with standardized barium hydroxide solutions. Samples of the acid or lactone under study were weighed into small glass weighing vessels and the weighing vessel containing the sample was transferred directly to a Pyrex test tube (32 × 300 mm.) after which 50 ml. of carbon dioxide-free water was added by means of a pipet. Runs at temperatures above 100° were carried out in heavy - walled test tubes of similar dimensions. Precautions were taken at each step to prevent the sample from picking up carbon dioxide from the atmosphere. The sealed tubes were heated in a constant temperature bath maintained at temperature by means of a boiling solvent for the desired period of time. The cooled sample tube was opened and the contents titrated immediately with standard barium hydroxide of the appropriate concentration. Titrations involving the addition of only small quantities of base were done under nitrogen which had been passed through a tube containing drierite.

The concentration of the samples was normally about 0.02–0.03 molal which required about 200 mg. of the compound per run. It was found that the concentration of the compound under study could be varied considerably without measurably affecting the observed equilibrium.

Perhaps it is worthwhile to point out that the equilibrium was established at *far* different rates for some of the compounds. Substitution in the 2-position slows the rate of establishment of equilibrium markedly. It required at least 30 days at 100° to establish equilibrium in the case of *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid while the 4-substituted compounds attained equilibrium in about 2 days at 100°. The same effect was observed in the solvolytic hydrolyses of *cis*-4-bromo-*cis*-3-hydroxycyclohexanecarboxylic acid lactone and the lactone of *cis*-2-bromo-*cis*-3-hydroxycyclohexanecarboxylic acid. Reaction was complete with the former in a matter of a few hours, while the 2-substituted compound had only reacted to the extent of 1.5% after 2 days. In all but one case, equilibrium was approached from both the hydroxy acid and the corresponding lactone.

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Conformational Analysis. XVIII. The Relative Stabilities of the *cis* and *trans* A/B Ring Junctures of Steroidal 4 and 6 Ketones[1,2]

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From optical rotation measurements in the ultraviolet region it has been found that cholestan-4-one contains 99% of the A/B *trans* and 1% A/B *cis* at equilibrium in methanol at 25°. For cholestan-6-one, the corresponding values are 88% *trans* and 12% *cis*. The conformational analysis of these systems is discussed.

Robins and Walker[4] first considered the conformational effects of converting alkyl substituted cyclohexane rings to cyclohexanones. The relative stabilities of their compounds were attributed to nonbonded interactions which were generalized by Klyne[5] as 2-alkyl and 3-alkyl ketone effects. Accurate experimental data on these effects is very sparse, but recent work on monocyclic cyclohexanones[6] has indicated that the 2-alkyl ketone effect of a methyl group is of negligible importance.

In the present work the 4- and 6-ketocholestanes have been chosen as systems in which to study these effects. These compounds are known in *cis* and *trans* forms, and the rotatory dispersion method[7] offers a convenient way to study quantitatively the epimerization reaction. The compounds were synthesized in general by literature procedures. A marked improvement in the conversion of Δ^5-cholestene to the $5\alpha,6\alpha$-epoxide was developed utilizing monoperphthalic acid in place of perbenzoic acid as the epoxidizing agent.

It was noted that the crude coprostane-6-one obtained in the present work contained an impurity having a very large negative optical rotation at the wave length used for the equilibration studies. Considerable care was therefore taken to obtain samples which were quite pure. For comparison purposes a sample of cholestan-4-one was also synthesized from Δ^4-cholestene by the hydroboration method of H. C. Brown,[8] followed by oxidation of the resulting alcohol.

Conformational analysis of the 6-ketones can be carried out by considering structures It and Ic. These structures should differ energetically from the 9-methyldecalins[9–11] only to the extent that an

(1) Paper XVII, N. L. Allinger, and M. A. Miller, J. Am. Chem. Soc., **83**, 2145 (1961).

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(3) Predoctoral Fellow of the Division of General Medical Sciences, U. S. Public Health Service, 1960–1962.

(4) P. A. Robins and J. Walker, *J. Chem. Soc.*, 3960 (1954); 1789 (1955); *Chem. & Ind.*, 772 (1955).

(5) W. Klyne, *Experientia*, **12**, 119 (1956).

(6) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).

(7) (a) N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960); (b) J. F. Biellmann, D. Francetic, and G. Ourisson, *Tetrahedron Letters*, No. **18**, 4 (1960).

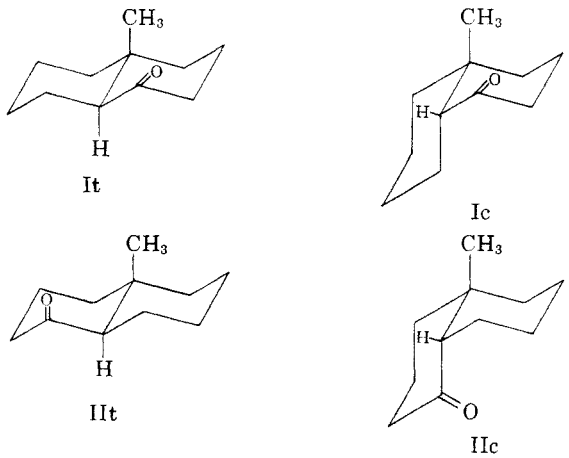
(8) (a) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956); (b) R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959); (c) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).

(9) N. L. Allinger and J. L. Coke, *J. Org. Chem.*, **26**, 2096 (1961).

(10) W. G. Dauben, O. Rohr, A. Labbauf, and F. D. Rossini, *J. Phys. Chem.*, **64**, 283 (1960).

(11) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 2118 (1952).

effect is exerted by the oxygen atom.[5] From this viewpoint, and neglecting specifically the distortions introduced into the molecule by the rest of the system, it should show a 2-alkyl ketone effect, (if such an effect existed) which Ic does not. For the isomerization of 9-methyldecalin *trans* $\rightleftharpoons$ *cis*, values for $\Delta H = +1.39 \pm 0.64$[10] and $+0.55 \pm 0.28$[9] kcal./mole have been reported, in agreement with the predicted value of 0.9 kcal./mole.[11] It is therefore predicted that for 6-ketocholestane, the *trans* isomer should be of lower enthalpy by this amount, and further, assuming that the entropy change for the isomerization is zero, the free energy for the isomerization is expected to favor the *trans* isomer by 0.9 kcal./mole. Experimentally, it was found that the 6-ketone contains 11.6% of the *cis* isomer at equilibrium, which corresponds to a free energy change of 1.20 kcal./mole. This value is only slightly larger than theory predicts, and is in reasonable agreement with both theory and experiment. These results indicate, in agreement with the earlier conclusion, that the 2-alkyl ketone effect as visualized by Robins and Walker and by Klyne is too small to really measure.



In the 4-ketones (IIt and IIc) the situation is a bit more complicated. The 2-alkylketone effect, if it existed, would be the same in both epimers, and hence does not enter into the problem at all. The *trans* epimer is energetically similar to the 6-ketone while the *cis* epimer shows another possible interaction needs to considered. This is the interaction of the oxygen atom with the 7α-hydrogen,[5] which is only 2.0 Å away (Dreiding models). The energy of this interaction was calculated knowing the distance separating the atoms and the energy constant for the interaction (ϵ 67.5 kcal./mole)[12] using the general method of Hill.[13] The energy calculated was 0.88 kcal./mole. The *cis* isomer should therefore be less stable here than with the corresponding hydrocarbons by this amount. Taking the enthalpy difference of the hydrocarbons as 0.9 kcal./mole, a free energy difference between the 4-ketones of 1.8 kcal./mole can be predicted.

The equilibrium for the reactions IIc $\rightleftharpoons$ IIt was studied, and it was found that the reaction went essentially to completion. The amount of coprostan-4-one at equilibrium was found to be about 1%. Because of the error in measuring a ratio this small, it can only be said that the free energy change here is greater than 2.1 kcal/mole. The agreement between theory and experiment is reasonable as far as can be told, and the results are summarized in Table I.

TABLE I

$-\Delta F$ for the Reaction *cis* $\rightleftharpoons$ *trans* (Kcal./Mole)

Cholestanone	Calcd.	Obs.
6-	0.9	1.2
4-	1.8	>2.1

From a comparison of the data on the 4- and 6-ketones it is seen that the interaction of the oxygen with the α-hydrogen at C-7 in IIc appears to have an energy of just about 1 kcal./mole, and consequently it can be predicted that *cis*-10-methyl-1-decalone will exist preferentially in the form Ic rather than the alternative form IIc. This compound has been prepared optically active and its absolute configuration has been established as enantiomerically related to coprostan-4-one.[14] The possible conformational structures then are (as far as rotatory dispersion is concerned) either "enantiomeric" to coprostane-4-one or "equivalent" to the coprostane-6-one. The rotatory dispersion curve of the sample of decalone[14] prepared is very similar to that of coprostane-6-one,[15] but of reduced amplitude consistent with the expected contamination by the *trans* isomer. Even so the amplitude of the bicyclic compound is three times that of coprostan-4-one. These data are not inconsistent with the conclusion that the *cis* isomer of the compound should exist in form Ic rather than IIc. Djerassi and Marshall[14] pointed out earlier that such an interpretation of their data was possible, and suggested the reason was one less axial methyl hydrogen interaction in Ic (their conformation D) than in IIc. When the total number of hydrogen-hydrogen interactions in both rings is counted however, it is seen to be the same in each conformation. In other words, the 3-alkyl ketone effect is the same in IIt and IIc, the methylene group in the latter filling the role of the methyl group in the former. The present interpretation is that with the *cis* isomer of the bicyclic ketone, Ic predominates over

(12) N. L. Allinger, J. Allinger, L. Freiberg, R. Czaja, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 5876 (1960).
(13) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).
(14) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).
(15) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

IIc, and this is primarily because of the interaction of the oxygen with the nearby hydrogen atom.

EXPERIMENTAL

5α,6α-Epoxycholestane. Cholesterol was converted to cholesteryl chloride[16] m.p. 96–98° with thionyl chloride. Reduction of the chloride with sodium and alcohol[17] gave cholest-5-ene, m.p. 89–91°. To 25 g. of this olefin in 150 ml. of ether was added dropwise a slight excess of monoperphthalic acid[18] in ether. The solution was allowed to stand for 3 hr., during which time additional monoperphthalic acid was added as indicated by testing with starch-iodide paper. The reaction mixture was then poured into water, the ether layer was separated, washed with water, dilute sodium bicarbonate solution and water. The ether was evaporated and the epoxide was crystallized from absolute ethanol, wt. 17.7 g., m.p. 76–76.2°.

Coprostan-6-one. The rearrangement of the epoxide was carried out with boron trifluoride–etherate [19] The chromatography was carried out using Merck acid-washed alumina which had been washed well with distilled water and activated by heating at 110° for 24 hr. Crystallization of the product from methanol gave the ketone, m.p. 132–133°.

Cholestan-6-one. The procedure used was the same as that described for the preparation of coprostan-6-one, except the material was chromatographed on basic alumina; yield 35%, m.p. 98–99°.

Coprostan-4-one.[20] This compound was obtained by rearrangement of the 4α,5α-epoxide,[19] needles, m.p. 104–106.5.° The purest sample used for the rotatory dispersion measurements had a m.p. of 108–109°.

Cholestane-4-one.[20] Sodium borohydride, 0.095 g., was dissolved in 5 ml. of diglyme, and to the stirred solution was added cautiously 0.212 g. of anhydrous aluminum chloride followed by 2.0 g. of Δ^4-cholestene. After 4 hr. the mixture was poured into water and the product was extracted with ether. The ether solution was washed with water and dilute bicarbonate solution. The ether was evaporated and to the residue was added 50 ml. of 2*N* sodium hydroxide in aqueous methanol followed by 5 ml. of 30% hydrogen peroxide. The solution was stirred for 15 min., diluted with water and extracted with ether. The ether extracts were washed with water, acidified potassium iodide solution, dilute sodium bicarbonate, and water. The solvent was evaporated and the residue was taken up in 75 ml. of acetic acid. A solution of 0.5 g. of chromium trioxide in 90% acetic acid was added and the mixture was allowed to stand for 5 hr. Benzene was then added and the mixture was stirred for 3 hr. The benzene layer was separated, washed with bicarbonate solution and water, and the benzene was evaporated. Chromatography of the residual oil on basic alumina gave .43 g. of product, m.p. 96–99.5°.

The same compound was obtained by chromatography of coprostan-4-one on basic alumina. The purest sample used for the rotatory dispersion measurements had a m.p. of 95.5–96°.

Rotatory dispersion measurements. The equipment and general procedure was described earlier.[7a] The curves for the compounds were all in reasonable agreement with those reported in the literature.[15] For the present equilibration studies rotations of the 6-ketones were measured at 318 mμ and those of the 4-ketones at 315 mμ utilizing a xenon light source. Equilibrium was approached from both sides by letting each compound stand 24 hr. in 0.4*N* potassium hydroxide solution in methanol. No change in the equilibrium point occurred after an additional 24 hr. The equilibrium point for the 4-ketones was 99.1 ± 2% *trans*, while that for the 6-ketones was 88.4 ± 2% *trans*.

DETROIT 2, MICH.

(16) H. Schmid and K. Kagi, *Helv. Chem. Acta.*, **33**, 1582 (1950).

(17) J. Mauthner and W. Suida, *Monatsh.*, **17**, 579 (1896).

(18) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., revised, D. C. Heath, Boston, p. 329.

(19) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

(20) The authors are also indebted to Dr. Carl Djerassi, Stanford University, for samples of this compound.

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Stereochemistry of the Cyclization of the Half-Esters of Diarylitaconic Acid

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The stereochemistry of the products obtained by the Stobbe condensation of 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone with dimethyl succinate and the dihydro-Stobbe products is proven. The conformational implications derived by a study of the cyclization of the dihydro-Stobbe products are discussed.

In the course of our investigation of certain lignans derived from podophyllin (*Podophyllum peltatum*) we wanted to prepare a quantity of 3-carbomethoxy-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone (Va), previously synthesized by Walker[1] and Gensler.[2]

From the Stobbe condensation of 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone with dimethyl succinate, we have isolated half-esters of diarylitaconic acid, Ia and Ib. Catalytic hydrogenation to the dihydro half-esters IIIa and IIIb and subsequent cyclization *via* the acid chloride afforded the respective tetralones, Va and Vb.

The tetralone, Va, which we prepared melted 5° higher than the reported[2] compound. This prompted us to investigate the geometry of the Stobbe isomers as well as the structures of the cyclized products Va and Vb. Heating Ib in the presence of acetic anhydride and anhydrous sodium acetate produced 1-acetoxy-3-carbomethoxy-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxynaphthalene,

(1) G. N. Walker, *J. Am. Chem. Soc.*, 75, 3390 (1953).

(2) W. J. Gensler, C. M. Samour, S. Y. Wang, and F. Johnson, *J. Am. Chem. Soc.*, 82, 1714 (1960).