added and after separation of the layers the ethyl acetate extract was washed thoroughly with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The total residue amounted to 33 mg., from which on recrystallization from acetone, 13.4 mg. of material melting at 227–229° was obtained. An additional recrystallization furnished analytically pure material, m.p. 230–231°, $[\alpha]^{23}D$ + 154° (absolute ethanol).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.18; H, 8.12.

The infrared spectrum of this material was identical with that obtained by the alternate procedure. Acetylation of 6 mg. of this material in 0.5 ml. of pyridine and 0.25 ml. of acetic anhydride at room temperature overnight gave after recrystallization from acetone–hexane 6 mg. of 11β,12β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate, m.p. 235–237°, $[\alpha]D$ +157° ($CHCl_3$), $\lambda_{max}^{alc.}$ 238 mμ (ε 16,700). Its infrared spectrum was found to be identical with that of a sample prepared by the alternate procedure.

12α-Fluoro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (12α-Fluorohydrocortisone 21-Acetate) (XXVIa).—Fifty milligrams of 11β,12β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate was dissolved in a mixture of 5 ml. of chloroform and 2.5 ml. of dry tetrahydrofuran contained in a polyethylene bottle and the solution cooled to −80° by means of an acetone–Dry Ice-bath. To this solution there was added slowly with stirring 2.0 ml. of hydrogen fluoride by means of a polyethylene pipet. The reaction mixture was maintained at −80° for 10 minutes, following which the acetone–Dry Ice-bath was replaced by an ice–salt-bath, thereby maintaining a reaction temperature of −10° for 6 hours. The reaction mixture was then pipetted into a stirred mixture of 50 ml. of chloroform and 50 ml. of ice-water in a polyethylene beaker and carefully neutralized with sodium bicarbonate. The chloroform solution was separated, washed with water, dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 17 mg. of 12α-fluorohydrocortisone 21-acetate melting at 228–229° and having $[\alpha]^{22}D$ +106° (chlf.); λ_{max}^{Nujol} 3.00, 5.75, 5.85 and 6.07μ.

Anal. Calcd. for $C_{23}H_{31}O_6F$ (422.48): C, 65.39; H, 7.39. Found: C, 65.22; H, 7.27.

12α-Chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (12α-Chlorohydrocortisone 21-Acetate) (XXVIb).—To a solution of 200 mg. of 11β,12β-oxido-Δ⁴-pregnene-17α,-21-diol-3,20-dione 21-acetate in 50 ml. of chloroform, cooled in an ice-bath, 3.55 ml. of a 1.08 *M* solution of hydrogen chloride in chloroform was added dropwise. After 1 hour at 0° the solution was neutralized with 5% sodium bicarbonate solution, washed with water and evaporated to dryness, *in vacuo*. Crystallization of the residue from acetone–hexane gave 82 mg. of 12α-chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-acetate, m.p. 255–256°, $[\alpha]^{23}D$ +120° (95% EtOH); λ_{max}^{Nujol} 2.71, 2.95, 5.76, 6.02, 6.21 μ.

Anal. Calcd. for $C_{23}H_{31}O_6Cl$ (438.93): C, 62.93; H, 7.12. Found: C, 62.71; H, 7.16.

12α-Chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (12α-Chlorohydrocortisone) (XXVII). (a) **From XXVIb.**—A suspension of 50 mg. of 12α-chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione in 5 ml. of methanol containing 0.12 ml. of 70% perchloric acid was stirred at room temperature for 17 hours, during which time the compound dissolved. The solution was neutralized with 5% $NaHCO_3$, diluted with 40 ml. of water and extracted with chloroform. The chloroform extract was washed with water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 30 mg. of XXVII, m.p. 210–212°, $[\alpha]^{23}D$ +86° (dioxane), $\lambda_{max}^{alc.}$ 239 mμ (ε 16,000); λ_{max}^{Nujol} 3.94, 5.90, 6.01, 6.22 μ.

Anal. Calcd. for $C_{21}H_{29}O_5Cl$ (396.90): C, 63.55; H, 7.36; Cl, 8.94. Found: C, 63.79; H, 7.93; Cl, 8.90.

(b) **From XXVb.**—To a solution of 70 mg. of XXVb in 10 ml. of dioxane 2.8 ml. of 2.5 *N* hydrochloric acid was added and the solution left at room temperature for 1 hour; ten 10 ml. each of chloroform and water were then added and the mixture neutralized with 5% $NaHCO_3$. The chloroform layer was separated, washed with water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone gave 30 mg. of XXVII.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

Conformational Analysis. XX. The Conformation of the Acetyl Side Chain of Pregnane-20-one[1,2]

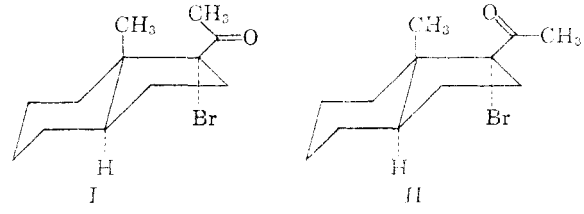
BY NORMAN L. ALLINGER AND MARGARET A. DAROOGE[3]

RECEIVED APRIL 19, 1961

Dipole moment measurements have been used to show that the preferred conformation of the side chain in the pregnane-20-one system is one in which the oxygen attached to C-20 is nearly eclipsed by C-16 and is slightly above the plane defined by carbons 16, 17 and 20.

In general there exist small barriers to rotation about single bonds. With the steroid system there exists a fairly high degree of rigidity and little opportunity for rotational isomers. In the special case of pregnane-20-one, however, the conformation of the side chain is not clear *a priori*. Since various chemical and biological properties of the compound are dependent on the "polarity" of such a system, and the "polarity" is in turn dependent on the side chain conformation, this conformation is of some interest.

Djerassi[4] has suggested from application of the α-haloketone rule[5] to 17α-bromo-5α-pregnane-3β-acetoxy-20-one that the latter has the side chain in the general conformation I rather than the general alternative II.



I II

The present work has been undertaken to try to answer the question of the orientation of the side chain in pregnane-20-one itself. Since it is known that the presence of a halogen atom in an α-halo

(1) Paper XIX, J. Allinger, N. L. Allinger, L. E. Geller and C. Djerassi, *J. Org. Chem.*, **26**, 3521 (1961).

(2) This research was supported in part by the Office of Ordnance Research, U. S. Army.

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

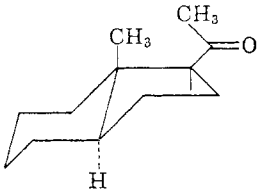
(4) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 128.

(5) Reference 4, p 120

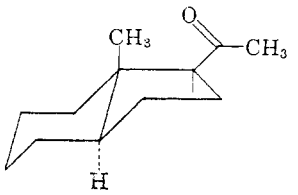
ketone causes various kinds of interactions,[6] the parent compound may differ from its halo derivatives in this respect. Removal of the halogen from the compound leads to a system to which the rotatory dispersion method is no longer easily applicable, and another experimental technique must be sought for solution of the problem.

An examination of the exact geometry of the system was made utilizing Dreiding stereomodels. In this case, and in *trans*-hydrindane systems in general, the cyclopentane ring is not free to pseudorotate.[7] Models indicate that the cyclopentane ring is in the half-chair form,[8] and that it is fairly inflexible. The subsequent discussion assumes that these indications are correct. It is clear that severe van der Waals repulsions between the side chain and the remainder of the system will occur in most of the rotational arrangements. The rotational barrier in acetone is rather small (0.8 kcal./mole[9]), and hence that portion of the barrier which is not due to van der Waals repulsions is neglected at this point.

The two groups of conformations in which there is little or no (less than about 1 kcal./mole) van der Waals repulsion energy can be represented approximately by III and IV. More exactly, looking

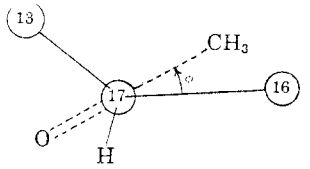


III



IV

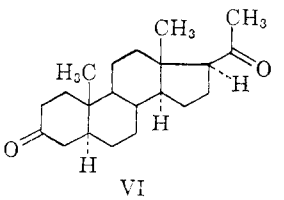
down the bond from carbon 17 toward carbon 20



V

as shown in formula V, and measuring the dihedral angle ϕ as shown, the strain-free conformations have ϕ in the range of 200–240° for III or 330–30° for IV.

To determine which of these groups of conformations in fact represent the actual molecule, a determination of the dipole moment of 5α-pregnane-3,20-dione (VI) was carried out. This particular



VI

compound was chosen because the 3-ketone provides another dipole moment of known magnitude and direction which will add vectorially to the 20-ketone and which will allow the desired differentiation to be made. The desired dione was already known, and its synthesis was straightforward. 5α-Pregnane-20-one, also a known compound, was prepared as a model. For the 3-ketone, the dipole moment of cholestanone has recently been determined under identical conditions, and the recorded value[10] was used.

Examination of models shows that the angle between the dipoles is close to 90° in IV, and it varies little as the dihedral angle is steadily increased from 330° to 30°. For conformation III, on the other hand, as ϕ goes from 240° to 200°, the angle between the dipoles goes from about 90° up to 140°. Hence, a large measured angle between the dipoles would be definitive, but an angle of around 90° would not be.

Using the experimental values for the dipole moments of 3-cholestanone (3.01 D.), 5α-pregnane-20-one (2.55 D.) and 5α-pregnane-3,20-dione (2.25 D.), the angle between the dipoles was calculated to be 133°. Conformation IV can therefore be eliminated as a possibility.

Since any value for the angle between the dipoles corresponds to two different rotational conformations, the other conformation was checked. It is one in which the C-18 and C-21 methyl groups have nearly the same geometrical relationship as 1,3-diaxial methyls on a cyclohexane ring. This is an arrangement known to be of very high energy,[11] and this conformation needs no further consideration.

The conformation of the side chain seems thus established as indicated, and this corresponds to the conformation found by Djerassi for the bromo derivative. Actually, of course, the 133° dipolar angle is a weighted average, and it may be assumed that the side chain oscillates about this value.

Experimental

Tigogenin.—The preparation was carried out by hydrogenation of diosgenin[12] according to the procedure of Marker, *et al.*[13] The compound was crystallized from ethyl acetate to m.p. 203–206.5°.

Δ^{16}-Pregnen-3β-ol-20-one.—The degradation of tigogenin was carried out according to the procedure described for diosgenin[13,14] except that the compound was heated in a sealed tube with acetic anhydride for only 4 hours. Δ^{16}-Pregnen-3β-ol-20-one was crystallized from methanol, m.p. 206–208° (reported[15] m.p. 201°).

5α-Pregnan-3β-ol-20-one.—Δ^{16}-Pregnen-3β-ol-20-one, 1.5 g., was hydrogenated with 0.15 g. of 10% palladium-on-barium sulfate in 50 ml. of ethyl acetate. The theoretical amount of hydrogen was taken up in 15 minutes and the solution was filtered. The solvent was evaporated and the

(6) For leading references see N. L. Allinger, J. Allinger, L. A. Freiberg, R. Czaja and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 5876 (1960).

(7) K. S. Pitzer and W. E. Donath, *ibid.*, **81**, 3213 (1959).

(8) F. V. Brutcher, Jr., T. Roberts, S. J. Barr and N. Pearson, *ibid.*, **81**, 4915 (1959).

(9) (a) J. D. Swalen and C. C. Costain, *J. Chem. Phys.*, **31**, 1562 (1959); (b) S. C. Schumann and J. G. Aston, *ibid.*, **6**, 485 (1938).

(10) N. L. Allinger, H. M. Blatter, M. A. DaRooge and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961).

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

(12) The authors are indebted to Dr. Carl Djerassi, Stanford University, for kindly furnishing this material.

(13) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *J. Am. Chem. Soc.*, **65**, 1199 (1943); **69**, 2167 (1947).

(14) R. E. Marker and E. Rohrmann, *ibid.*, **61**, 3592 (1939); **62**, 518 (1940).

(15) W. Klyne, B. Schacter and G. F. Marrian, *Biochem. J.*, **43**, 231 (1948).

residue was crystallized from methanol to give 1.25 g. of material, m.p. 193–195.5° (reported[16] m.p. 194°).

5α-Pregnan-3,20-dione.—5α-Pregnan-3β-ol-20-one, 1.1 g., was dissolved in 50 ml. of acetone (previously distilled from potassium permanganate) and 1.5 ml. of Jones reagent (8 *N* in H_2SO_4·H_2O) was added dropwise over a 15-minute period. The mixture was allowed to stand at room temperature 1.0 hr. Water was added and the solid was removed by filtration. The solid was crystallized from methanol and gave 890 mg. of plates, m.p. 202–202.5° (reported[17] m.p. 200.5°).

Δ²-22α,25α,5α-Spirostene was prepared by synthesizing tigogenin tosylate and then eliminating the tosyl group by heating in γ-collidine. Crystallization of the product from methanol yielded needles, m.p. 183–185° (reported[18] m.p. 182–184°).

22α,25α,5α-Spirostane was prepared by hydrogenation of 2.3 g. of Δ²-22α,25α,5α spirostene in 50 ml. of ethanol with 100 mg. of 10% palladium-on-carbon. The solution was filtered and the solvent was removed. The residue was crystallized from methanol and gave 2.2 g. of plates, m.p. 175–178° (reported[18] m.p. 173–175°).

5α-Pregnane-20-one.—Δ²-22α,25α,5α-Spirostane, 2.2 g., was heated in a sealed tube with 6 ml. of acetic anhydride for 4 hours. After cooling, the mixture was poured into a flask and 4 ml. of water was added. The mixture was warmed slightly to decompose the excess acetic anhydride. Acetic acid, 25 ml., was added and the mixture was cooled to 10°. A solution of 750 mg. of chromium trioxide in 5 ml. 80% acetic acid was added slowly over a 20-min. period. The mixture was allowed to stir at room temperature for 1.5 hours and was poured into water and extracted with chloroform. The chloroform was washed well with water, sodium bicarbonate solution, water and then was dried. After removal of the solvent a waxy solid was obtained. This solid was dissolved in 50 ml. of ethyl acetate with 200 mg. of palladium-on-barium sulfate catalyst and subjected to atmospheric hydrogenation. The theoretical amount of hydrogen was taken up in 15 minutes. The solution was filtered, the solvent was removed and the residue was crystallized from methanol to give 1.3 g. of colorless needles, m.p. 115–115.5° (reported[19] m.p. 115°).

(16) W. Taylor, *Biochem. J.*, **60**, 380 (1955); **62**, 332 (1956).

(17) S. Lieberman, K. Dobringer, B. R. Hill, L. F. Fieser and C. P. Rhoads, *J. Biol. Chem.*, **172**, 263 (1948).

(18) J. Pataki, G. Rosenkranz and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 5375 (1951).

TABLE I

DIPOLE MOMENT DATA; BENZENE SOLVENT, 25°

N_2	d_{12}	ϵ_{12}
5α-Pregnan-3,20-dione (VI)		
0.000000000	0.873855	2.2748
.000447794	.874108	2.2786
.00103232	.874635	2.2831
.00111081	.874705	2.2837
.00135417	.874764	2.2858
α = 8.052	β = 0.744	$P_e + P_a$ = 100.08
d_1 = 0.87383	$P_{2\infty}$ = 203.5	μ = 2.25
5α-Pregnane-20-one		
0.000000000	0.873739	2.2743
.00028062	.873838	2.2770
.00047926	.874048	2.2793
.00083567	....	2.2826
.00115865	0.874348	2.2859
α = 10.01	β = 0.553	$P_e + P_a$ = 100.12
d_1 = 0.87373	$P_{2\infty}$ = 233.3	μ = 2.55

Dipole Moments.—The dipole moments of 5α-pregnan-20-one and 5α-pregnan-3,20-dione were run in benzene at 25° and the moment of 3-cholestanone was reported earlier.[10] The data are given in Table I. The dipole moment apparatus used has been previously described.[10] The moments were calculated by essentially the method of Halverstadt and Kumler[20] utilizing an IBM 650 computer as previously described.[21] Because of the high molecular weights of these compounds, an attempt was made to account approximately for atomic polarizability by taking $P_e + P_a = 1.10\ M_D$, where the latter was found from the table of Vogel.[22] The experimental error is ± 0.03 D.

(19) H. Wieland, O. Schlichting and R. Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926).

(20) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(21) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

(22) A. I. Vogel, W. T. Cresswell, G. J. Jeffrey and J. Leicester, *Chemistry & Industry*, 358 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY, ITHACA, N. Y.]

Ultraviolet Spectra of Several Hydro- and Functional Group Derivatives of Bicycloheptadiene Containing 7-Spiro Substituents

BY CHARLES F. WILCOX, JR., AND RHODA R. CRAIG[1]

RECEIVED MAY 2, 1961

The ultraviolet spectra of several spirocyclopropane and spirocyclopentane bridge substituted [2.2.1]bicyclic systems containing olefin and dimethyl maleate chromophores are analyzed. It is shown that these chromophores couple weakly in contrast to the strong coupling in the geometrically related [2.2.1]bicycloheptadiene. The bathochromic shifts caused by bridge substituents increase with their size which can be interpreted either as steric control of the planarity of the maleate chromophore or an increase in the polarizability of the substituents. A probable charge transfer band is identified and its abnormally high intensity discussed. No unique band related to the spirocyclopropane group is observed.

The preparation of various unsaturated [2.2.1]-bicyclic molecules with 7-spirocyclopropane and 7-spirocyclopentane substituents has been described and their ground state properties discussed.[2] This paper is concerned with the ultraviolet spectra of compounds I, II, III, IV, V, and VI and the degree to which the bridge substituent affects the spectra either by direct interaction with the maleate or double bond chromophores, or by modifying the interaction between this pair of chromophores. Because of the similar geometry of these molecules to that of bicycloheptadiene VII, whose spectrum has been analyzed,[3] these compounds offer further insight into the factors which determine the interaction of non-conjugated chromophores.

(1) Taken from the dissertation submitted by R. R. Craig to Cornell University for the Ph.D. degree, June, 1961.

(2) C. F. Wilcox and R. R. Craig, in press.

(3) C. F. Wilcox, Jr., S. Winstein and W. G. McMillan, *J. Am. Chem. Soc.*, **82**, 5450 (1960).