Tetrahedron. Vol. 26, pp. 4947 to 4952. Pergamon Press 1970. Printed in Great Britain

A NEW CIRCULAR DICHROISM STUDY OF KETAL FORMATION OF SOME STEROIDAL KETONES

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(*Received in the USA* 5 *June* 1970; *Received in the UK for publication* 16 *June* 1970)

Abstract—Polycyclic ketones react reversibly with methanol, ethanol, and isopropanol in presence of hydrogen chloride. Treatment of 5α-cholestan-3-one (2) in acidic methanol solution gives the crystalline dimethyl ketal (7). In optically active substances, the percentage of ketal formed is easily followed by RD and CD, and is a function of structural and stereochemical factors. Furthermore, the reversibility of the ketone ⇌ ketal reaction is strongly dependent on the amount of water present in the reactive medium.

Résumé—On montre que les céto-stéroides en solution dans le méthanol conduisent à un diméthyl acétal en milieu acide. L'étude par dichroisme circulaire révèle que tant la structure que la stéréochimie du composé cétonique, comme la nature de l'alcool utilisé gouvernent l'équilibre cétone ⇌ cétal. Celui-ci dépend également de la quantité d'eau présente dans le milieu.

THE conversion of the CO group into a hemiketal (hemiacetal), or a ketal (acetal) has been known for a long time.[1–3] More recently, the reaction of certain aliphatic and monocyclic ketones with methanol in the presence of acid has been studied quantitatively by several authors.[4–7]

McCoy *et al.*[5] detected cyclohexanone dimethylketal by mass spectral examination of the reaction mixture and by the disappearance of the CO frequency in IR as well as appearance of OMe groups. Suter and Guedin[8] reported that when acid solutions of simple aliphatic ketones and methanol were introduced into a mass spectrometer, the resulting mass peaks indicated that some ketal was formed. The criterion used by Wheeler[4] was the lowering of the UV extinction coefficient of the CO chromophore absorbing in the 290 nm region.

Such techniques encounter some practical drawbacks. On the one hand, IR measurements are not always convenient for equilibrium studies, since they require a substantial amount of material. Moreover, polar solvents (such as methanol) cannot be used routinely. On the other hand, UV absorption measurements of saturated ketones and aldehydes are often unsatisfactory because of unsharp maxima and low extinction coefficients. Furthermore, the UV method is not easily applicable to substances which contain strongly absorbing chromophores (e.g. conjugated acids, esters, aromatic rings, etc.).

If the substance is optically active, the conversion of a carbonyl compound into its hemiketal or its ketal derivative should result in the decrease of the Cotton effect observed either by RD or CD.[9] This is illustrated by the plain RD curves of various

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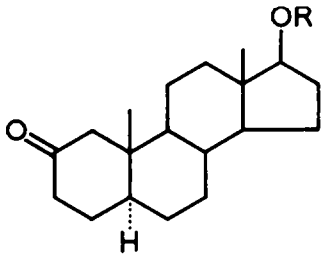
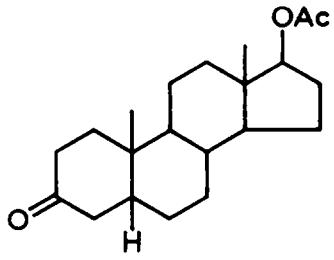


1a; R = H

b; R = Ac



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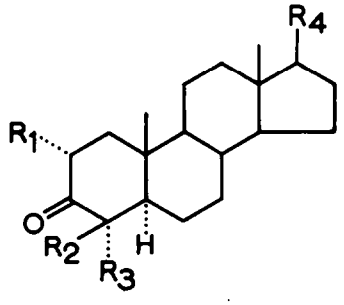

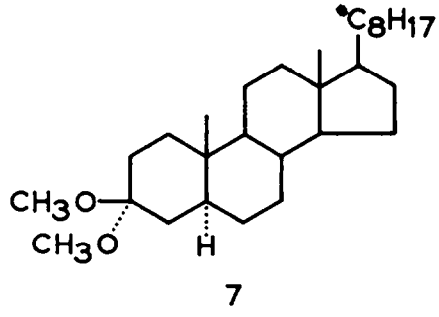

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2: $R_1 = R_2 = R_3 = H$; $R_4 = C_8H_{17}$

4; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = OH$

5; $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = OH$

6; $R_1 = H$; $R_2 = R_3 = CH_3$; $R_4 = C_8H_{17}$

carbohydrates in which the CO function is masked by acetal formation[10] and the contrasting Cotton effect RD curves obtained with polyacetylated aldehydo-sugars and fructose in which acetal or ketal formation is hampered.[11]

These conditions led Djerassi[12] to investigate by RD the effect of the nature of the solvent, as well as the influence of structural and stereochemical factors on the extent of (hemi) ketal formation. By measuring the RD of optically active ketones in methanol solution, adding a drop of hydrochloric acid, and after a suitable time interval repeating the RD determination, Djerassi *et al.*[12, 13] have shown that the hemiketal or ketal formation is translated into a proportional decrease of the Cotton effect.

In spite of these studies, some doubt still existed about the hemiketal *versus* ketal nature of the species devoid of UV absorption and Cotton effect. Although several authors[5–7] agreed that linear ketones and aldehydes, as well as monocyclic saturated ketones form mainly ketals (acetals) in methanol solution in the presence of an acid, there was no chemical or spectroscopic evidence available to support either the ketal or the hemiketal formation in polycyclic ketones. Furthermore, the reports men-

tioning the amount of ketal formed with such simple ketones as cyclohexanone in acidic methanol solution, are conflicting.[4–7]

In this work we wish to report some studies made with the steroidal ketones (**1** to **6**) in order to decide what species (ketal or hemiketal) is formed, and to find out which factors influence the ketone ⇌ ketal equilibrium.

Introduction of hydrochloric acid to a methanol solution of 5α-cholestan-3-one (**2**), followed by addition of anhydrous sodium bicarbonate, allowed us to isolate and identify the dimethyl ketal (**7**). The formation of this crystalline compound (**7**), characterized by the absence of a CO band in its IR spectrum, two OMe signals, appearing respectively at 3·14 δ and 3·19 δ in the NMR spectrum, and the mass spectrum molecular ion (M^+ 432·39), strongly indicate that the ketal and not the hemiketal is formed under these conditions.

The Table lists the steroidal ketones which were investigated. The CD molecular ellipticity ($[\theta]$) was obtained at 20°, in anhydrous methanol, ethanol, and isopropyl alcohol solution, since ketal formation is known to be very responsive to the size of the alcohol.[12–14] The Table also reports the molecular ellipticity values ($[\theta]^1$) after addition of a standardized amount of acid (Experimental), and the percent reduction in the magnitude of the Cotton effect (%Δ).

TABLE

Compound	Methanol	Ethanol	2-Propanol
1a	$[\theta]_{291}$ = 6293 $[\theta]^1$ = 2876 %Δ = 54	$[\theta]_{292}$ = 6138 $[\theta]^1$ = 5206 %Δ = 15	$[\theta]_{292}$ = 6742 $[\theta]^1$ = 6376 %Δ = 5
1b	$[\theta]_{292}$ = 6525 $[\theta]^1$ = 1775 %Δ = 73	$[\theta]_{292}$ = 6138 $[\theta]^1$ = 5206 %Δ = 15	$[\theta]_{293}$ = 6199 $[\theta]^1$ = 5818 %Δ = 6
2	$[\theta]_{289}$ = 4185 $[\theta]^1$ = 168 %Δ = 96	$[\theta]_{290}$ = 4339 $[\theta]^1$ = 696 %Δ = 84	$[\theta]_{290}$ = 3682 $[\theta]^1$ = 2762 %Δ = 25
3	$[\theta]_{289}$ = −1339 $[\theta]^1$ = 0 %Δ = 100	$[\theta]_{291}$ = −1411 $[\theta]^1$ = −92 %Δ = 94	$[\theta]_{290}$ = −1471 $[\theta]^1$ = −844 %Δ = 43
4	$[\theta]_{290}$ = 3901 $[\theta]^1$ = 2900 %Δ = 26	$[\theta]_{291}$ = 3805 $[\theta]^1$ = 3601 %Δ = 5	$[\theta]_{292}$ = 3642 $[\theta]^1$ = 3509 %Δ = 4
5	$[\theta]_{289}$ = 3509 $[\theta]^1$ = 2986 %Δ = 15	$[\theta]_{288}$ = 3448 $[\theta]^1$ = 3270 %Δ = 5	$[\theta]_{289}$ = 3607 $[\theta]^1$ = 3456 %Δ = 4
6	$[\theta]_{307}$ = −864 $[\theta]^1$ = −709 %Δ = 18		$[\theta]_{309}$ = −701 $[\theta]^1$ = −701 %Δ = 0

When 17β-hydroxyandrostan-2-one (**1a**) in methanol solution was treated with acid, the Cotton effect was reduced by 54%. The corresponding 17-acetate (**1b**) showed 73% formation of the ketal. As indicated by Djerassi,[12] the fact that the

2-keto-steroid (**1b**) could not be converted entirely to its ketal is due to steric factors, *in extenso* the 1,3-diaxial interactions between the 2β-OMe and the 10β-Me groups. However, the amount of ketal formed (up to 73% *viz* 12% reported earlier) indicates that the 1,3-diaxial interactions are not as strong as indicated previously, so that other factors may be involved in the ketone ⇌ ketal equilibrium (see below). In agreement with previous observations,[13] only a small proportion of ketal is formed in ethanol (15%) and 2-propanol solution (5%). This is attributed to steric factors inherent to the nature of the ketal.

The 3-keto-steroid 5α-cholestan-3-one (**2**) gave 96% of the dimethyl ketal (**7**), 84% of diethyl ketal, and 25% of the corresponding diisopropyl ketal. Still more striking is the quantitative dimethyl ketal formation in the case of the 3-keto-5β-steroid (**3**). Moreover, the diethyl ketal was formed in 94% and the diisopropyl ketal in 43% yield. These results emphasize the influence of the stereochemistry at C-5 on the amount of ketal formed and seem to indicate that the 3-keto chromophore is less hindered in the 5βH-series than in the 5αH-series and/or that there are less steric interactions in the ketals derived from the 3-keto-5β-steroid (**3**) than in the 5α-compound (**2**).

Each of the 3-keto-steroids (**4**, **5** and **6**) have alkyl-substituents either at C-2 or at C-4. Provided that the precautions mentioned in the Experimental are taken, in these three cases, although substantially reduced, the formation of ketal in acidic methanol solution, is not fully inhibited. Even *gem*-dialkylation in the cyclohexanone ring, such as in 4,4-dimethyl-cholestanone (**6**), does not completely inhibit conversion to the ketal. The reduced ketal formation, ranging from 18 to 26%, can be used as a diagnosis for the presence of an alkyl substituent vicinal to the keto-group.[12, 13]

The difference in ketal formation observed between compounds **4** and **5** in methanol solution (see Table) may mean that an equatorial Me group at C-4 causes more steric hindrance than an equatorial Me at C-2. Moreover, it is worth noting that the value of %Δ of the *gem*-dimethyl-cholestanone (**6**) in methanol solution is higher (18%) than that of **5** (15%), *in extenso* two Me groups at C-4 are no worse sterically than the equatorial one in **5**. In both compounds **5** and **6**, the really severe interaction comes from the equatorial Me group at C-4, which, in the ketal, is *gauche* to both OMe groups at C-3. The slight difference in %Δ-values between **5** and **6**, may be due to changes of conformation occurring in ring A of these polycyclic compounds.

The difference noted in the ketal formation in the case of alcohol (**1a**) and its acetate (**1b**) seems to indicate that the time required to reach a constant equilibrium may vary from one substance to another. Indeed, it was observed that addition of hydrochloric acid to cholestanone (**2**) in isopropyl alcohol is not accompanied by an immediate decrease of the magnitude of the Cotton effect. The formation of the ketal is not spontaneous but takes some time to level off.

In the case of 2-keto-steroids, whilst only 12% of ketal was formed under previously described conditions,[13a] with the precautions indicated in the experimental, the ketone ⇌ ketal equilibrium can be displaced to the right. This seems to indicate that in order to get high ketal formation, the medium has to be *absolutely* anhydrous. Indeed, this has been clearly shown in the case of a 3-keto-steroid. Addition of a trace of concentrated hydrochloric acid to a dry methanol solution of 5α-cholestan-3-one (**2**) gave 96% of the ketal (**7**), (see Table). Introduction of one microliter of water to this solution shifted the ketone ⇌ ketal equilibrium to the left, and addition of further

microliters of water regenerated increasing amounts of ketone (2) (Experimental). This observation emphasizes that the amount of ketal formed is not only a function of the structure and stereochemistry of the keto-compound and of the nature of the solvent, but if the solution investigated is not strictly anhydrous, the results become meaningless.

In summary, the RD or CD ketal study, initially developed by Djerassi *et al.*[12, 13] can provide valuable information. However, before drawing structural and/or stereochemical conclusions from such an experiment, one should make sure that all precautions have been taken to avoid presence of moisture in the reaction medium.

EXPERIMENTAL

The microanalysis is due to Alfred Bernhardt, Mikroanalytisches Laboratorium, West Germany. The RD and CD curves were obtained with a JASCO/UV-5 spectropolarimeter equipped with a CD attachment. The NMR spectrum was recorded at 60 MHz in deuteriochloroform solution containing TMS, as an internal reference. We are indebted to Syntex, S.A., Mexico for a generous gift of steroids.

Dry EtOH was prepared according to the procedure described in ref. 15. Dry MeOH was prepared according to the procedure of Fieser (ref. 15, p. 289) starting with Fisher spectro-analyzed. Dry 2-propanol was prepared by distillation of Fisher 2-propanol over Mg turnings.

All alcohol additions and solution transfers were done with dry syringes in a dry nitrogen atmosphere.

Standardized additions of acid to alcoholic solutions of ketones. After each spectrum of the pure compound in dry alcohol was run, approximately 25 μl of standardized alcoholic HCl (in the same alcohol) was added. When the curve amplitude stabilized to a minimum value (usually 45 min), the spectrum was run again. The cell (water-jacketed), was then washed several times with the solvent, and the base line was determined. All spectra were recorded at 20 ± 1° in a water-jacketed 10 mm quartz cell maintained at this temp with an Ultra-Kryomat TK-30 cooling unit.

Standardized alcoholic acid solns were prepared by passing dry HCl gas through the dry alcohol and then titrating a portion of the soln with standardized 0·010N NaOH using phenolphthalein as an indicator. The acid solns thus prepared showed the following normalities: 0·117N HCl in MeOH; 0·104N HCl in EtOH; 0·167N HCl in i-PrOH.

RD and CD of 5α-cholestan-3-one (2)

Preparation of dimethyl ketal (7). A soln was prepared by dissolving 151·2 mg of 2 in MeOH (Fisher spectroanalyzed) and diluting to 50 ml. Approximately 3 ml of this soln was used in a 0·1 dm cell to obtain the RD curve: $[\phi]_{700}$ + 134°; $[\phi]_{589}$ + 153°; $[\phi]_{305\cdot5}$ + 3121°; $[\phi]_{287}$ 0°; $[\phi]_{268}$ − 2240°; $[\phi]_{230}$ − 1614°; $[\phi]_{215}$ − 1532°; a = + 54. A minute trace of conc HCl was added by dipping a needle into the acid, wiping lightly with tissue and momentarily inserting the needle into the sample. 15 min were allowed for equilibration and then the RD spectrum was recorded again. The Cotton effect was almost imperceptible on the plain positive curve obtained, so another 3 ml sample of the original soln was used for CD measurements to determine quantitatively the extent of ketal formation. The original soln gave a molecular ellipticity of: $[\theta]_{233}$ 0; $[\theta]_{289}$ + 4084; $[\theta]_{239}$ 0; Γ = 33 mμ.

Addition of a trace of acid as above reduced this to: $[\theta]_{289}$ + 168, a 96% reduction. Addition of one microliter of water shifted the equilibrium to give $[\theta]_{289}$ + 211. Addition of more water gave the following results, total μl water added ($[\theta]_{289}$): 5 (337), 10 (674), 20 (926), 30 (1179), 40 (1410), 50 (1600), 60 (1810), 80 (2126), 100 (2379), 150 (2910), 200 (3221) and 250 (3452).

The remainder of the original soln (approximately 44 ml) was treated with a trace of conc HCl and after 30 min solid $NaHCO_3$ (*ca* 0·5 g) which had been dried one hr at 110° was added. After shaking, the material was filtered and the filtrate evaporated on the rotary evaporator to give 150 mg of a gum which slowly crystallized on cooling. Recrystallization from ether gave 7 as a white crystalline solid: m.p. 83·5–84°; $[\alpha]_D$ + 23°; ν_{max}^{KBr} 1110, 1060 cm^{-1}; NMR ($CDCl_3$) Me singlets at δ 0·65 (3H), δ 0·79 (6H), δ 0·91 (6H), δ 3·14 (3H) and δ 3·19 (3H). Mol. wt: 432·397, mass spectrum: M^+ at *m/e* 432·390. (Found: C, 80·28; H, 12·08. Calc for $C_{29}H_{52}O_2$: C, 80·49; H, 12·11%).

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