finally 250 ml. of water. After drying over $MgSO_4$ the ether solution was evaporated to a yellow oil. The oil was distilled through a 4-inch Vigreux head and 83 g., b.p. 135–139° at 0.02 mm., of a colorless viscous oil was recovered which crystallized on standing at room temperature. The product was readily recrystallized from ether–hexane; m.p. 57–58°.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.09; H, 9.37.

Preparation of 6-Hydroxyhexanophenone (VI).—A solution of 7.7 g. of diol VIa in 250 ml. of *t*-butyl alcohol containing 3% H_2O was cooled to 10° and 15 g. of N-bromoacetamide was added under vigorous stirring. A red-orange color developed slowly after the addition was completed. After 4 hours the solution was diluted with 500 ml. of ethyl acetate and 500 ml. of ether and washed twice with 100-ml. portions of 5% aqueous NaOH and finally with 100 ml. of H_2O. After drying with $MgSO_4$ the solvent was removed on a steam-bath, under a dry nitrogen stream, leaving behind 6.5 g. of a pale yellow oil.

A portion of this residue (3.0 g.) was dissolved in ether and hexane added to a point just short of a permanent precipitate. On standing in the cold less than 1.0 g. of a white, waxy solid crystallized, m.p. 28–32°. Recrystallization raised the m.p. to 32–34° with a second crop at 31–33°. This fraction proved to be a side reaction product and was set aside for later examination.

A second 3.0-g. portion of the pale yellow oil was dissolved in 20 ml. of absolute ethanol containing 2 ml. of glacial acetic and 5.0 g. of Girard reagent T (Araphoe Chemical Co.). After 10 minutes of reflux the mixture was diluted with 50 ml. of H_2O and 50 ml. of saturated $NaHCO_3$, then extracted twice with 200-ml. portions of ether to remove non-carbonyl impurities. The aqueous layer was treated with 25 ml. of concd. HCl, warmed for 15 min. on a steam-plate and finally extracted twice with 200-ml. portions of ether. The combined ether extracts were washed once with 50 ml. of H_2O, dried over $MgSO_4$ and evaporated to a clear, colorless oil weighing 1.9 g., $n^{22.8}D$ 1.5324.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.90; H, 8.50.

A sample of the crude oil gave an immediate, copious precipitate with 2,4-dinitrophenylhydrazine in perchloric acid solution. The m.p. after washing and drying was 97°, but on recrystallization from ethanol the derivative melted very sharply at 137° and depressed the m.p. of the DNPH derivative of II. Undoubtedly the two melting points correspond to crystalline modifications resembling in this respect the DNPH derivative of acetaldehyde.

TABLE II

ULTRAVIOLET ABSORPTION DATA[b]

Compound	λ_{max}, mμ	ϵ_{max} (10^{-3})
Hexanophenone	240	13.0
Acetophenone[a]	240	13.1
Propiophenone[a]	240	12.9
n-Butyrophenone	240	13.1
i-Butyrophenone	240	12.7
n-Valerophenone	240	12.8
6-Hydroxyhexanophenone	242	12.7
Benzoylvaleric acid	240	13.1
1-Phenyl-1,6-hexanediol	255	0.21

[a] Note that in H_2O solution these substances have a somewhat smaller ϵ_{max} (approx. 11,900) and λ_{max} is bathochromically displaced by more than 5 mμ. L. Daub and J. M. Vandenbelt (THIS JOURNAL, 69, 2714 (1947)) have reported for acetophenone λ_{max} 245.5 and ϵ_{max} 9800 in H_2O. [b] Solvent, methanol.

Acknowledgment.—We are obliged to the Hercules Research Center. Wilmington, Del., for the Opportunity afforded to R. T. K. for the frequent use of various instruments and facilities.

NEWARK, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XXII.[1] Detection and Stereochemical Implication of Hemiketal Formation[2,3]

BY CARL DJERASSI, L. A. MITSCHER[4] AND B. J. MITSCHER

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The effect of hydrochloric acid upon the shape and intensity of optical rotatory dispersion curves of saturated carbonyl compounds in alcoholic solution was determined. The results are interpretable in terms of hemiketal formation, which was found to be very sensitive to steric and conformational factors. Hemiketal formation is most pronounced in methanol solution and practically inhibited in isopropyl alcohol. It is also affected by ring size, α-alkyl substituents and generation of new 1,3-diaxial interactions, not present in the parent ketone. Since this simple experimental modification—determination of optical rotatory dispersion followed by addition of hydrochloric acid and repetition of the dispersion measurement—offers a valuable means of differentiating between ketones in various steric environments as well as diketones situated in different rings, it is proposed that this be used as a routine adjunct to optical rotatory dispersion measurements.

Hemiketal formation of carbonyl compounds is often difficult to measure by isolation of the actual compound,[5] particularly when the equilibrium lies on the ketone (or aldehyde) side, and recourse is usually taken to physical measurements. Ultraviolet spectroscopy has proved to be particularly useful in this connection[6] by measuring the diminution in extinction of the ultraviolet absorption maximum in the 280–320 mμ region associated with the saturated carbonyl group. Experimentally, this is performed[6] by determining the change in intensity of this maximum in methanol solution produced by the addition of a drop of hydrochloric acid, which is sufficient to catalyze the formation of the hemiketal. Unfortunately, the extinction coefficient of a saturated ketone or aldehyde is of a very low order of magnitude—often completely obscured by absorption of other

(1) Paper XXI, C. Djerassi and G. W. Krakower, THIS JOURNAL, **81**, 237 (1959).

(2) Supported by the National Cancer Institute (grant No. CY-2919) of the National Institutes of Health, U. S. Public Health Service.

(3) Some of the results were first reported at a Meeting of the Japanese Chemical and Pharmaceutical Societies at the University of Tokyo, March 13, 1958.

(4) U. S. Public Health Service predoctorate research fellow, 1956–1958.

(5) There are, of course, important exceptions, notably in the sugar series.

(6) The most recent detailed study has been carried out by O. H. Wheeler, THIS JOURNAL, **79**, 4191 (1957), who has also reviewed the pertinent literature; see also ref. 15.

chromophores—thus affecting seriously the ease and accuracy of the experimental measurements. Furthermore, large concentrations have to be employed which preclude work with insoluble or rare substances.

Optical rotatory dispersion[7] usually does not suffer from any of these limitations. The single Cotton effect[8] associated with optically active, saturated carbonyl compounds produces usually very large rotations in an accessible region (300–340 mμ) of the spectrum of the order of several hundred or thousand degrees in terms of specific rotation, in contrast to the rather low rotation values (increasing only gradually in the ultraviolet) of the corresponding alcohols. Consequently, dilute solutions requiring only 1–2 mg. of sample are sufficient for this work. Since hemiketals do not exhibit maximal absorption in the relevant ultraviolet region, they would not be expected[9,10] to exhibit Cotton effect curves and this has been verified[11] experimentally in the carbohydrate series. For semi-quantitative purposes, one can assume that the specific rotation of the hemiketal in the 300 mμ region approximates that of the corresponding alcohol and using that premise, hemiketal formation can then be determined by simply noting the reduction in amplitude[8] of the initial peak[8] (or trough in the case of a negative Cotton effect curve) produced by the addition of a drop of hydrochloric acid to the methanol solution of the carbonyl compound in question. Furthermore, by noting the time required to reach a constant, reduced rotation value, there should be available a semi-quantitative index not only of the *extent* but also of the *rate* of hemiketal production. It is with this background in mind that our experimental work was undertaken.

General Experimental Procedure

All measurements were carried out with a photoelectric spectropolarimeter[12] using a mechanically oscillating polarizer drive,[13] the symmetrical angle being set at 5°; in a few cases where the intensity was insufficient to obtain satisfactory readings, settings of 10 and 15° were employed with concomitant loss in accuracy. A glass-jacketed Sylvania K-100 concentrated arc Zirconium lamp was employed between 700–315 mμ, while below this wave length a 150 watt Xenon arc lamp (Hanovia 10 C-1) was substituted operating on direct current with a special power supply unit.

The substance (1–2 mg.) was dissolved in 2 cc. of methanol (Eastman Kodak spectra grade) and introduced into a stoppered, center-fill polarimeter tube (10 cm., 3.5 mm. bore, total capacity somewhat less than 2 cc.) with cemented-on fused quartz cover glasses. The rotatory dispersion curve was then measured as described earlier,[10] readings being taken in 2–2.5 mμ intervals near the regions of peaks, troughs or inflections. The solution was then transferred to a volumetric flask containing 0.01 cc. of concd. hydrochloric acid, mixed thoroughly and returned to the polarimeter tube, the total time elapsed being less than 3 min. As soon as sensitivity returned (see discussion below), readings were taken at the previously observed peak or trough wave length (whichever occurred at the higher wave length) using the smallest possible symmetrical angle setting until at least two successive identical values were obtained, indicating that equilibrium had been reached. Once the readings were constant, the measurement of the rotatory dispersion curve was completed in the usual manner although as seen in Figs. 1–4, this is probably not necessary in the vast majority of cases, the change in amplitude at the wave length corresponding to the peak or trough offering the necessary information. Temperatures were recorded for each run, but no thermostatically-controlled jacketed polarimeter tubes were employed since the room temperature fluctuations for any given experiment did not exceed 1.5°. The blank values with pure methanol were not changed by the addition of hydrochloric acid and hence were also employed in the measurement of the "acid curve."

The data are reported using the expression $(a - b)/a \times 100$ = % hemiketal formation,[14] where a = specific rotation of peak or trough and b = specific rotation at the same peak or trough wave length after the addition of hydrochloric acid.[15] The figure given in parentheses below each structural formula refers to the extent of hemiketal formation determined by the above procedure and *these values are to be considered minimal ones* since the rotation of the hemiketal (unavailable in the absence of the pure substance) has not been considered. As pointed out above, this can probably be equated to the rotation of the corresponding alcohol, but even this has not been taken into consideration in the above expression for the following reasons. In many cases the rotatory dispersion of the corresponding alcohol has not been measured because it would have involved synthesis of the substance and past experience in our laboratory with a variety of alcohols[16] has shown that the specific rotation of the alcohol is usually small[17] compared to that of the ketone in the region of the peak or trough and may often be within the error (usually not lower than 5% with the dilute solutions employed in this study) of reproducibility of the rotation measurement of the carbonyl compound.

Discussion

The effect of hydrochloric acid addition was first examined with (+)-3-methylcyclohexanone (I). In methanol solution (Fig. 1), a very rapid (less than 3 min.) reduction in amplitude of the peak at 307.5 mμ was observed to the extent of 93%, indicating nearly complete conversion to the hemiketal in excellent agreement with the results recorded in the ultraviolet spectrophotometric study[6] with cyclohexanone. Since hemiketal formation is known[6,18,19] to be very responsive to the size of the alcohol, the above reaction was repeated in ethyl and isopropyl alcoholic solution. In the former, only 33% of hemiketal was indicated while

(7) For pertinent review of optical rotatory dispersion studies of carbonyl compounds carried out in our laboratory, see C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

(8) For nomenclature of optical rotatory dispersion data see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(9) T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., New York, N. Y., 1935.

(10) For a brief discussion on the relation of ultraviolet absorption and anomalous rotatory dispersion, see C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955).

(11) For pertinent references see Chapter XXII in ref. 9; C. L. Hudson, M. L. Wolfrom and T. M. Lowry, *J. Chem. Soc.*, 1179 (1933); R. W. Herbert, E. L. Hirst and C. E. Wood, *ibid.*, 1151 (1934).

(12) E. Brand, E. Washburn, B. F. Erlanger, E. Ellenbogen, J. Daniel, F. Lippmann and M. Scheu, THIS JOURNAL, **76**, 5037 (1954); H. Rudolph, *J. Opt. Soc. Amer.*, **45**, 50 (1955).

(13) H. Rudolph, *Proc. Instrum. Soc. Amer.*, Sept., 1956 (paper No. 56-3-1).

(14) Kinetic studies (ref. 6) have shown that hemiketals rather than ketals are produced under the presently employed experimental conditions.

(15) See also O. H. Wheeler and J. L. Mateos, *Anal. Chem.*, **29**, 538 (1957).

(16) For leading references see footnotes 1 and 7.

(17) More serious errors would be introduced only if the plain dispersion rises (or falls) rather steeply, which is usually due to other substituents (see for instance C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3761, Fig. 1 (1956), where this situation is illustrated with a steroidal hydroxy etianic acid), or where the sign of the Cotton effect curve of the ketone is opposite to that of the plain dispersion curve of the corresponding alcohol (see relevant data with steroidal sapogenins by C. Djerassi and R. Ehrlich, *ibid.*, **78**, 440 (1956)). Neither one of these situations appears to apply to the examples discussed in the present paper except for the aldehyde XXXV.

(18) I. L. Gandity, *Z. physik. Chem.*, **48**, 228 (1941).

(19) C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955), and references cited therein.

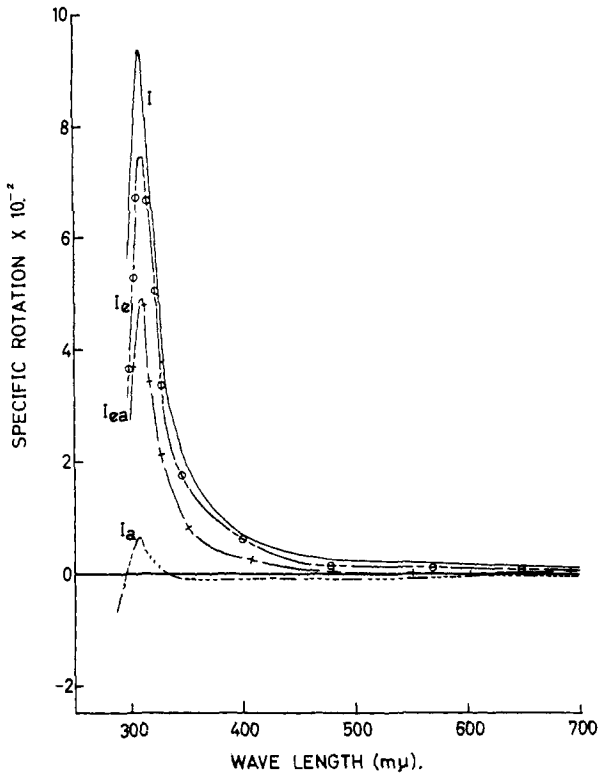


Fig. 1.—Optical rotatory dispersion curves of (+)-3-methylcyclohexanone in methanol (I), methanol–hydrochloric acid (I_a), ethanol (I_e) and ethanol–hydrochloric acid (I_{ea}).

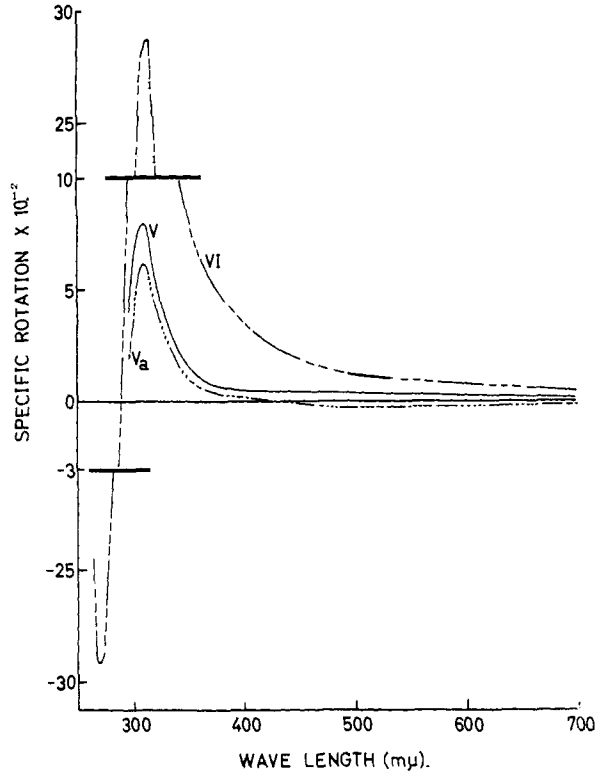


Fig. 2.—Optical rotatory dispersion curves of (+)-2,5-dimethylcyclohexanone in methanol (V) and in methanol–hydrochloric acid (V_a) and of (+)-2,2,5-trimethylcyclohexanone in methanol (VI).

none appeared to be formed in isopropyl alcohol, which again is in accordance with expectation. Consequently all subsequent measurements were conducted in methanol solution.

The effect of ring size upon addition reactions (including hemiketal formation[6]) to cyclic ketones has been discussed in detail by Brown[20] and cyclopentanone and cycloheptanone would be expected to be considerably less reactive than cyclohexanone. In agreement with this postulate are the rotatory dispersion results with (+)-3-methylcyclopentanone (II) and (−)-3-methylcycloheptanone (III),[1] both of them reacting only to the extent of 24 and 21% respectively.[21] (+)-Camphor (IV) should not only show the reduced reactivity of a cyclopentanone, but this reduction should be emphasized greatly by the additional alkyl substituents. Indeed, no change was observed in its rotatory dispersion curve in methanol solution in the presence of hydrochloric acid and less than 3% hemiketal formation has been noted by the ultraviolet spectrophotometric technique.[6]

The availability in this Laboratory[22] of a series of alkylated cyclohexanones permitted a more detailed study of the effect of alkyl substitution upon hemiketal production. Thus (+)-2,5-di-

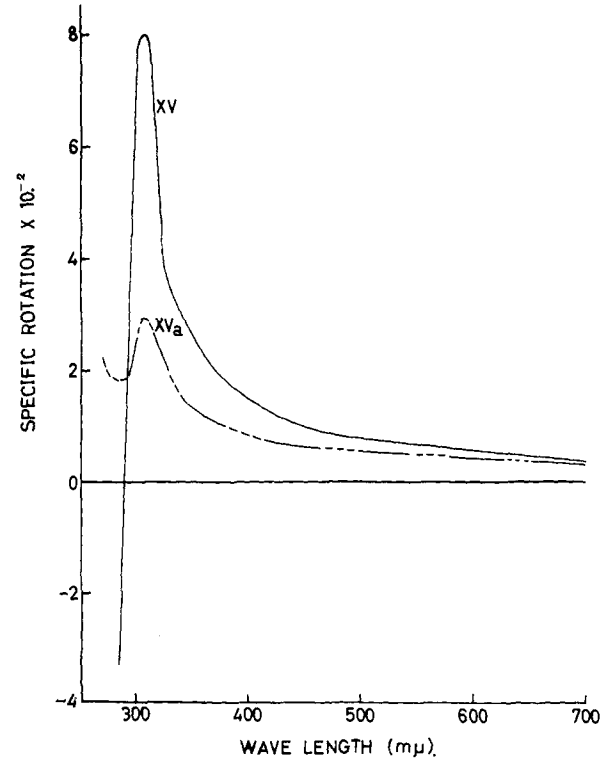


Fig. 3.—Optical rotatory dispersion curves of cholestan-3-one in methanol (XV) and in methanol–hydrochloric acid (XV_a).

(20) See H. C. Brown, *J. Chem. Soc.*, 1248 (1956), and references cited therein.

(21) The ultraviolet data (ref. 6) also show that 3-methylcyclopentanone and cycloheptanone react to approximately the same extent, but the absolute figures (42 and 37%) are higher than observed by the rotatory dispersion method.

(22) Work to be published with J. Osiecki and E. J. Eisenbraun.

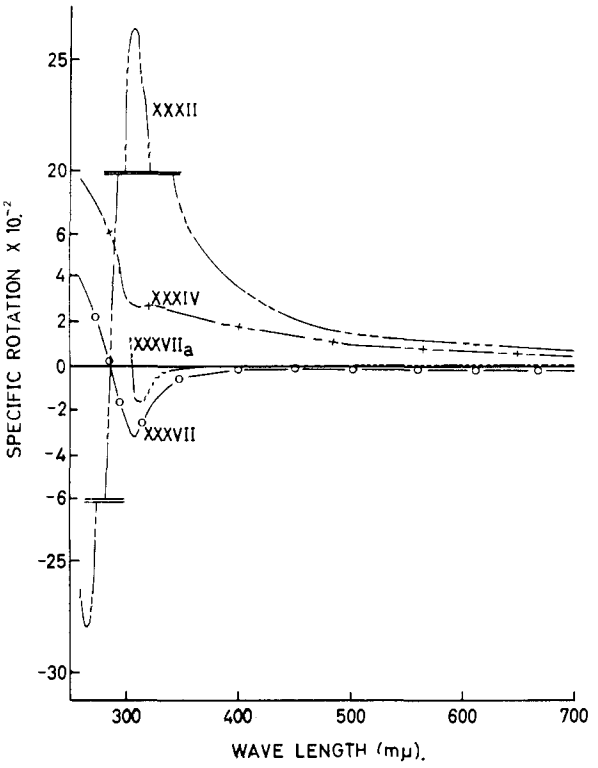


Fig. 4.—Optical rotatory dispersion curves of allopregnan-20-one (XXXII) and 3β-acetoxyhexanordammaran-20-one (XXXIV) in methanol, and of cholestan-3β-ol-22-one in methanol (XXXVII) and in methanol-hydrochloric acid (XXXVII$_a$).

methylcyclohexanone (V) formed an equilibrium mixture consisting only of 25% of hemiketal (as compared to 93% in the case of I) while no reaction was observed when a *gem*-dimethyl moiety was introduced as in (+)-2,2,5-trimethylcyclohexanone (VI) (see Fig. 2). Identical results were observed with the two C-2 isomeric methylmenthones (VII)[22] and this subject will be covered again in a discussion of alkylated steroids (*vide infra*).

We should now like to turn to a consideration of optically active bicyclic ketones which have been prepared recently in this Laboratory.[23-25] (+)-*trans*-8-Methyl-5-hydroxyhydrindan-2-one (VIII) suffered a reduction in amplitude of the rotatory dispersion peak of 25%, virtually identical with that observed with the monocyclic (+)-3-methylcyclopentanone (II). On the other hand, when the carbonyl group was placed in the six-membered ring, hemiketal formation ranging between 68–74% was encountered in three different examples (IX, X, XI) irrespective of whether the second ring was five- (IX) or six-membered (X, XI). This represents independent support for the conclusion drawn earlier[24]—based on the coincidence in shape of the rotatory dispersion curves of IX, X and cholestan-3-one (XV)—that no major conformational distortion is involved in the *trans*-8-methylhydrindan-5-one (IX) system in so far as the six-membered ring is concerned.

A very instructive illustration of the power of the presently reported modification of rotatory dispersion measurement can be found in the completely different behavior of the two position isomers (+)-*trans*-8,9-dimethyl-3-decalone (XI) and (+)-*trans*-8,9-dimethyl-2-decalone (XII). Formally, the 2-decalone derivative XII is analogous to 3-methylcyclohexanone (I), which was found to be converted almost entirely (93%) to the hemiketal, yet the 2-decalone (XII) reacted only to a negligible extent (9%) in marked contrast to the 68% observed with the 3-decalone XI. However, the monocyclic ketone I is conformationally flexible and therefore exists almost exclusively in that chair form in which the methyl group occupies the equatorial orientation. On the other hand, the *trans*-decalones XI and XII are conformationally frozen with the angular 9-methyl group being axial and in the hemiketal XIII, corresponding to (+)-*trans*-8,9-dimethyl-2-decalone (XII), there is now set up a new and very unfavorable 1,3-diaxial interaction between the hydroxyl and methyl groups which reflects itself in the fact that the equilibrium XII $\rightleftarrows$ XIII is largely on the side of the ketone XII. The importance of this observation is discussed below in connection with the analogous steroid ketones.

When the carbonyl function is moved next to the angular group as in (+)-*trans*-9-methyl-1-decalone (XIV), no change in rotatory dispersion amplitude is observed upon adding acid, since *gem*-dialkylation in cyclohexanones (*e.g.*, VI, VII) completely inhibits conversion to the hemiketal.

With the above information on mono- and bicyclic ketones as a guide, an examination of hemiketal formation in steroidal ketones was undertaken. Our knowledge[7,26] of the relation between structure and optical rotatory dispersion is probably more precise in the steroid field than in any other area of organic chemistry and it was important to see whether the hydrochloric acid-methanol technique would offer any further refinements. Three 3-keto-5α-steroids were examined—cholestan-3-one (XV) (Fig. 3), dihydrotestosterone (XVI) and 19-nordihydrotestosterone (XVII)—and in all of them hemiketal formation was observed to the extent of 64–75%, in excellent agreement with the results in the bicyclic series (IX, X, XI) considering the possible areas of experimental error mentioned above under "General Experimental Procedure." As an example of a 2-keto-5α-steroid, there was available[27] androstan-17β-ol-2-one propionate (XVIII) and in accordance with our observations in the *trans*-2-decalone series (XII, 9% hemiketal), only 12% of hemiketal was formed. A secure differentiation between an unknown pair of 2- and 3-keto-5α-steroids is presently impossible on ultraviolet or infrared spectroscopic grounds and even optical rotatory dispersion was not too useful in this connection

(23) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956).

(24) C. Djerassi, D. Marshall and T. Nakano, *ibid.*, **80**, 4853 (1958).

(25) L. Zalkow, R. Mauli, F. X. Markley and C. Djerassi, Abstracts Division of Org. Chem., A.C.S. Meeting, Chicago, Ill., Sept., 1958, p. 26-P.

(26) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958), and earlier references.

(27) R. R. Engle and C. Djerassi, Abstracts, Division of Medicinal Chemistry, A.C.S. Meeting, Chicago, Ill., Sept 1958, p. 15-O.

since both types of ketones exhibit[28] a positive Cotton effect curve with some difference in amplitude which, however, is subject to some alteration by the presence of other substituents. A virtually unambiguous solution to this problem is now available since 2-keto-5α-steroids as well as their bicyclic analogs suffer only a minor reduction in amplitude in the presence of hydrochloric acid in contrast to the major one observed by their 3-keto isomers.[29]

The stereochemical situation existing in cholestan-4-one (XIX) is substantially the same as in the 2-keto steroid XVIII, a new hydroxyl–methyl 1,3-diaxial interaction being set up in the hemiketal and the formation of only 9% of hemiketal is understandable. The epimeric 6-keto-steroids cholestan-6-one (XX) and coprostan-6-one (XXI) represent an interesting pair. *A priori*, they would be expected to behave very similarly to cholestan-4-one (XIX), but in actual fact cholestan-6-one (XX) exhibited a small increase in amplitude of *ca.* 3%, while coprostan-6-one (XXI) showed a decrease of 14%. These results suggest that rotatory dispersion determination of hemiketal formation can probably not be applied safely to ketones with an easily invertible adjacent center. It has been shown earlier[23] that both ketones (XX, XXI) are characterized by negative Cotton effect curves, the thermodynamically less stable coprostan-6-one (XXI) showing a greater negative rotation. Therefore, any inversion at C-5 of XXI would result in decreased amplitude and it is possible that a certain extent of inversion is already produced at room temperature with methanolic hydrochloric acid. Whether the 3% increase in the amplitude of cholestan-6-one (XX) is due to experimental error or to equilibration cannot be determined with the information at hand.

While 7-keto-5α-steroids can very roughly be considered quasi-enantiomeric with 3-keto-5α-steroids, their respective Cotton effect curves being of opposite sign,[28] hemiketal formation is considerably repressed in androstane-3β,17β-diol-7-one diacetate (XXII) as compared to dihydrotestosterone (XVI) (24% *vs.* 69%) and this is undoubtedly due to increased substitution of the former. In accordance with expectation, the hindered 11-keto group (XXIII) reacted only to a slight extent and this was obliterated completely when an additional substituent (bromine) was placed next to it (XXIV). Similarly, the lack of hemiketal formation in 12-keto steroids (XXV, XXVI) is expected since the carbonyl group is flanked by two alkyl substituents on one side (*cf.* VI, VII).

The already reduced reactivity of a cyclopentanone (*e.g.*, II *vs.* I; VIII *vs.* IX) would be expected to be emphasized by additional alkyl substitution and it is not surprising that androstan-17-one (XXVIII) and coprostan-16-one (XXX) do not react with methanol in the presence of hydrochloric acid. When the substituent is removed, as in androstan-3β-ol-16-one (XXXI), the extent of hemiketal formation approximates (17% *vs.* 25%) that of the bicyclic analog VIII.

These results appeared to offer a means of differentiating between two carbonyl groups of differing reactivity situated in the same molecule and androstane-3,17-dione is a particularly suitable substrate since there exists essentially no interaction between the two functional groups.[30] Furthermore, androstan-3-one (XXVII) was found to react to a particularly large extent with methanol. forming 81% of hemiketal, so that the contribution of the 3-keto function could be eliminated almost completely by the addition of acid. The lack of interaction is demonstrated by the fact that in terms of molecular rotation, the peaks of the observed and calculated (sum of XXVII and XXVIII) dispersion curves of androstane-3,17-dione (XXIX) were +7790° and 7560°. Furthermore, the "acid curve" of androstane-3,17-dione (XXIX) in which the contribution of the 3-keto group is virtually removed by hemiketal formation exhibited a peak of +2625°, in extremely good agreement with the original peak value of +2698° of androstan-17-one (XXVIII).

Quantitative assessments of steric factors operating in addition reactions of aliphatic ketones are very scarce[31] and it seemed important, therefore, to extend the present study of hemiketal formation to some typical cases.

The first substance to be investigated was the steroidal methyl ketone allopregnan-20-one (XXXII) (Fig. 4) and essentially no reaction with methanol was observed. This result seems interpretable on the basis of the "rule of six" (*vide infra*) and furthermore appears to be a consequence of the particular spatial situation imposed by the angular methyl group; a similar observation was made with 21-norcholestan-3β-ol-20-one (XXXIII). That the angular methyl group imposes an orientation upon the methyl ketone grouping different from that which it would assume when the methyl group is replaced by hydrogen is suggested by the dispersion curves collected in Fig. 4. It will be noted that the dispersion curve of 3β-acetoxyhexanordammaran-20-one (XXXIV)[32] which possesses the identical stereochemistry[33] at positions 13, 14 and 17 but lacks the angular methyl group at C-13[34] is strikingly different from that of the methyl ketone XXXII. Since the shape of any given ketonic Cotton effect curve appears to be largely a reflection of the asymmetric environment in which the carbonyl group is placed,[26] the simplest explanation for the differences observed in Fig. 4 is that the acetyl group of XXXIV has assumed a

(28) C. Djerassi, W. Closson and A. E. Lippman, THIS JOURNAL, **78**, 3163 (1956).

(29) Acetic acid cannot be substituted for hydrochloric acid, since in the case of cholestan-3-oue (XV) only a 6% diminution in amplitude was encountered.

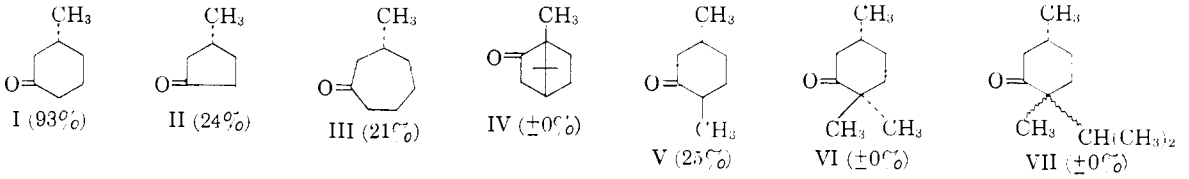
(30) As pointed out by W. Klyne and C. Djerassi, *Angew. Chem.*, **69**, 683 (1957), a calculated curve of a dicarbonyl compound should be constructed from the sum of the molecular rotatory dispersion curves of the two monofunctional analogs rather than dividing the sum by half as was done erroneously in one of our earlier papers (THIS JOURNAL, **78**, 3761 (1956)).

(31) See M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, New York, 1956, pp. 235–237.

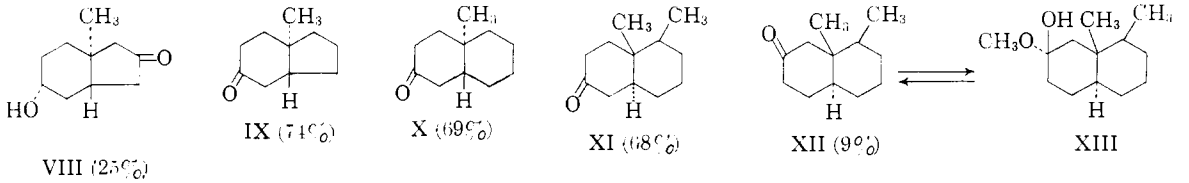
(32) J. S. Mills, *J. Chem. Soc.*, 2196 (1956).

(33) J. F. Biellmann, P. Crabbé and G. Ourisson, *Tetrahedron*, **3**, 303 (1958).

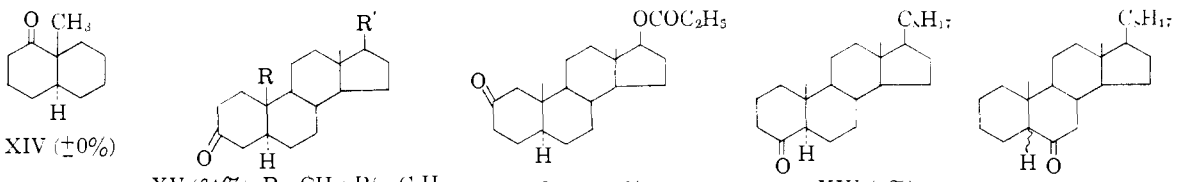
(34) On the basis of the rotatory dispersion results reported in ref. 26, we feel confident that the presence of the methyl group at C-14 in XXXIV does not have an important effect.



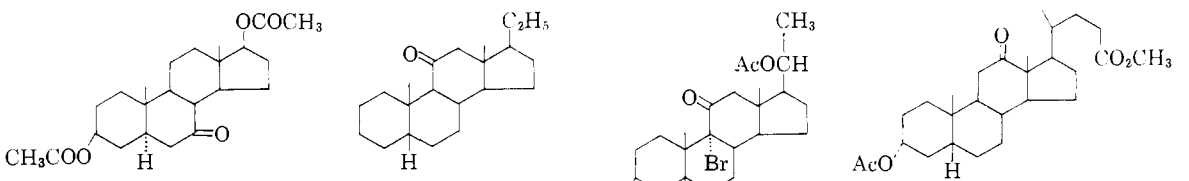
I (93%) II (24%) III (21%) IV (±0%) V (25%) VI (±0%) VII (±0%)



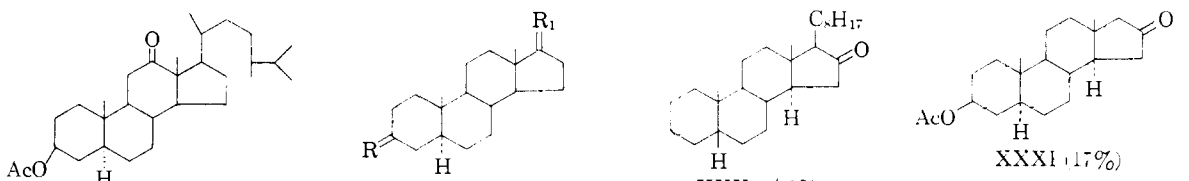
VIII (25%) IX (74%) X (69%) XI (68%) XII (9%) XIII



XIV (±0%) XV (64%), R = CH_3; R' = C_8H_{17} XVI (69%), R = CH_3; R' = OH XVII (75%), R = H; R' = OH XVIII (12%) XIX (9%) XX, 5α-H XXI, 5β-H



XXII (24%) XXIII (10%) XXIV (±0%) XXV (±1%)



XXVI (±0%) XXVII (81%), R = O; R' = H_2 XXVIII (±1%), R = H_2; R' = O XXIX, R = R' = O XXX, (±0%) XXXI (17%)

different "free-rotational" orientation which is not possible in XXXII or XXXIII[35] because of the C-13 angular methyl group. Aldehydes are known to be more reactive[36] than ketones and this is demonstrated by the rapid formation of a (hemi)-acetal[37] from the steroidal aldehyde XXXV as well as of citronellal (XXXVI). When the keto group is moved to the 22-position, as in cholestan-3β-ol-22-one (XXXVII), reactivity toward methanol is restored to an appreciable extent as illustrated in Fig. 4 where 41% of hemiketal formation is indicated. Quite striking, therefore, is the observation that when the rotatory dispersion curve of the isomeric 23-ketone XXXVIII was measured under identical conditions, it showed only 8% of hemiketal and this appears to be a good example of the operation of the "rule of six."[38] Further cases of aliphatic ketones where alkyl substitution greatly affects hemiketal formation are 3-methyl-3-phenylhexan-4-one (XXXIX)[39] and 3,4,6-trimethyl-5-oxoheptanoic acid (XL).[40]

Finally several alkylated 3-keto steroids were examined which are derived from the three ketones, XV, XVI and XVII, where hemiketal formation to the extent of 64–75% had been observed. In all nine examples (XLI–XLIX) from the cholestan-3-one, dihydrotestosterone or 19-nordihydrotestosterone series, introduction of even one alkyl substituent greatly reduced hemiketal production.

(35) The pertinent dispersion data of this substance have already been reported by C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

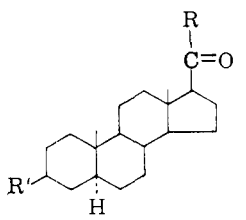
(36) See p. 241 in ref. 31.

(37) This is one example where the extent of (hemi)-acetal formation cannot be determined quantitatively since the positive Cotton effect curve of the aldehyde XXXV is actually reduced to negative rotation values in the presence of acid. The alcohol corresponding to XXXV is not known, but its rotatory dispersion curve would definitely be characterized by a negative plain curve as has been demonstrated for Δ^5-unsaturated steroids (ref. 28).

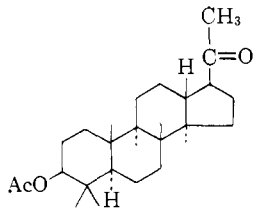
(38) M. S. Newman, THIS JOURNAL, **72**, 4783 (1950).

(39) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952).

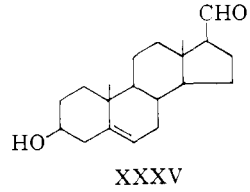
(40) W. D. Burrows and R. H. Eastman, *ibid.*, **79**, 3756 (1957).



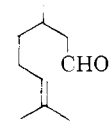
XXXII (±1%), R = CH_3; R' = H
XXXIII (±1%), R = C_6H_{13}; R' = OH



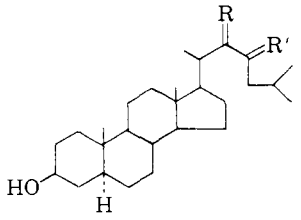
XXXIV



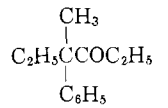
XXXV



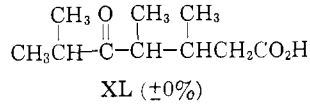
XXXVI (67%)



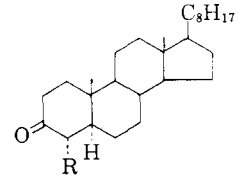
XXXVII (41%), R = O; R' = H_2
XXXVIII (8%), R = H_2; R' = O



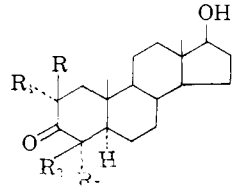
XXXIX (14%)



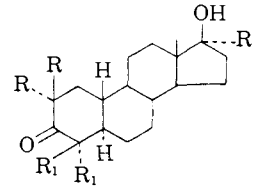
XL (±0%)



XLI (17%), R = CH_3
XLII (±0%), R = C_2H_5



XLIII (±0%), R = CH_3; R_1 = R_2 = R_3 = H
XLIV (±0%), R = R_1 = CH_3; R_2 = R_3 = H
XLV (8%), R = R_1 = R_2 = H; R_3 = CH_3
XLVI (±0%), R = R_1 = H; R_2 = R_3 = CH_3



XLVII (±0%), R = H; R_1 = CH_3
XLVIII (±0%), R = CH_3; R_1 = H
XLIX (±0%), R = H; R_1 = CH_2
5,6-double bond

As pointed out in a recent communication,[41] this observation proved to be of great importance in locating the unknown methyl group in the cactus sterol lophenol (4α-methyl-Δ⁷-cholesten-3β-ol).

One factor, incident to this work, should be mentioned although no rational explanation can be offered at this time. In many, but not all, of the cases where a reaction between methanol and the ketone could be demonstrated in the presence of acid, there occurred a complete loss of sensitivity upon the addition of hydrochloric acid and no rotation measurements could be made for several minutes and in a few isolated instances for several hours. The most likely explanation—formation of a transient intermediate which absorbed in the 280–330 mμ region and prevented transmission of sufficient light—was excluded by scanning the ultraviolet absorption spectrum of cholestan-3-one (XV) ("blanking-out time" 15–25 min.) in the identical methanol–hydrochloric acid solution in a recording spectrophotometer. No change in absorption was noted of a sufficient order of magnitude to explain the striking loss of sensitivity in the early stages of the rotatory dispersion measurements.

The above rotatory dispersion results, though not of a completely quantitative nature, clearly offer so much useful information with many saturated[42] carbonyl compounds that the methanol–hydrochloric acid technique should be incorporated as a routine procedure in most dispersion measurements of such compounds. Within the restrictions outlined in this paper and provided optically active substrates are accessible, it probably represents the simplest and quickest method currently available for determining the extent of hemiketal production.

Experimental Results[43]

(+)-3-Methylcyclohexanone (I), R.D. (Fig. 1) in methanol (*c* 0.168): $[\alpha]_{700}$ +12.5°, $[\alpha]_{589}$ +16.5°, $[\alpha]_{307.5}$ +936°, $[\alpha]_{305}$ +859°, $[\alpha]_{270}$ −1352°, $[\alpha]_{240}$ −960°; acid study (12 min.), $[\alpha]_{700}$ +9°, $[\alpha]_{589}$ −5°, $[\alpha]_{307.5}$ +60.5°, $[\alpha]_{290}$ −40.5°: at 307.5 mμ, 3 min. = +62°, 8 min. = +65°, 12 min. = +60.5°.

In ethanol (*c* 0.161): $[\alpha]_{700}$ +7.5°, $[\alpha]_{589}$ +12°, $[\alpha]_{310}$ +745°, $[\alpha]_{300}$ +435°, $[\alpha]_{290}$ −37°; acid study (32 min.), $[\alpha]_{700}$ −1°, $[\alpha]_{589}$ 0°, $[\alpha]_{310}$ +492°, $[\alpha]_{300}$ +302°: at 310 mμ, 3 min. = +488°, 6 min. = +467°, 9 min. = +491°, 16 min. = +438°, 21 min. = +492°.

In isopropyl alcohol (*c* 0.093): $[\alpha]_{700}$ +1°, $[\alpha]_{589}$ +11°, $[\alpha]_{310}$ +991°, $[\alpha]_{290}$ −72°; acid study (95 min.), $[\alpha]_{700}$ +16°, $[\alpha]_{589}$ +31°, $[\alpha]_{310}$ +1064°, $[\alpha]_{305}$ +1070°: at 310 mμ, 83 min. = +1080°, 90 min. = +1041°, 95 min. = +1064°.

(+)-3-Methylcyclopentanone (II), R.D. in methanol (*c* 0.070): $[\alpha]_{700}$ −39°, $[\alpha]_{589}$ −30°, $[\alpha]_{310}$ +4550°, $[\alpha]_{300}$ +2652°; acid study (25 min.), $[\alpha]_{700}$ +43°, $[\alpha]_{589}$ +57°, $[\alpha]_{310}$

(41) C. Djerassi, J. S. Mills and R. Villotti, THIS JOURNAL, **80**, 1005 (1958).

(42) Preliminary experiments with testosterone and progesterone indicate that such unsaturated ketones do not react with methanol under our conditions.

(43) The experimental results are recorded in the manner outlined earlier (ref. 8). Where no source is given, the substance came from the collection of the authors. After the original methanol curve, there is reported for most substances the equilibration time in acid, the acid curve and finally the rate of change of rotation at the peak or trough. The first time figure reported represents also the extent of "blanking-out" mentioned above in the discussion. Where no change in acid was observed and the dispersion curve had already been recorded in one of our earlier papers, no data are reported.

+3605°, $[\alpha]_{302.5}$ +3465°: at 310 mμ, 18 min. = +3650°, 20 min. = +3525°, 25 min. = +3605°.

(−)-**3-Methylcycloheptanone** (III), R.D. in methanol (*c* 0.159): $[\alpha]_{700}$ −25°, $[\alpha]_{589}$ −38°, $[\alpha]_{302.5}$ −587°, $[\alpha]_{290}$ −218°; acid study (15 min.), $[\alpha]_{700}$ −70°, $[\alpha]_{589}$ −152°, $[\alpha]_{302.5}$ −464°, $[\alpha]_{295}$ −344°: at 307.5 mμ, 4 min. = −452°, 10 min. = −464°.

(+)-**2,5-Dimethylcyclohexanone** (V), R.D. (Fig. 2) in methanol (*c* 0.127): $[\alpha]_{700}$ +15°, $[\alpha]_{589}$ +15°, $[\alpha]_{310}$ +817°, $[\alpha]_{300}$ +626°; acid study (25 min.), $[\alpha]_{700}$ −2°, $[\alpha]_{589}$ −12°, $[\alpha]_{310}$ +626°, $[\alpha]_{300}$ +347°: at 310 mμ, 3 min. = +607°, 8 min. = +646°, 10 min. = +598°, 15 min. = +633°, 20 min. = +626°.

(+)-**2,2,5-Trimethylcyclohexanone** (VI), R.D. (Fig. 2) in methanol (*c* 0.074): $[\alpha]_{700}$ +58°, $[\alpha]_{589}$ +78°, $[\alpha]_{312.5}$ +2870°; (*c* 0.015): $[\alpha]_{270}$ −2910°, $[\alpha]_{265}$ −2705°; acid study (*c* 0.074, 20 min.), $[\alpha]_{700}$ + 63.5°, $[\alpha]_{589}$ +70°, $[\alpha]_{312.5}$ +2865°, $[\alpha]_{300}$ +1536°: at 312.5 mμ, 15 min. = +2870°.

(+)-*trans*-**8-Methyl-5-hydroxyhydrindan-2-one** (VIII),[24] R.D. in methanol (*c* 0.027): $[\alpha]_{700}$ +160°, $[\alpha]_{589}$ +250°, $[\alpha]_{312.5}$ +6733°; (*c* 0.020): $[\alpha]_{282.5}$ −5525°; acid study, $[\alpha]_{700}$ +130°, $[\alpha]_{589}$ +190°, $[\alpha]_{312.5}$ +5045°, $[\alpha]_{285}$ −3495°.

(−)-*trans*-**8-Methylhydrindan-5-one** (IX),[24] R.D. in methanol (*c* 0.150): $[\alpha]_{700}$ −42°, $[\alpha]_{589}$ −64°, $[\alpha]_{316}$ −1413°; (*c* 0.030): $[\alpha]_{272.5}$ +1286°, $[\alpha]_{267.5}$ +846°; acid study (75 min.), $[\alpha]_{700}$ −3°, $[\alpha]_{589}$ −10°, $[\alpha]_{310}$ −366°, $[\alpha]_{285}$ +86°, $[\alpha]_{275}$ −86°.

(−)-*trans*-**9-Methyl-3-decalone** (X), R.D. in methanol (*c* 0.116): $[\alpha]_{700}$ −12°, $[\alpha]_{589}$ −40°, $[\alpha]_{307.5}$ −1637°, $[\alpha]_{295}$ −1175°; acid study (*c* 0.0232, 48 min.), $[\alpha]_{710}$ −17°, $[\alpha]_{589}$ −38°, $[\alpha]_{307.5}$ −436°, $[\alpha]_{300}$ −388°: at 307.5 mμ, 48 min. = −436°.

(+)-*trans*-**8,9-Dimethyl-3-decalone** (XI),[25] R.D. in methanol (*c* 0.112): $[\alpha]_{700}$ +53°, $[\alpha]_{589}$ +57°; (*c* 0.0215): $[\alpha]_{307.5}$ +1630°, $[\alpha]_{285}$ −335°; acid study (20 min.), $[\alpha]_{700}$ +40°, $[\alpha]_{589}$ +35°, $[\alpha]_{307.5}$ +493°, $[\alpha]_{290}$ +298°, $[\alpha]_{280}$ +675°: at 307.5 mμ, 7 min. = +519°, 10 min. = +519°, 15 min. = +442°, 20 min. = +493°.

(+)-*trans*-**8,9-Dimethyl-2-decalone** (XII),[25] R.D. in methanol (*c* 0.078): $[\alpha]_{700}$ +69°, $[\alpha]_{589}$ +86°, $[\alpha]_{307.5}$ + 1755°, $[\alpha]_{270}$ −2220°; acid study (35 min.), $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +67°, $[\alpha]_{307.5}$ +1552°, $[\alpha]_{290}$ −319°: at 307.5 mμ, 20 min. = +1538°, 35 min. = +1552°.

Cholestan-3-one (XV), R.D. (Fig. 3) in methanol (*c* 0.155): $[\alpha]_{700}$ + 37°, $[\alpha]_{589}$ +48°, $[\alpha]_{307.5}$ +803°, $[\alpha]_{280}$ −275°; acid study (70 min.), $[\alpha]_{700}$ +31°, $[\alpha]_{589}$ +42°, $[\alpha]_{307.5}$ +293°, $[\alpha]_{285}$ +104°, $[\alpha]_{270}$ +218°: at 307.5 mμ, 50 min. = +332°, 55 min. = +312°, 60 min. = +288°, 70 min. = +293°. Readings in acid solution could be obtained after 15 min. down to 310 mμ, but the first measurement at the peak (307.5 mμ) was only possible after 50 min.

A spectrophotometric study to examine a possible source of the "blanking-out" effect was performed: a methanol solution (identical concentration as in the rotatory dispersion work) of cholestan-3-one was examined spectroscopically over the range 270–340 mμ in a Beckman DK model recording spectrophotometer, the appropriate amount of hydrochloric acid was added and scanning over the same spectral range was performed immediately. The light transmission of the acidified solution over this range was reduced only by 2%.

Dihydrotestosterone (XVI) (Syntex, S.A.), R.D. in methanol (*c* 0.086): $[\alpha]_{700}$ +35°, $[\alpha]_{589}$ +52°, $[\alpha]_{307.5}$ +900°, $[\alpha]_{270}$ −988°; acid study (25 min.), $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +27°, $[\alpha]_{307.5}$ +285°, $[\alpha]_{270}$ −93°: at 307.5 mμ, 3 min. = +525°, 15 min. = +484°, 18 min. = +553°, 19 min. = +549°, 20 min. = +338°, 22 min. = +285°.

Dihydro-19-nortestosterone (XVII) (Syntex, S.A.), R.D. in methanol (*c* 0.090): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +27°, $[\alpha]_{307.5}$ +1115°, $[\alpha]_{280}$ −489°; acid study (30 min.), $[\alpha]_{700}$ +7.5°, $[\alpha]_{589}$ +8.5°, $[\alpha]_{307.5}$ +296°, $[\alpha]_{277.5}$ −74°: at 307.5 mμ, 20 min. = +341°, 25 min. = +296°.

Androstan-17β-ol-2-one propionate (XVIII),[27] R.D. in methanol (*c* 0.080): $[\alpha]_{700}$ −1°, $[\alpha]_{589}$ +3°, $[\alpha]_{310}$ +1063°, $[\alpha]_{285}$ −1121°; acid study (25 min.), $[\alpha]_{700}$ +8°, $[\alpha]_{589}$ +10°, $[\alpha]_{310}$ +933°, $[\alpha]_{297.5}$ +75.5°: at 310 mμ, 11 min. = +935°, 15 min. = +934°, 20 min. = +933°.

Cholestan-6-one (XX) (C. W. Shoppee), R.D. in methanol (*c* 0.0965): $[\alpha]_{700}$ +1°, $[\alpha]_{589}$ −3°, $[\alpha]_{307.5}$ −726°, $[\alpha]_{295}$ −23°; acid study (40 min.), $[\alpha]_{700}$ −5°, $[\alpha]_{589}$ −5°, $[\alpha]_{307.5}$ −745°, $[\alpha]_{305}$ −698°: at 307.5 mμ, 30 min. = −705°, 37 min. = −752°, 38 min. = −745°.

Coprostan-6-one (XXI) (C. W. Shoppee), R.D. in methanol (*c* 0.053):[44] $[\alpha]_{700}$ −34°, $[\alpha]_{589}$ −44°, $[\alpha]_{312.5}$ − 1731°, $[\alpha]_{305}$ −1439°; acid study (35 min.), $[\alpha]_{700}$ −13°, $[\alpha]_{589}$ −48°, $[\alpha]_{312.5}$ −1486°, $[\alpha]_{310}$ −1355°: at 312.5 mμ, 15, 20 and 25 min. = −1358°, 30 min. = −1486°.

Androstane-3β,17β-diol-7-one diacetate (XXII) (A. Bowers), R.D. in methanol (*c* 0.082): $[\alpha]_{700}$ −18.5°, $[\alpha]_{589}$ −32°, $[\alpha]_{310}$ −457°; (*c* 0.016): $[\alpha]_{285}$ −166°; acid study (30 min.), $[\alpha]_{700}$ −6°, $[\alpha]_{589}$ −18°, $[\alpha]_{310}$ −349°, $[\alpha]_{290}$ +160°: at 310 mμ, 10 min. = −288°, 15 min. = −251°, 20 min. = −374°, 25 min. = −349°.

Pregnan-11-one (XXIII) (E. Batres),[45] R.D. in methanol (*c* 0.099): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +21°, $[\alpha]_{325}$ +329°, $[\alpha]_{297.5}$ −370°; acid study (40 min.), $[\alpha]_{700}$ +9°, $[\alpha]_{589}$ +15°, $[\alpha]_{325}$ +296°, $[\alpha]_{305}$ −474°: at 325 mμ, 3 min. = +319°, 15 min. = +283°, 20 min. = +292°, 25 min. = +300°, 30 min. = +282°, 35 min. = +296°.

9α-Bromopregnane-3α,20β-diol-11-one diacetate (XXIV) (E. R. H. Jones), R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +136°, $[\alpha]_{589}$ +192°, $[\alpha]_{350}$ +2110°, $[\alpha]_{290}$ −1840°, $[\alpha]_{285}$ −1804°; acid study, $[\alpha]_{589}$ +200°, $[\alpha]_{350}$ +2162°, $[\alpha]_{295}$ −1610°.

Methyl 3α-acetoxy-12-ketocholanate (XXV) (T. Reichstein), R.D. in methanol (*c* 0.112): $[\alpha]_{700}$ +81°, $[\alpha]_{589}$ +108°, $[\alpha]_{302.5}$ +759°, $[\alpha]_{285}$ +566°; acid study (50 min.), $[\alpha]_{700}$ +79°, $[\alpha]_{589}$ +101°, $[\alpha]_{302.5}$ +748°, $[\alpha]_{295}$ +648°: at 302.5 mμ, 25 min. = +892°, 30 min. = +782°, 35 min. = +760°, 40 min. = +758°, 45 min. = +748°.

Ergostan-3β-ol-12-one acetate (XXVI) (W. G. Dauben), R.D. in methanol (*c* 0.092): $[\alpha]_{700}$ +37°, $[\alpha]_{589}$ +41°, $[\alpha]_{705}$ +616°, $[\alpha]_{280}$ +41°; acid study (15 min.), $[\alpha]_{700}$ +33°, $[\alpha]_{589}$ +39°, $[\alpha]_{305}$ +612°, $[\alpha]_{290}$ +308°: at 305 mμ, 10 min. = +611°.

Androstan-3-one (XXVII) (Syntex, S.A.), R.D. in methanol (*c* 0.092): $[\alpha]_{700}$ +28.5°, $[\alpha]_{589}$ +34°, $[\alpha]_{307.5}$ +945°, $[\alpha]_{270}$ −1050°; acid study (40 min.), $[\alpha]_{700}$ +18°, $[\alpha]_{589}$ +8°, $[\alpha]_{307.5}$ +182°, $[\alpha]_{275}$ −293°: at 307.5 mμ, 5 min. = +603°, 30 min. = +193°, 32 min. = +199°, 35 min. = +181°.

Androstan-17-one (XXVIII) (Syntex, S.A.), R.D. in methanol (*c* 0.073): $[\alpha]_{700}$ +73°, $[\alpha]_{589}$ +106°, $[\alpha]_{312.5}$ +2698°, $[\alpha]_{275}$ −2660°, $[\alpha]_{265}$ −1865°; acid study (40 min.), $[\alpha]_{700}$ +106°, $[\alpha]_{589}$ +106°, $[\alpha]_{312.5}$ +2660°: at 312.5 mμ, 6 min. = +2742°, 10 min. = +2720°, 18 min. = +7222°, 35 min. = +2660°.

Androstane-3,17-dione (XXIX) (Syntex, S.A.), R.D. in methanol (*c* 0.082): $[\alpha]_{700}$ +90°, $[\alpha]_{589}$ +170°; (*c* 0.016): $[\alpha]_{312.5}$ +4000°, $[\alpha]_{305}$ +3190°; acid study (95 min.), $[\alpha]_{700}$ +110°, $[\alpha]_{589}$ +146°, $[\alpha]_{312.5}$ +2625°, $[\alpha]_{305}$ +1500°: at 312.5 mμ, 40 min. = +2970°, 45 min. = +3110°, 50 min. = +2840°, 55 min. = +2620°, 60 min. = +2550°, 90 min. = +2625°.

Androstan-3β-ol-16-one (XXXI) (F. Sorm), R.D. in methanol (*c* 0.243 to 320 mμ, then *c* 0.0243):[46] $[\alpha]_{700}$ −101°, $[\alpha]_{589}$ −159°, $[\alpha]_{315}$ −5202°, $[\alpha]_{295}$ +420°; acid study, $[\alpha]_{700}$ −100°, $[\alpha]_{589}$ −170°, $[\alpha]_{315}$ −4706°, $[\alpha]_{295}$ +320°.

Allopregnan-20-one (XXXII) (Syntex, S.A.), R.D. (Fig. 4) in methanol (*c* 0.054): $[\alpha]_{700}$ +58°, $[\alpha]_{589}$ +97°, $[\alpha]_{307.5}$ +2640°, $[\alpha]_{265}$ −2798°, $[\alpha]_{261}$ −2770°; acid study (30 min.), $[\alpha]_{700}$ +70°, $[\alpha]_{589}$ +95°, $[\alpha]_{307.5}$ +2662°, $[\alpha]_{290}$ +534°: at 307.5 mμ, 5 min. = +2665°, 10 min. = +2660°, 15 min. = +2658°, 23 min. = +2662°.

3β-Acetoxyhexanordammaran-20-one (XXXIV) (J. S. Mills),[32] R.D. (Fig. 4) in methanol (*c* 0.103): $[\alpha]_{700}$ +53°, $[\alpha]_{589}$ +76°, $[\alpha]_{323}$ +278°, $[\alpha]_{311}$ +264°, $[\alpha]_{257.5}$ +818°.

21-Nor-Δ⁵-pregnen-3β ol-20-al (XXXV) (A. Bowers), R.D. in methanol (*c* 0.047): $[\alpha]_{700}$ −34°, $[\alpha]_{589}$ −85°, $[\alpha]_{320}$ +258°, $[\alpha]_{280}$ −1225°; acid study (12 min.), $[\alpha]_{700}$ −71°, $[\alpha]_{589}$ −73°, $[\alpha]_{320}$ −221°, $[\alpha]_{300}$ −274°, $[\alpha]_{280}$ −468°; at 320 mμ, 2 min. = −193°, 4 min. = −189°, 8 min. = −221°.

(44) In an earlier reported curve (C. Djerassi and W. Closson THIS JOURNAL, **78**, 3761 (1956)) a trough value at 312.5 mμ of −2240° was observed. These measurements were made over two years ago and it is possible that the sample had partially isomerized on standing to cholestan-4-one (trough −780°). This does not change the conclusions drawn in the discussion of the present paper.

(45) F. Sondheimer, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 1090 (1957).

(46) The great dilution is probably responsible for the fact that in this instance the trough value differs by *ca.* 10% from that recorded earlier (ref. 23).

Cholestan-3β-ol-22-one (XXXVII) (A. Ercoli), R.D. (Fig. 4) in methanol (*c* 0.090): $[\alpha]_{700}$ −20°, $[\alpha]_{589}$ −14° $[\alpha]_{310}$ −305°, $[\alpha]_{270}$ +400°; acid study (40 min.), $[\alpha]_{700}$ +5°, $[\alpha]_{589}$ +2°, $[\alpha]_{310}$ −180°, $[\alpha]_{302.5}$ +87°: at 310 mμ, 35 min. = −180°.

Cholestan-3β-ol-23-one (XXXVIII) (A. Ercoli), R.D. in methanol (*c* 0.121): $[\alpha]_{700}$ + 10°, $[\alpha]_{589}$ +10°, $[\alpha]_{310}$ −317°, $[\alpha]_{265}$ +870°, $[\alpha]_{262.5}$ +830°; acid study (20 min.), $[\alpha]_{312.5}$ −294°: at 310 mμ, 3 min. = −301°, 10 min. = −227°, 15 min. = −231°.

3-Methyl-3-phenylhexan-4-one (XXXIX) (D. J. Cram),[39] R.D. in methanol (*c* 0.14): $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +61°, $[\alpha]_{315}$ +1588°, $[\alpha]_{307.5}$ +1176°; acid study (98 min.), $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +57°, $[\alpha]_{315}$ +1349°, $[\alpha]_{310}$ +1278°: at 315 mμ, 94 min. = +1349°.

3,4,6-Trimethyl-5-oxoheptanoic acid (XL) (R. H. Eastman),[40] R.D. in methanol (*c* 0.110): $[\alpha]_{700}$ +36°, $[\alpha]_{589}$ +43°, $[\alpha]_{315}$ +914°, $[\alpha]_{300}$ +393°; acid study (20 min.), $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +40°, $[\alpha]_{315}$ +930°, $[\alpha]_{310}$ +836°: at 315 mμ, 17 min. = +930°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS]

O-Acylhydroxylamines. I. Synthesis of O-Benzoylhydroxylamine[1]

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O-Benzoylhydroxylamine has been synthesized by taking advantage of the ease of cleavage of the carbo-*t*-butoxy group. The hydrochloride was obtained analytically pure whereas the free base was found to be an unstable oil which suffered O-to-N rearrangement of the benzoyl group.

Previously[2] it has been shown that oxidation of 1,1-dibenzylhydrazines by means of mercuric oxide yields bibenzyls. The reaction has been postulated[3] to proceed through intermediates such as I. Because of the relationship between intermediates such as I and aliphatic diazo compounds, syntheses of the latter have been modified to provide new routes to bibenzyls. Alkaline deg-

$(C_6H_5CH_2)_2\overset{+}{N}{=}\overset{-}{N}$ (I) $(C_6H_5CH_2)_2NOH$ (II) H_2NOSO_3H (III)

radation of 1,1-dibenzyl-2-benzenesulfonhydrazide gave, as expected, a high yield of bibenzyl.[4] A second synthetic route to diazo compounds has now been examined. Forster[5] found that certain ketone oximes such as benzil monoxime, on treatment with chloramine, yielded the corresponding diazo compounds. When aqueous solutions of chloramine were mixed with a suspension of N,N-dibenzylhydroxylamine (II) in aqueous alkali no evidence for bibenzyl formation was obtained. Furthermore numerous attempts to apply the Forster reaction to the synthesis of simple diazo compounds such as diazofluorene were unsuccessful. Since these difficulties may have been due to the nature of chloramine, an unstable gaseous substance most easily handled in dilute aqueous solution, attention was directed toward the synthesis of O-acyl and O-sulfonyl derivatives of hydroxylamine as substitutes for chloramine. Hydroxylamine-O-sulfonic acid[5,6] (III) has already been shown to undergo many reactions analogous to those of chloramine although its insolubility in organic solvents hinders its widespread utilization. Simple N-unsubstituted O-acylhydroxylamines are unknown except for the O-anthranoyl[7,8] and O-carbamoyl[9-13] derivatives. In this paper a synthesis of O-benzoylhydroxylamine (VIII) is reported. The method employed took advantage of the extreme ease of cleavage of the carbo-*t*-butoxy group.[14-16] Analogous preliminary attempts to use the carbobenzoxy group were unsuccessful.[17]

t-Butyl N-hydroxycarbamate (V) was obtained (80%) by treatment of a mixture of *t*-butyl azidoformate and aqueous hydroxylamine hydrochloride with sodium hydroxide. When the reaction was carried out by dropwise addition of the azide to the other reactants or at temperatures above that of the room the O,N-diacylated derivative *t*-butyl N-*t*-butyloxycarbonyloxycarbamate was formed. For preparative purposes a better yield of this compound was obtained by treatment of the hydroxamic acid V with the azide IV in a separate reaction. The hydroxamic acid V reacted normally

$$N_3COOCMe_3 \xrightarrow{NH_2OH} NHOHCOOCMe_3 \xrightarrow{C_6H_5COCl}$$

IV V

$$C_6H_5COONHCOOCMe_3 \xrightarrow{HCl} C_6H_5COONH_3Cl \xrightarrow{HCO_3^-} C_6H_5COONH_2$$

VI VII VIII

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