

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 $k_1 = 121 \text{ sec.}^{-1}$ (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, $\Delta F^* = 9700 \text{ cal./mole}$ 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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THE PARTIAL SYNTHESIS OF β -HYDROXY-17-KETOSTEROIDS. A NOVEL APPROACH

Sir:

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

5 α -Androstane- β ,17 β -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% CrO₃ 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 m μ . Excess CrO₃ was destroyed with a few drops of saturated NaHSO₃ solution and the

(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).

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 β -hydroxy-5 α -androstane-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 β -hydroxyl.

Similarly, starting with androst-5-ene- β ,17 β -diol and 19-nor-5 α -androstane- β ,17 β -diol,⁴ dehydroepiandrosterone and β -hydroxy-19-nor-5 α -androstane-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°, $[\alpha]_D^{20} + 108^\circ$; $\lambda_{\text{max}}^{\text{KBr}}$ 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 CrO₃ in 80% acetic acid resulted in a dione (λ_{max} 5.75 and 5.85 μ), identical to the oxidation product of 17 β -hydroxy-19-nor-5 α -androstane-3-one⁶ and to 19-nor-5 α -androstane-3,17-dione.⁷

(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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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).