# REACTIVITY STUDIES ON NATURAL PRODUCTS

## IV. DISSOCIATION CONSTANTS OF THE CYANOHYDRINS OF SOME STEROID KETONES[1]

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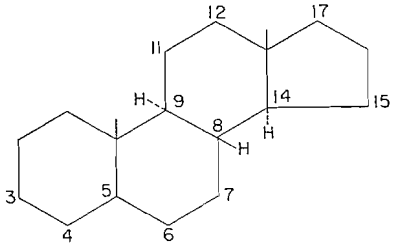
ABSTRACT

The dissociation constants of the cyanohydrins of 3-, 6-, and 7-ketocholestane, 3-keto-coprostane, $\Delta^4$- and $\Delta^5$-cholestenone, and $\Delta^7$-, $\Delta^{8(9)}$-, $\Delta^{8(14)}$-, and $\Delta^{14}$-ergosten-3-one have been measured in 80% dioxane at 25.0°. Cholestan-3-one and coprostan-3-one have essentially the same reactivity. 6- and 7-Ketocholestane show "eclipsing" effects of neighboring hydrogen atoms. $\Delta^4$- and $\Delta^5$-Cholestenone are less reactive than cholestanone owing to the electronic effect of the double bond, but $\Delta^7$-, $\Delta^{8(9)}$-, $\Delta^{8(14)}$-, and $\Delta^{14}$-ergostenone are more reactive, the effect decreasing with the distance of the double bond from the 3-keto group.

## INTRODUCTION

While quantitative studies have been made on the reactivity of steroid esters and alcohols (1, 2), few quantitative data have been published on the relative reactivity towards addition reactions of a keto group in various positions of the steroid molecule, the only work of this nature being studies of the rates of oxime formation of 3-, 4-, 6-, and 7-ketocholestane (3), and of the borohydride reduction of 3- and 20-ketopregnanone (4). It is known that certain postions, e.g., 11 and 12, are unreactive with respect to a 3-keto group, but no systematic study has been made of the reactivity of groups in rings A and B, where reactivity differences would be expected to be small. The determination of ketone–cyanohydrin equilibria provides a convenient method of studying ketone reactivity towards addition reactions (5), and the dissociation constants of the cyanohydrins of 3-keto-cholestane and -coprostane (rings A/B *trans* and *cis*, respectively), 6- and 7-keto-cholestane, and 3-keto steroids with double bonds in positions 4,5,7,8(9),8(14), and 14 have been measured in 80% dioxane–water at 25.0° (see Table I), to investigate the influence of substitution in various positions, of *cis–trans* ring A/B fusion, and the effect of double bonds.




Cholestan-3-one and coprostan-3-one differ only in the nature of the ring A/B fusion. The *trans* fusion in the former case gives the molecule a continuous zigzag form, whereas the *cis* fusion, in the latter, leads to an L-shaped structure (6, 7). In cholestane the methyl group at C-10 and the 9—10 bond are *axial and equatorial* respectively (with respect to ring A), and in the second case are reversed, but in both cases the hydrogen atom at

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TABLE I

DISSOCIATION CONSTANTS OF CYANOHYDRINS[a]

| | $K \times 10^2$ | Ratio[b] |
|---|---|---|
| Cyclopentanone | 56.0±1.0 | 9.3 |
| Cyclohexanone | 6.00±0.10 | 1.0 |
| Cholestan-3-one | 5.42±0.05 | 0.90 |
| Coprostan-3-one | 5.97±0.09 | 1.0 |
| Cholestan-6-one | 7.22±0.13 | 1.2 |
| Cholestan-7-one | 1.25±0.01 | 0.21 |
| $\Delta^4$-Cholesten-3-one | 38.4±0.60 | 6.4 |
| $\Delta^5$-Cholesten-3-one | 7.94±0.15 | 1.3 |
| $\Delta^7$-Ergosten-3-one | 4.09±0.14 | 0.68 |
| $\Delta^{8(9)}$-Ergosten-3-one | 3.97±0.12 | 0.66 |
| $\Delta^{8(14)}$-Ergosten-3-one | 4.50±0.02 | 0.75 |
| $\Delta^{14}$-Ergosten-3-one | 5.43±0.02 | 0.90 |

[a]*In 80% dioxane at 25.0°±0.1°.*
[b]*Ratio of dissociation constant to cyclohexanone = 1.0.*

C-5, one carbon atom nearer, is axial and the 5—6 bond equatorial and thus no large steric effect to cyanohydrin formation due to "axial crowding" (5) would be expected, and both these ketones have essentially the same cyanohydrin dissociation constant as cyclohexanone. The small increased reactivity of cholestanone with respect to cyclohexanone may be due to an "equatorial crowding" effect (5) similar to that observed in alkyl cyclohexanones, whereby the large internal carbonyl angle of the ketone distorts both rings A and B. The distortion is relieved in forming an addition product and addition is, therefore, facilitated.

6- and 7-Ketocholestane both have an extra alkyl substituent in the $\alpha$-position, and this will exert an inductive effect which will increase the dissociation constant (5). However, the 6-ketone shows only a small increase while the 7-ketone actually shows a large decrease in dissociation constant and another effect must be operating. Construction of models shows that in the case of the 7-ketone the steric geometry of the steroid molecule is such that an $\alpha$-hydrogen atom at C-15 is brought very close to the carbonyl group. Addition to the keto group gives a staggered structure and reduces the unfavorable oxygen–hydrogen interactions and is thus favored (8). This shielding or "eclipsing" effect has previously been observed to affect the stabilities of $\alpha$-decalone and the 1,4-ketoperhydrophenanthrenes (9). In the case of the 6-ketone the small "eclipsing" effect of the hydrogen atoms on C-4 will tend to increase the extent of cyanohydrin formation, but there will be an "axial crowding" effect (5) in the cyanohydrin, between the methyl group at C-10 (2) and the cyanide (or hydroxyl) group. The net result of these opposing effects is a small decrease in reactivity, with respect to cholestan-3-one.

$\Delta^4$- and $\Delta^5$-Cholestan-3-one are both less reactive towards cyanohydrin formation than 3-cholestanone. In the former case, addition to the ketone grouping will destroy the resonance conjugation of the $\alpha,\beta$-unsaturated ketone system and hence cyanohydrin formation will be difficult. (Whether addition was 1,4 as well as 1,2 was not determined. However, the reaction was unimolecular in ketone and cyanide.) The decreased reactivity of $\Delta^4$-3-keto steriods, as compared to 3-keto steroids, towards dioxalan formation (10), ketal formation (11), and borohydride reduction (12) has previously been noted. In the $\Delta^5$-compound there will be an inductive (or hyperconjugative) donation of electrons by the double bond to the ketone group (analogous to double-bond participation in the solvolysis of cholesteryl-*p*-toluene sulphonate (13)) and this will decrease the polarity of the ketone grouping and reduce nucleophilic attack of cyanide ion.

In contrast to the behavior of the $\Delta^4$- and $\Delta^5$-compounds, the four ergosten-3-ones ($\Delta^7$, $\Delta^{8(9)}$, $\Delta^{8(14)}$, and $\Delta^{(14)}$) show increased reactivity but in an order decreasing with distance of the double bond from the ketone grouping, until no effect is apparent in the $\Delta^{14}$-compound. This effect is probably not electronic, since the double bonds are too far removed from the keto group, and though the $\Delta^4$- and $\Delta^5$-ketones show displacements of ketone absorption in both the ultraviolet and the infrared (see Table II) due to electronic effects, the ergostenones are no different from cholestanone.

TABLE II

ABSORPTION SPECTRA OF KETONES

| | I. R., cm.$^{-1}$ | U. V.,[c] m$\mu$ |
|---|---|---|
| Cholestan-3-one | 1716[a] | 280 (73) |
| Coprostan-3-one | 1714[a] | 280 (73) |
| $\Delta^4$-Cholesten-3-one | 1627, 1675[a] | 240.5 (18,000)[d] |
| | | 312 (100) |
| $\Delta^5$-Cholesten-3-one | 1683, 1724[a] | 285 (100) |
| $\Delta^7$-Ergosten-3-one | 1712[b] | 280 (59) |
| $\Delta^{8(9)}$-Ergosten-3-one | 1715[b] | 280 (57) |
| $\Delta^{8(14)}$-Ergosten-3-one | 1718[b] | 280 (56) |
| $\Delta^{14}$-Ergosten-3-one | 1715[b] | 280 (62) |

[a] *In carbon tetrachloride solution. K. Dobriner, E. R. Katzenellenbogen, and R. N. Jones. Infrared absorption spectra of steroids—An atlas. Interscience Publishers, Inc., New York, N. Y. 1953.*

[b] *Present work, as nujol mulls.*

[c] *As ethanolic solutions. Present work, unless otherwise stated.*

[d] *Ref. 40.*

Cyclohexene exists in a preferred "half-chair" conformation (14, 15), in which all the angles are slightly distorted (16), and introduction of a double bond into the steroid nucleus will lead to an over-all flattening of the rings. This will slightly distort ring A and introduce small non-bonded interactions. Cyclohexanone, itself, is a slightly distorted structure and its reactivity is due partly to the tendency to form an undistorted addition product (8). The presence of a keto group in ring A will introduce non-bonded interactions in this ring, and these will be increased by the conformational distortions produced by a double bond in a neighboring ring. Thus addition to the keto group, which will partially relieve the unfavorable interactions, will take place more readily than in the case of the saturated ketones. The effect of $\Delta^7$ and $\Delta^{8(9)}$ double bonds, which are on either side of the C-3 to C-8 axis of rings A and B, is the same. A $\Delta^{8(14)}$ double bond, which is exocyclic to these two rings, has less effect and a $\Delta^{14}$ double bond, one more carbon atom remote and in another ring, has no measurable effect. Barton and co-workers (17, 18) have recently shown the operation of long-range effects in the mutarotation of steroid 5,6-dibromides and in the condensation of 3-keto triterpenes with benzaldehyde and has introduced the term "conformational transmission" for the transmission of distortions through a molecule by flexing of valency angles and alteration of atomic co-ordinates. Since no electronic interactions are involved and the effect is purely a steric one, it will manifest itself in an entropy term, and Barton and Head observed no difference in the energy of activation for the dibromides studied, but found small differences in the frequency factor. In the present work the maximum difference, between $\Delta^{8(9)}$-ergosten-3-one and cholestan-3-one, corresponds to a free-energy difference of only 0.18 kcal.

The ketones were generally prepared by standard methods (see Experimental), but in the course of the work some interesting observations were made. Ergosteryl acetate is

hydrogenated in ethyl acetate under ordinary conditions to $\Delta^7$-ergostenyl acetate, but with Raney nickel at high temperature and pressure the product formed was $\Delta^{8(14)}$-ergostenyl acetate. This isomerization has previously been noted with platinum oxide in acetic acid (19). As an alternative to oxidation with chromium trioxide in acetic acid and benzene (20), or Oppenauer oxidation (21), the oxidation of some of the unsaturated alcohols with chromium trioxide in pyridine (the Sarett reagent (22)) was investigated. Cholesterol itself gave a mixture consisting largely of $\Delta^4$-cholestenone but oxidation of $\Delta^7$-ergostenol proceeded without rearrangement. This reagent has been recently used for the oxidation of ursa-9(11),12-dien-3-ol (23) without rearrangement of the double bond. However, it was found that use of only a small excess of chromium trioxide in acetic acid and benzene gave better yields, and this method was generally employed. The isomerization of $\Delta^{8(14)}$-ergostenone to $\Delta^{14}$-ergostenone with hydrogen chloride in chloroform (24, 25) proved to be incomplete (26, 27). Various conditions of time and temperature were tried but the best yield obtained was only a 20% conversion. The isomerization of the corresponding acetate or alcohol gave poorer yields.

## EXPERIMENTAL

### *Ketones*

Cyclopentanone and cyclohexanone were specimens which had been previously prepared in this laboratory (5).

Cholestanone, m.p. 129°–130°, was prepared by oxidation of cholestanol (28), and coprostanone, m.p. 61°–63°, $(\alpha)_D$ +36°, by reduction of cholestenone (21) over a palladium charcoal catalyst in ethyl acetate, with the addition of two drops of piperidine. $\Delta^5$-Cholestenone was prepared by the oxidation and subsequent zinc-dust reduction of cholesterol dibromide (29).

### *Cholestan-6-one*

Cholesterol was converted to cholesteryl bromide, m.p. 97°–98°, $(\alpha)_D$ −20° (lit. m.p. 97°–99°, $(\alpha)_D$ −21.6° (30)), with phosphorus tribromide in benzene (31) and the bromide nitrated with fuming nitric acid and sodium nitrite to 3-bromo-6-nitrocholest-5-ene, m.p. 153°–155°, $\lambda_{max}$ 262 mμ, ε 2200. Zinc-dust reduction (32) gave the required ketone.

### *Cholestan-7-one*

Cholesteryl acetate was oxidized with *t*-butyl chromate (33) to 7-ketocholesteryl acetate, m.p. 157°–160°, $(\alpha)_D$ −86°, which was converted by refluxing with concentrated hydrochloric acid to $\Delta^{3,5}$-cholestadien-7-one, m.p. 112°–113° (lit. m.p. 112° (34)). Reduction of this compound with platinum oxide in ethyl acetate gave the required ketone, m.p. 116°–118°, $(\alpha)_D$ −28°, $\lambda_{max}$ 292 mμ, ε 70 (lit. m.p. 116°–118° (35)).

### $\Delta^7$-*Ergosten-3-one*

Hydrogenation of ergosterol in ethyl acetate and ether at 30 lb. pressure with a platinum oxide catalyst gave $\Delta^7$-ergosten-3-ol. Oxidation by the method of Oppenauer, with chromium trioxide (1.2 equiv.) in acetic acid and benzene, or by the method of Sarett, gave the ketone, m.p. 159°–160°, $(\alpha)_D$ +22° (lit. m.p. 159°, $(\alpha)_D$ +22° (36)), in about 50% yield in each case. Hydrogenation of ergosteryl acetate in ethyl acetate and acetic acid at 30 lb. pressure with a 5% palladium–charcoal catalyst, or in ethyl acetate at 1000 lb. pressure and 100° using a Raney nickel catalyst, gave $\Delta^{8(14)}$-ergostenyl acetate.

### $\Delta^{8(14)}$-*Ergosten-3-one*

Oxidation of $\Delta^{8(14)}$-ergostenol with chromium trioxide in acetic acid and benzene gave

the ketone, m.p. 128°–129°, $(\alpha)_D$ +31.5° (lit. m.p. 129°–130°, $(\alpha)_D$ +30° (36)), in 70% yield. Oppenauer oxidation gave a 50% yield.

*$\Delta^{8(9)}$-Ergosten-3-one*

This was prepared by oxidation of $\Delta^{8(9)}$-ergostenol (37) with chromium trioxide in benzene and acetic acid, and had m.p. 118°–120°, $(\alpha)_D$ +70°.

*$\Delta^{14}$-Ergosten-3-one*

This was prepared by isomerization of $\Delta^{8(14)}$-ergosten-3-one with hydrogen chloride in chloroform. The method gave only partial conversion, but the two isomers could be separated by careful chromatography on neutral alumina using hexane as eluent. The highest conversion (20%) was obtained by saturating with hydrogen chloride at 0° and allowing to stand 3–4 days in a refrigerator at *ca.* 5°. Poorer conversions were obtained with the alcohol or acetate. The pure ketone had m.p. 149°–150°, $(\alpha)_D$ +40° (lit. m.p. 149°–151°, $(\alpha)_D^{20}$ +36.4° (26)).

*Solvents*

Dioxane (Matheson, Coleman, and Bell) was refluxed with potassium hydroxide and fractionated from a fresh quantity. This dioxane (80 vol.) was mixed with distilled water (20 vol.), and the resulting solvent had $d_4^{25}$ 1.0345.

*Cyanohydrin Formation*

Some preliminary experiments were carried out to find a suitable solvent. The steroids were not sufficiently soluble in ethanol. The dissociation constants of the cyanohydrin of cyclopentanone in anhydrous dioxane and 95% dioxane at 25° were *ca.* $700\times10^{-2}$ and $200\times10^{-2}$ respectively. Accordingly 80% dioxane was chosen as a solvent in which the steroids were reasonably soluble and which gave convenient dissociation constants. The procedure adopted was to dissolve the ketone (0.2–0.4 g.) in 80% dioxane in a 100 ml. graduated flask and then to add a solution of hydrogen cyanide (10 ml. of *ca.* 0.15 *N*), prepared from sodium cyanide and sulphuric acid and dissolved in 80% dioxane. A catalyst solution (1 ml.) of 2% tri-*n*-propylamine in 80% dioxane was added and the flask made up to the mark and allowed to equilibrate in a bath at 25.0°±0.1° for 6 hours. Aliquots (10 ml.) of the solution were withdrawn, added to excess silver nitrate (*ca.* 0.1 *N*) containing 0.5% nitric acid, and the excess silver nitrate titrated with potassium thiocyanate (0.05 *N*), using ferric ammonium sulphate as indicator (38, 39). Each experiment was repeated three or more times and the results, together with their mean standard deviations, are given in Table I.

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