.055
77.0	0.205	223.0	−0.057
95.5	0.167	00.0	−0.658
107.5	0.136		

[a] After this reading the polarimeter tube was emptied and refilled with another aliquot of reaction solution which had been kept in the thermostat. The points obtained after this time were not used to calculate the rate constant, but only to demonstrate qualitatively the absence of gross contamination of the original aliquot in transfer.

The results of a typical rate run are given in Table III.

The change in rotation in each case followed pseudo first order kinetics. The order of the reaction with respect to base was found by using different base concentrations in a few cases. It was concluded that, as expected, the reactions were second order overall, first order in ketone and first order in base.

The second order rate constants for the reversible reactions

$$A \underset{k'}{\overset{k}{\rightleftarrows}} B$$

were found using equations (1), (2), and (3), where t is elapsed time, α is the observed rotation at time t, α_0 and α_∞ are the values of rotation at $t = 0$ and $t = \infty$ respectively. For the irreversible reactions the expression simplifies to (4).

$$k + k' = \frac{\ln(\alpha - \alpha_\infty) - \ln(\alpha_0 - \alpha_\infty)}{(t)\,(\mathrm{OH}^-)} \qquad (1)$$

$$k + k' = k_0 \qquad (2)$$

$$k = k_0 \frac{(B)}{(\mathrm{A} + \mathrm{B})} \qquad (3)$$

$$k = \frac{\ln(\alpha_0 - \alpha_\infty) - \ln(\alpha - \alpha_\infty)}{(t)\,(\mathrm{OH}^-)} \qquad (4)$$

In cases where the rates were determined at two temperatures the thermodynamic quantities were found from equation (5)–(7).

$$\Delta F_1\ddagger = -RT_1 \ln K_1\ddagger \text{ where } K_1\ddagger = \frac{hk_1}{kT_1} \qquad (5)$$

$$\Delta S\ddagger = R(T_2 \ln K_2\ddagger - T_1 \ln K_1\ddagger)/(T_2 - T_1) \qquad (6)$$

$$\Delta H\ddagger = \frac{RT_1T_2 \ln (K_2\ddagger/K_1\ddagger)}{T_2 - T_1} \qquad (7)$$

Where k is Boltzmann's constant, k_1 is the rate constant at a temperature T_1, and the other symbols have the usual meanings.

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