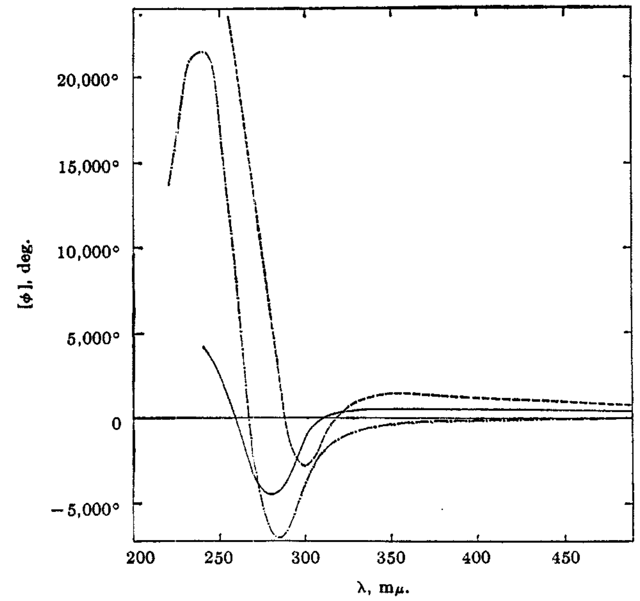

Figure 1.—1,3-Cholestadiene (III), ———; pyronimbic acid (II), - - - -; 3,17 β-diacetoxy-1,3-androstadiene (IV), – · · – ·.

absolute stereochemistry of nimbin, the ORD of II is also of interest in the understanding of the "complex" curves[5b] hitherto observed exclusively in a group of steroidal 1,3-dienes. The ORD curve[6] of II is given in Figure 1 and is compared with those of 1,3-cholestadiene (III) and 3,17β-diacetoxy-1,3-androstadiene[7] (IV). Dreiding models of II with both possible *trans* configurations at the juncture of rings A and B, *i.e.*, 5α,10β and 5β,10α, show that the diene system is skewed in the sense of a left-handed helix in the former, and of a right-handed one in the latter. Consequently, theory[5] predicts a negative Cottone ffect associated with the absorption band at longest wavelength (280 mμ) for the 5α,10β configuration, and a positive one for 5β,10α. Since the ORD curve of II (Figure 1) shows a *negative* Cotton effect, the former alternative applies, and II is correctly represented by the formula shown.[8] The fact that IV exhibits the negative Cotton effect predicted from the chirality of its diene proves that the presence of an enol ester group on the chromophore does not interfere with the validity of the rules connecting this chirality with the sign of the Cotton effect. Some other examples of enolic dienes obeying these rules are given in ref 5a and b.

The ORD curves of II–IV belong to the "complex" type[5b] characterized by a relatively weak Cotton effect superimposed upon a strong background of opposite rotation. Such "complex" curves had thus far been observed consistently and exclusively with steroidal 1,3-dienes; II is the only compound found up to now to give this type of curve without actually being a 1,3-dienic steroid.

Since bicyclic compounds with the same $\Delta^{1,3}$ chromophore (compounds 2–4 of ref 5b) show intense, almost symmetrical, Cotton effects with little background influence, it is tempting to assume that the tendency to avoid a marked nonbonded interaction between the hydrogens at positions 1 and 11α in the steroid $\Delta^{1,3}$-dienes leads to a flattening of the chromophore with consequent weakening[9] of the Cotton effect. The "complex" curve of II, which lacks the proton at C-1, shows that this effect can at least not be the *only* cause for the appearance of such curves.

The large molar rotation of II at the sodium D line (+478°) *opposite* in sign to that of the Cotton effect again emphasizes the danger of using $[\alpha]_D$ values for stereochemical assignments *even in the case of dissymmetric chromophores.*

See Table I for experimental data.

TABLE I
EXPERIMENTAL DATA

Compd	$[\Phi]_{extremum}$	$\lambda_{extremum}$ mμ	Solvent	Concn, g/100 ml
1,3-Cholestadiene	−5,000	280	Cyclohexane	0.071
	+4,200	235		
Pyronimbic acid	−2,800	302	Dichloromethane	0.049
	+23,600	255		
3,17β-Diacetoxy-1,3-androstadiene	−5,900	285	Isooctane	0.050
	+21,500	240		

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[6] The ORD curves of II and IV were determined on a Cary 60 spectropolarimeter, that of III on a Rudolph recording spectropolarimeter.

[7] R. Wiechert and G. Schulz, *Chem. Ber.*, **98**, 3165 (1965).

[8] Dreiding models show that the diene system in both C-9 epimers of pyronimbic acid has the same chirality. Consequently, the sign of the Cotton effect should be the same in either case.

[9] E. Charney, *Tetrahedron*, **21**, 3127 (1965).

Conformation of the 17β Side Chain of C-20 Oxygenated Pregnane Derivatives as Determined by Nuclear Magnetic Resonance Coupling Constants[1a,b]

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February 8, 1966

Pronounced differences in the behavior of epimeric C-20 alcohols in the Barton reaction,[2] lead tetraacetate oxidation, and other reactions used in the functionalization of C-18 have been attributed to differences in the spatial relationship to the C-18 group[3] of the reactive oxygen intermediates involved. Related differences in solvolytic reactions have been rationalized on the same basis.[4]

Attempts have been made to define these relationships using calculations based on van der Waals radii and molecular rotations.[4] More recently, Klyne[5] and Diassi[6] suggested from hydrogen-bonding studies that the conformation of the 17β side chain is such that the 20-hydrogen is usually on the same side of the steroid nucleus as the C-18 methyl group. None of these studies was able to specify the exact conforma-

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[1] (a) From the Ph.D. Thesis of H. Lee, University of California, San Francisco, Calif., 1966. (b) This investigation was supported in part by a Public Health Service research Grant (AM-05016) from the National Institute of Arthritis and Metabolic Disease, U. S. Public Health Service. (c) To whom inquiries concerning this work should be addresed.

[2] *Cf.*, A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian, and D. H. R. Barton, *J. Am. Chem. Soc.*, **82**, 2973 (1960).

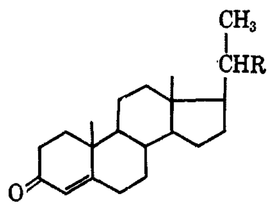
[3] *Cf.* L. Velluz, G. Muller, R. Bardoneschi, and A. Poittevin, *Compt. Rend.*, **250**, 725 (1960).

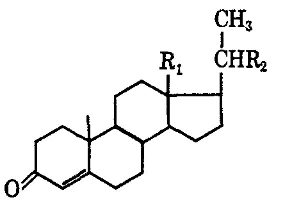
[4] D. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962).

[5] J. C. Danilewicz and W. Klyne, *J. Chem. Soc.*, 1306 (1965).

[6] A. I. Cohen, B. Keeler, E. Beker, and P. A. Diassi, *J. Org. Chem.*, **30**, 2175 (1965).

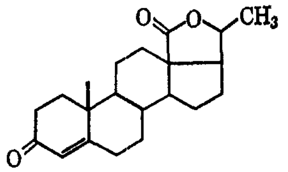
CHART I



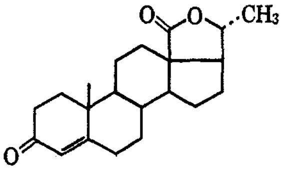


1, R = α-OH (7)
2, R = β-OH (7)
3, R = α-OAc (7)
4, R = β-OAc (7)
5, R = α-OTs (13)
6, R = β-OTs (13)

7, R_1 = CHNOH; R_2 = α-OH (2, 8)
8, R_1 = CHNOH; R_2 = β-OH (2, 8)
9, R_1 = CN; R_2 = α-OTs (13)
10, R_1 = CN; R_2 = β-OTs (13)



11 (8)



12 (8)

tions of the side chain, nor is the behavior of compounds bearing hydrogen-bonding groups necessarily representative of analagous compounds lacking such groups. The conformation could, on the other hand, be assigned from the Karplus equation dihedral angles if the coupling constants between the 17α-hydrogen and the 20-hydrogen were known, and this was done in the present work. The coupling constants of 12 representative compounds (Chart I) of 18-functionalized and nonfunctionalized compounds as well as 18 → 20 cyclized compounds in deuteriochloroform solution are listed in Table I. Within experimental error (±0.3 cps), the same values were obtained in benzene solution.

TABLE I

COUPLING CONSTANTS AND DIHEDRAL ANGLES

Compd	J_{A_3X}	J_{BX}	Angles, deg	
			Calcd[a]	Obsd[b]
1	6.0	7.5	155	...
2	6.3	9.0	173	...
3	6.0	7.3	153	...
4	6.0	9.7	180	...
5	6.5	8.4	161	...
6	6.0	9.6	180	...
7	6.5	3.5	129	...
8	6.0	9.0	173	...
9	6.5	7.0	151	...
10	6.2	9.2	180	...
11	6.5	4.7	38	32
12	6.5	0	84	90

[a] From the Karplus equation. [b] From Dreiding models.

The coupling pattern of the proton on C-20 is compatible with an A_3BX system where A_3 arises from protons on C-21 and B is the 17α proton. The coupling constant between A_3 and X is obtained from the doublet corresponding to three protons arising from C-21; this magnitude of J_{A_3X} (6.0–7.0 cps) would be expected from a freely rotating methyl group and was invariant with the configuration at C-20.

J_{BX} was, however, dependent on the configuration at C-20. The coupling constant is 7.0–7.5 cps for the 20α-substituted compounds, and 9.0–9.7 cps for the 20β-substituted derivatives. J_{BX} in the 18 → 20 cyclized compounds is quite different from that of the foregoing noncyclic compounds, although J_{A_3X} is similar, indicating that the rigid cyclic system does not possess the same conformation as the noncyclic system.

The dihedral-angle (ϕ) dependence of the vicinal proton coupling constants ($J_{HH'}$) can be expressed by the Karplus equation,[9] which is applicable to closely

$$J_{HH'} = A + B \cos \phi + C \cos 2\phi$$

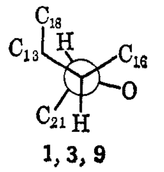
related systems of this nature, where $A = 4.22$, $B = -0.5$, and $C = 4.5$.

Dihedral angles calculated from the Karplus equation were in good agreement (±6°) with the observed values obtained from Dreiding models for **11** and **12** (Table I). In the open-chain compounds, the coupling constant is not affected by the nature of the groups on C-13, or by the substituents on the hydroxyl group.

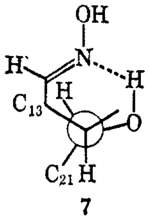
Although the Karplus plot affords two dihedral angles for each value of J, it is well accepted[4–6,10] that the C-21 methyl group can at most rotate within an arc subtending the 120° angle bisected by the 17α-hydrogen. Therefore in the acyclic side-chain compounds, the dihedral angle between 17α-H and 20-H must be larger than 60°. For the 20β-hydroxy compounds, calculation by the Karplus equation[9] indicates that the 20α- and 17α-hydrogens are fully staggered (180°). This is in harmony with the conformation proposed by Glick and Hirschmann.[4] On the other hand for the 20α epimers, the following conformations can be drawn for the different compounds (Chart II).

CHART II

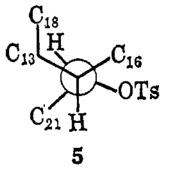
CONFORMATIONS OF 20α-OXYGENATED PREGNANE DERIVATIVES



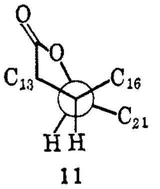
1, 3, 9
A



7
B



5
C



11
D

The most stable average conformation is neither staggered (dihedral angle 180°) nor eclipsed (dihedral angle 120°), *but the intermediate of these two (dihedral angle 153°)*. In a sense, this is comparable with the twisted boat form of the cyclohexane ring[11] and is the result of the increased interaction between C-21 and C-18 or C-12 when the dihedral angle increased to 180°

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(7) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(8) A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian, and D. H. R. Barton, *Tetrahedron*, **18**, 373 (1962).

(9) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(10) *Cf.* J. W. Corcoran and H. Hirschmann, *ibid.*, **78**, 2325 (1956).

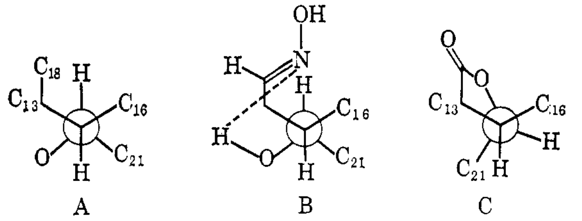
(11) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *ibid.*, **83**, 606 (1961).

in the staggered form, and between C-21 and the 17α-hydrogen and/or the 20α-hydroxyl group and C-16 when the dihedral angle decreases to 120° in the eclipsed form.

Of special interest is 18-oximino-20α-hydroxypregn-4-en-3-one[7] in which $J_{17\alpha\text{-H},20\beta\text{-H}}$ decreases to 3.5 cps (dihedral angle 130°), presumably owing to hydrogen bonding between the 20α-hydroxyl proton and the oximino nitrogen atom. This is confirmed by the downfield shift of the hydroxyl hydrogen to 208 cps from the normal chemical shift of about 96 cps in this series of compounds. The identity of this peak was demonstrated by exchange with D_2O which also exchanged with the oxime hydroxyl group at 554 cps. The same phenomenon has been observed for *syn*-19-oximino-5α-androstane-2β,3α,17β-triol 3,17-diacetate by Kwok and Wolff.[12] The nmr spectrum of 18-oximino-20β-hydroxypregn-4-en-one[8] also indicates hydrogen bonding between the hydroxyl and oximino groups. The coupling values in the 20β-hydroxy series, however, are less subject to variation by different substituents. This probably is due not only to the rather stable staggered conformation (Chart III), but also to the formation of a hydrogen bond without altering the geometry of the conformation shown in Chart III. The distance between the hydroxyl oxygen and C-18 is about 2.8 A for the 20β-hydroxy compound (Chart IIA) and about 3.5 A for the 20α-hydroxy compound (Chart IA) as measured by models.

CHART III

CONFORMATIONS OF 20β-OXYGENATED PREGNANE DERIVATIVES



Experimental Section

Materials.—Compounds **1–4**, **7**, **8**, **11**, and **12** were obtained by literature methods as indicated, or by modifications of these methods. Compounds **5**, **6**, **9**, and **10** were obtained as part of another investigation.[13]

Nmr Spectra.—Spectra were obtained on a Varian HA-100 instrument on samples in deuteriochloroform or benzene solution using tetramethylsilane as internal standard.

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[12] R. Kwok and M. E. Wolff, *Chem. Ind.* (London), 1194 (1962).

[13] H. Lee and M. E. Wolff, in preparation.

A Convenient Synthesis of Dihydrojasmone[1]

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Givaudan Corporation, Clifton, New Jersey

Received March 25, 1966

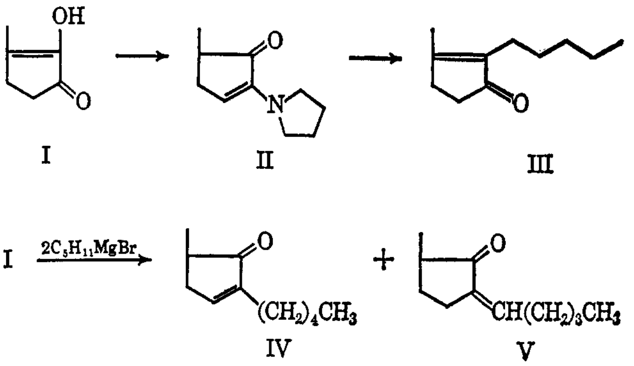
The primary odorous principle of jasmine flowers is jasmone which is 3-methyl-2-(2-*cis*-pentenyl)cyclopent-2-en-1-one.[2,3] This material is very expensive because it is found only in small quantities in nature. Although several syntheses of jasmone have been recorded[4,5] it cannot be considered an economical perfumery material.

Dihydrojasmone (III) is closely related to jasmone both in structure and odor and is useful in perfumery.[6] Dihydrojasmone has been synthesized by several cyclization procedures but in either low yield or purity or both.[7]

Recently, a synthesis starting with 3-methylcyclopent-2-en-2-ol-1-one, a material readily available from both natural and synthetic sources has been described by Erickson and Collins.[8] In this process the C-1 keto group was protected as a ketal while the C-2 keto group was treated with Grignard reagents. The protection required three steps and resulted in an over-all yield of 40%.

In our process, 3-methylcyclopent-2-en-2-ol-1-one (I, Scheme I) was treated with pyrrolidine in boiling benzene to give a 95% yield of 2-N-pyrrolidino-5-methylcyclopent-2-en-1-one (II). Treatment of (II) with *n*-amylmagnesium bromide, followed by hydrolysis and dehydration, gave dihydrojasmone (III) in 68% yield.

SCHEME I



When 3-methylcyclopent-2-en-2-ol-1-one is treated directly with 2 moles of a Grignard reagent followed by hydrolysis and dehydration 1-*n*-amyl-3-methylcyclopent-1(5)-en-2-one (IV) and 1-*n*-pentylidene-3-methylcyclopentan-2-one (V) are formed.[9]

Experimental Section

2-N-Pyrrolidino-5-methylcyclopent-2-en-1-one (II).—A mixture of 56 g (0.5 mole) of 3-methylcyclopent-2-en-2-ol-1-one (I), 42.6 g (0.6 mole) of pyrrolidine, and 500 ml of benzene was refluxed under nitrogen with removal of water for 1 hr. The benzene was removed at 60 mm by heating to 60°. The residue was distilled under nitrogen through a 37-cm column packed with glass halices to give 78 g (95%) of the enamine: bp 85–90° (0.4 mm); $n^{20}{}_D$ 1.5285; λ_{max} 5.90 and 6.20 μ. This material could not be further characterized owing to its instability.

2-*n*-Amyl-3-methylcyclopent-2-en-1-one (III, Dihydrojasmone).—The Grignard reagent was prepared from 113 g of *n*-amyl bromide (0.75 mole), 18 g of magnesium turnings (0.75 g-atom), and 250 ml of dry ether. To this Grignard reagent was added dropwise with constant agitation a solution of 78 g of 2-N-pyr-

---

[1] Much of this work was presented at the First Middle Atlantic Regional Meeting, Philadelphia, Pa., Feb 3, 1966.

[2] L. Ruzicka and M. Pfeiffer, *Helv. Chim. Acta*, **16**, 1208 (1933).

[3] W. Treff and H. Werner, *Ber.*, **66**, 1521 (1933).

[4] G. Stork and R. Borch, *J. Am. Chem. Soc.*, **86**, 936 (1964).

[5] G. Büchi and H. Wüest, *J. Org. Chem.*, **31**, 977 (1966).

[6] T. F. West, H. J. Strausz, and D. H. R. Barton, "Synthetic Perfumes," Edward Arnold and Co., London, 1959, p 151.

[7] J. H. Amin, *et al.*, *Ind. J. Chem.*, **2**, 14 (1964), and references cited in this article.

[8] J. L. E. Erickson and F. E. Collins, Jr., *J. Org. Chem.*, **30**, 1050 (1965).

[9] J. L. E. Erickson, J. Dorsky, and W. M. Easter, Jr., U. S. Patent 3,137,731 (1964).