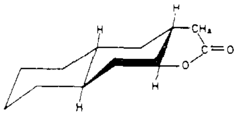
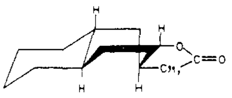
port herewith experiments which establish the enthalpy difference between these two forms in the vapor phase at 25° as 5.3 ± 0.3 kcal./mole.

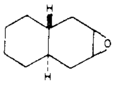
The *trans–syn–trans* and *trans–anti–trans* lactones I and II, like the corresponding stereoisomers in the perhydroanthracene series,[3,4] differ in that the central ring assumes the chair conformation in the former and a boat in the latter. We have prepared this pair of lactones in quantity and in a high state of purity for precision combustion calorimetry and heat of vaporization determinations.



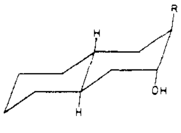
I



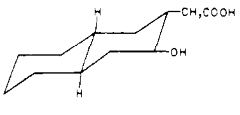
II



III



IV



V

The known[5] *trans*-Δ^2-octalin oxide III on reaction with sodiomalonic ester afforded the diaxial[6] adduct IV (R = $CH(COOEt)_2$), m.p. 60–63° (C, 65.5; H, 9.01). Saponification yielded the corresponding diacid, m.p. 166–167° dec., which, on heating in pyridine solution, underwent decarboxylation to give the diaxial hydroxy acid IV (R = CH_2COOH), m.p. 107.5–108° and 116–117° (C, 67.8; H, 9.25). Lactonization, which can occur only if the substituted ring flips into the boat form, required somewhat forcing conditions, *i.e.*, treatment with N,N′-dicyclohexylcarbodiimide or with *p*-toluenesulfonic acid in refluxing xylene. The lactone, II, thus obtained, melted at 49.6–50.3° (C, 74.2; H, 9.19), and on hydrolysis regenerated the 117° hydroxy acid showing that no rearrangement had occurred during lactonization.

Mild chromic acid oxidation of IV (R = CH_2COOH) afforded the corresponding keto acid, m.p. 97.5–98.5° and 106–107° (C, 68.6; H, 8.67), which retained the axial orientation of the acetic acid residue as shown by its ready isomerization with aqueous sodium hydroxide into an isomeric keto acid V (=O in place of —OH), m.p. 75–77° and 91.5–92° (C, 68.8; H, 8.36). Reduction of this substance with sodium and isopropyl alcohol afforded the diequatorial hydroxy acid V, m.p. 156–156.3° (C, 68.1; H, 9.47) which on treatment with *p*-toluenesulfonic acid in refluxing benzene was transformed into the corresponding lactone I, m.p. 41.8–42.5° (C, 73.9; H, 9.33). Hydrolysis of I regenerated the original hydroxy acid V.

From four combustions of each lactone (0.5–0.8 g. samples) in high precision calorimeters[7] (accuracy 0.02% or better) the enthalpy of II was found to be greater than that of I by 5.5 ± 0.2 kcal./mole. The vapor pressures of I and II were measured by the Knudsen effusion technique over the range 240 to 310° K. with a vacuum microbalance[8] and the heats of sublimation evaluated from the slopes of log P *vs.* $1/T$. The values thus determined were practically identical, that for I being 0.2 ± 0.2 kcal./mole greater than that of II. Hence, the enthalpy of the vapor of I is less than that of II by 5.3 ± 0.3 kcal./mole at 25°. This value is considered to represent ΔH for the conversion of the chair to the boat form of cyclohexane. The non-cancelling interactions (produced by the terminal rings on the central ring of I and II) appear to be small and are probably within the experimental error. A critical analysis of these interactions will be given in a future definitive publication.[9]

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[3] W. S. Johnson, *Experientia*, **7**, 315 (1951).

[4] W. S. Johnson, THIS JOURNAL, **75**, 1498 (1953).

[5] W. Hückel and H. Naab, *Ann.*, **502**, 136 (1933).

[6] *Cf.* E. L. Eliel in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 130.

[7] (a) To be described by Margaret A. Frisch, Ph.D. dissertation, University of Wisconsin, 1960. (b) Some of the runs were performed at the Argonne National Laboratory in collaboration with W. N. Hubbard.

[8] L. H. Spinar, Ph.D. Thesis, University of Wisconsin, 1957.

[9] This work was supported, in part, by grants from the National Institutes of Health, the National Science Foundation, and the Wisconsin Alumni Research Foundation.

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RECEIVED DECEMBER 5, 1959

THE ENERGY BARRIER FOR THE CHAIR-CHAIR INTERCONVERSION OF CYCLOHEXANE

Sir:

One of the questions of conformational analysis regarding cyclohexane is the energy barrier for the chair–chair interconversion.[1] We have obtained evidence from low temperature studies of the nuclear magnetic resonance spectrum of cyclohexane which provides a reliable estimate of this barrier.[2] At low temperatures, the n.m.r. spectrum of cyclohexane shows progressive broadening and ultimate separation into two broad peaks. A solution of cyclohexane (3 *M*) in carbon disulfide remains liquid below −110°. Below −50° the single C–H peak of cyclohexane (−85.2 c./s. from tetramethylsilane internal standard) begins to broaden rapidly. At a temperature of −64.9°, the peak has changed to a single broadly rounded peak with a half-width of 31 cycles. At −70° two distinct peaks are observed, which are incompletely resolved. This character persists to the lowest temperatures studied. Care was taken throughout to observe a sharp peak for the internal standard tetramethylsilane in order to eliminate any possible band broadening due to viscosity effects.

These results clearly show that the rate of the chair–chair interconversion has been slowed to the point that the average lifetime τ at −66.5° is of the same order of magnitude as the difference ($\nu_a - \nu_e$) for the equatorial and axial protons. From

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[1] Estimates of 9–10 kcal./mole (C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946)) and 14 kcal./mole (C. S. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947)) have been made.

[2] The measurements were carried out with a Varian Associates n.m.r. spectrophotometer, Model No. V-4311, operated at 60 mc.

TABLE I

SEPARATION OF AXIAL AND EQUATORIAL PROTON RESONANCE ABSORPTIONS IN CYCLOHEXANE AT LOW TEMPERATURES[a,b]

Temp., °C.	C–H$_a$ [c]	C–H$_e$ [c]	Average C–H$_a$, C–H$_e$ [d]	(C–H$_a$) – (C–H$_e$) [e]
−72.1	−75.7	−95.3	−85.5	19.6
−73.2	−74.6	−96.2	−85.4	21.6
−82.0	−72.4	−97.9	−85.1	25.5
−85.2	−72.0	−99.5	−85.7	27.5
−86.3	−72.2	−98.9	−85.5	26.7
−95.8	−72.2	−99.9	−86.0	27.7
−106 ± 3	−69.8	−97.4	−83.6	27.6

[a] The solution was 3 *M* cyclohexane in carbon disulfide and contained 0.04 ml. of tetramethylsilane/ml. of solution. [b] The signal occurring at higher field was assumed to be due to the axial hydrogen. [c] Apparent shift of peak maximum from tetramethylsilane in c./s. [d] c./s. from tetramethylsilane. [e] c./s.

the data at very low temperatures, this difference is 27.3 cycles per second.

It is thus possible to calculate a rate constant,[3] k_1 = 121 sec.$^{-1}$ (at −66.5°) for the chair–chair interconversion and to provide a good estimate of the energy barrier. Assuming an unstable intermediate with an equal probability of returning to either conformation, correcting for the resulting statistical factor of two, and applying the Eyring equation, ΔF^* = 9700 cal./mole for this process. Since ΔS^* is probably small, this also represents a close approximation for ΔH^*.

(3) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, New York, N. Y., 1959, p. 223.

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RECEIVED JANUARY 18, 1960

THE PARTIAL SYNTHESIS OF 3β-HYDROXY-17-KETOSTEROIDS. A NOVEL APPROACH

Sir:

We wish to report a novel approach to the semimicro synthesis of certain 3β-hydroxy-17-ketosteroids. Previous preparation of 3β-hydroxy-17-ketosteroids from the corresponding diols required numerous steps,[1,2,3] and mixtures often resulted. By protecting the 3β-hydroxyl through digitonide formation, the unprotected hydroxyl can be oxidized selectively.

5α-Androstane-3β,17β-diol (10 mg.) was dissolved in 2.5 ml. of 90% ethanol and treated with 2.5 ml. of digitonin solution (20 mg./ml. 90% ethanol) for 20 hours at room temperature. The resulting digitonide was centrifuged, washed with cold 90% ethanol and then ether to remove any free steroid. The dried digitonide was dissolved in 2.0 ml. of glacial acetic acid and 2.0 ml. of 1.2% CrO$_3$ in 60% acetic acid was added and stirred for about 30 minutes. The reaction could be followed by measuring the rapid increase in absorption at 568 mμ. Excess CrO$_3$ was destroyed with a few drops of saturated NaHSO$_3$ solution and the oxidized digitonide precipitated with 50 ml. of water. The precipitate was centrifuged, washed with water and dried by repeated additions of absolute ethanol and evaporation in a stream of nitrogen. The infrared spectrum showed a band near 5.75 μ identical to that of the digitonide of 3β-hydroxy-5α-androstan-17-one.

The digitonide was dissolved in a minimal volume of pyridine and let stand for 20 hours. Ether (50 ml.) was added and the digitonin was centrifuged and washed twice with ether. The combined ether washings and supernatant were washed with 0.2 *N* HCl, 0.1 *N* NaOH and with water till neutral, dried over sodium sulfate and evaporated to dryness. The infrared spectrum and melting point of the isolated material were identical to those of an authentic sample of epiandrosterone. The yield of 17-ketosteroid based on the amount of digitonide oxidized was approximately 50%. Oxidation under similar conditions of epiandrosterone digitonide resulted in no oxidation, indicating complete protection of the 3β-hydroxyl.

Similarly, starting with androst-5-ene-3β,17β-diol and 19-nor-5α-androstane-3β,17β-diol,[4] dehydroepiandrosterone and 3β-hydroxy-19-nor-5α-androstan-17-one (I), respectively, were prepared. The synthesis of (I) has not been described previously. Crystallization of (I) from methylene chloride and ether yielded colorless needles, m.p. 177–179°, $[\alpha]^{20}\text{D}$ + 108°; $\lambda_{\max.}^{\text{KBr}}$ 2.80 (OH), 5.75 μ (cyclopentyl C=O), 9.0, 9.1, 9.25, 9.45, 9.65, 9.83 9.9 μ. (I) was identical to a metabolite of 19-nortestosterone.[5] Oxidation of (I) with CrO$_3$ in 80% acetic acid resulted in a dione ($\lambda_{\max.}$ 5.75 and 5.85 μ), identical to the oxidation product of 17β-hydroxy-19-nor-5α-androstan-3-one[6] and to 19-nor-5α-androstane-3,17-dione.[7]

(1) E. Elisberg, H. Vanderhaeghe and T. F. Gallagher, THIS JOURNAL, **74**, 2814 (1952).

(2) M. Gut and M. Uskokovic, *J. Org. Chem.*, **24**, 673 (1959).

(3) C. Djerassi, A. J. Mason and M. Gorman, THIS JOURNAL, **77**, 4925 (1955).

(4) This compound did not form an insoluble digitonide. The entire reaction mixture was dried and the oxidation was carried out on the whole mixture.

(5) D. Kupfer and E. Forchielli, *Fed. Proc.*, Abstract forwarded for April Meetings.

(6) This compound was kindly supplied by Dr. Milan Uskokovic.

(7) This compound was kindly supplied by Dr. Mika Hayano.

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RECEIVED JANUARY 13, 1960

CHEMICAL EFFECTS ARISING FROM SELECTIVE SOLVATION: SELECTIVE SOLVATION AS A FACTOR IN THE ALKYLATION OF AMBIDENT ANIONS

Sir:

Ordinarily, the alkylation of phenolic salts in solution produces the ether (oxygen alkylation) in quantitative yields (Table I).[2] It has now been found, however, that, in certain selected solvents, solutions of phenolic salts undergo much carbon alkylation (Table I); these solvents are water, phenol and fluorinated alcohols.

It is proposed that, whereas phenoxide ions react exclusively at oxygen when dissolved in most sol-

(1) This research was supported by the United States Air Force under Contract No. AF49(638)-324 monitored by the A. F. Office of Scientific Research of the Air Research and Development Command.

(2) N. Kornblum and A. P. Lurie, THIS JOURNAL, **81**, 2705 (1959).