Studies on the Synthesis of Enol Acetates of the Δ^1-3-Keto AB-*trans* Steroid System[1]

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Contrary to earlier reports, it is shown that the Δ^1-3-keto AB-*trans* steroid system can yield the enol acetate derivative when treated with acetic anhydride in the presence of a perchloric acid catalyst. Four other products are formed as well and the structures of three of these were elucidated. It was found further that the yields of some of the products are governed by equilibria which disfavor enol acetate formation in the present case.

In connection with another problem, we wished to prepare the enol acetate of a Δ^1-3-keto steroid (A), and perusal of the literature revealed reports that this system does not react to give such a derivative.[2] A reason advanced to explain this supposition is that the enolization of an α,β-unsaturated keto system normally requires the removal of a hydrogen atom from the position γ to the keto group, and the only way that system B can stabilize itself in the form of an enol derivative requires the presence of a hydrogen atom at C-10. When such is not the case (as in C-10 methyl steroids) the formation of enol derivatives fails.[2a]

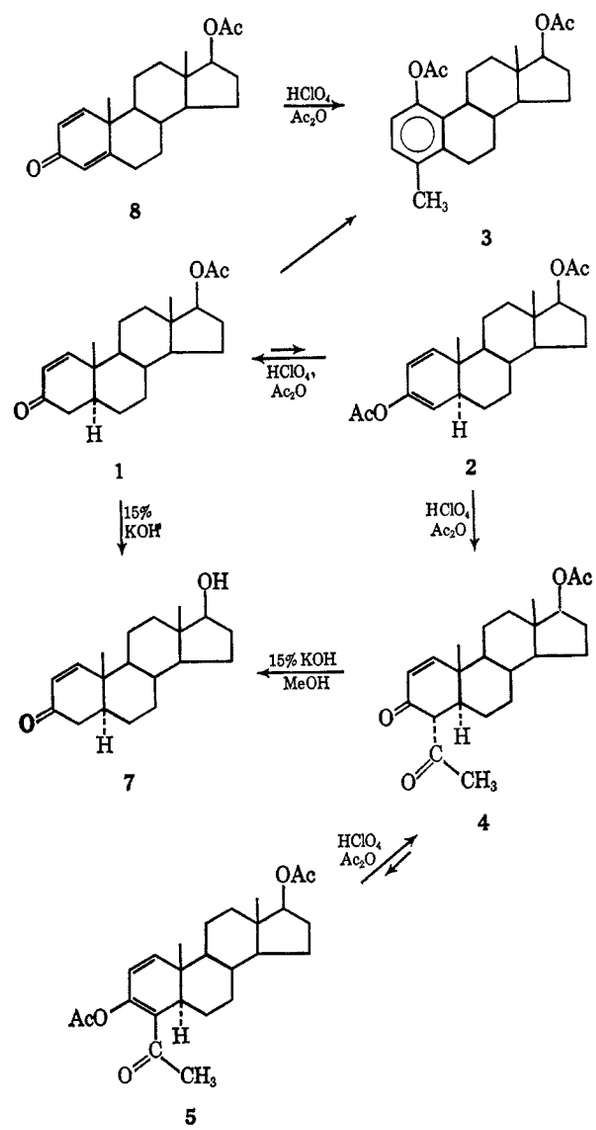
A B

Although this explanation has some distinct merit in any discussion on the *ease* and *direction* of enolization of α,β-unsaturated ketones where more than one direction of enolization is available, we failed to see why such reasoning precludes the possible loss of a C-4 hydrogen atom in system A under proper enolization conditions. We therefore elected to study more fully the behavior of system A when treated under conditions normally leading to enol acetate formation.

Edwards and Rao[2c] recently reported the use of two reagents to carry out enol lactonizations and enol acetylations of steroids. These agents, termed reagents a and b, consist of 1 *M* acetic anhydride solutions in ethyl acetate containing perchloric acid in concentrations of 10^{-3} and 10^{-2} *M*, respectively. In view of the high yields of O acylation frequently obtained with the use of acetic anhydride–perchloric acid mixtures, we chose to reexamine the reagents used by Edwards and Rao,[2c] despite the fact that these workers reported no success with their reagent a (10^{-3} *M* $HClO_4$) in the enol acetylation of 5α-androst-1-ene-3,17-dione and 17β-hydroxy-5α-androst-1-en-3-one. Since these authors made no mention of studying the effects of reagent b on these steroids, we began our investigation with this reagent.

When the androstenone **1** was treated with reagent b for 4 hr at room temperature, thin layer chromatography (tlc) showed the presence of six compounds in the reaction mixture. These were successfully separated by column chromatography and identified as the starting material **1** (46%), the desired enol acetate **2** (11%), the rearranged aromatic compound **3** (3%), the diketone **4** (15%), the ketone enol acetate **5** (3.5%), and a ketone of unknown structure (6, 1.5%). The structure of **3** was established by preparing the same compound in essentially quantitative yield from dienone **8** using reagent b.[2c] Presumably this compound originates in the reaction mixture *via* the same intermediate (**8**) formed by the perchlorate oxidation of **1** (see Scheme I).

SCHEME I



Information for the structure of diketone **4** was forthcoming from its elemental analysis, a positive iodoform test, the ultraviolet absorption spectrum which was indicative of an α,β-unsaturated ketone [λ_{max} 231 (log

(1) This work was supported by Grant AM09003, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) For example, for recent such allegations see (a) R. Wiechert and G. Schulz, *Chem. Ber.*, **98**, 3165 (1965); (b) H. Mueller and R. Wiechert, German Patent, 1,189,076 (1965); *Chem. Abstr.*, **63**, 1836*g* (1965); (c) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

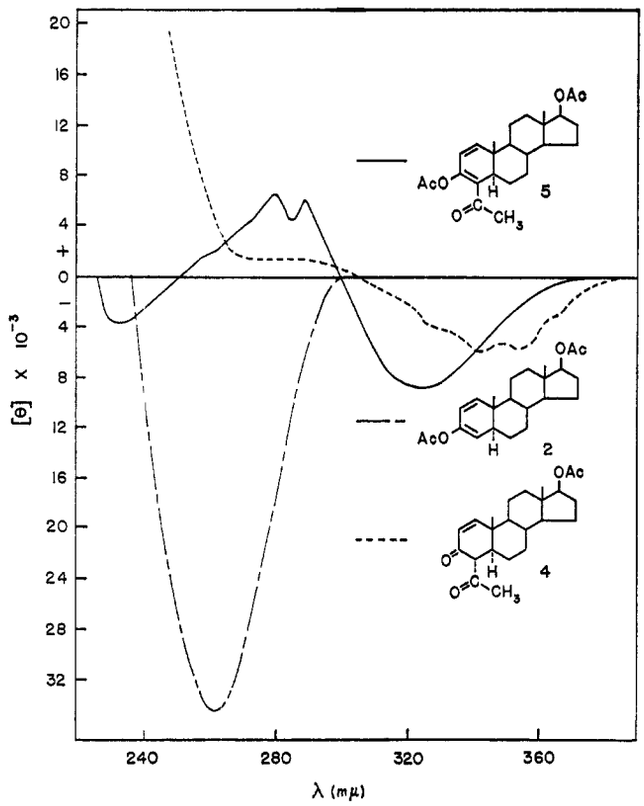


Figure 1.—Circular dichroism curves of acetylated 5α-androstane derivatives (in dioxane).

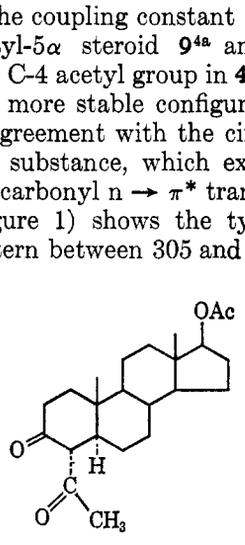
ε 4.023)], and the infrared spectrum which showed the presence of both unconjugated and conjugated keto groups.

Further, the nuclear magnetic resonance (nmr) spectrum of **4** showed that the Δ^1-3-keto system was intact and a proton signal (doublet, J = 12.5 cps) appeared at 3.43 ppm which is assigned to the C-4 hydrogen atom.[3] The magnitude of the coupling of the C-4 proton with the one at the α-C-5 position indicates that the two are *trans* disposed and has the same value as the coupling constant (12.5 cps) reported for the 4α-acetyl-5α steroid **9**[4a] and its 4β-acetyl-5β isomer.[4b] The C-4 acetyl group in **4** thus has the thermodynamically more stable configuration. This structure is also in agreement with the circular dichroism spectrum for this substance, which exhibits the expected peaks in the carbonyl n → π* transition region. The spectrum (Figure 1) shows the typical negative Cotton effect pattern between 305 and 385 associated with Δ^1-3-keto steroids,[5] while the unconjugated carbonyl group has a low-energy transition at 282 mμ.

Further support for the structure was obtained by treating diketone **4** with methanolic potassium hydroxide solution which effected β-diketone cleavage and gave hydroxy ketone **7**. Cleavage of the C-4 acetyl moiety in preference to ring A opening is in accord with the findings of studies on the base-catalyzed cleavage of 6-acyl-2-cyclohexen-1-ones.[6,7]

An initially disturbing circumstance concerning compound **5** was the fact that it exhibits an ultraviolet absorption maximum (287 mμ) considerably lower than that predicted by the Woodward rules as modified by Scott (318 mμ),[8] whereas infrared, nmr, and other analytical data were in agreement with the structure shown. The explanation became clear upon the inspection of molecular models which showed excessive molecular crowding of the C-4 acetyl system when it is coplanar with the diene system. This crowding is alleviated considerably when the acetyl group is turned out of the plane containing the double bonds. In this respect, it is of interest to note that Gorodetsky and Mazur[4a] found that the C-4 acetyl group in the diketone **10** is *not* in conjugation with the Δ^4-3-keto chromophore and its infrared spectrum exhibits a saturated ketone band at 1712 cm^{-1} (5.84 μ). The acetyl group of **5**, on the other hand, gives rise to an infrared band at 1680 cm^{-1} (5.95 μ). This, coupled with the fact that the observed ultraviolet absorption spectrum for **5** is somewhat higher than the calculated value for the ring A homoannular diene system (268 mμ),[9] tends to favor at least a partial conjugation of the C-4 acetyl group in **5**.

The circular dichroism curve for this compound (Figure 1) shows a negative Cotton effect of medium intensity at 324 mμ in the carbonyl n → π* transition region, which reflects the partial conjugation of the acetyl group. The multiple positive Cotton effect which the curve exhibits between 250 and 300 mμ is of interest because it nicely demonstrates how additional conjugation can drastically (and in most cases as yet unpredictably) affect the circular dichroism curve.



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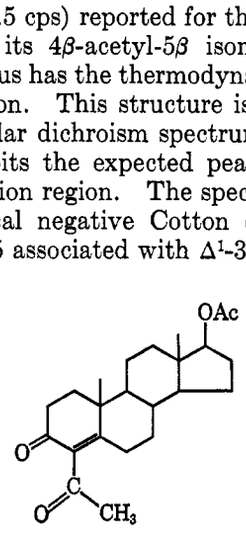

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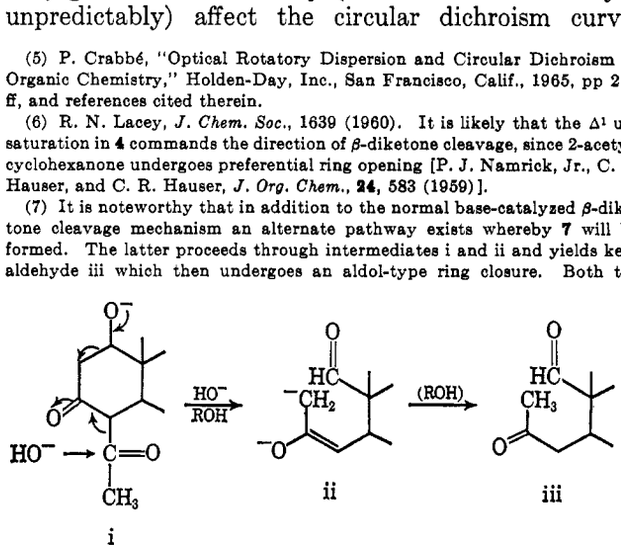
(3) In the starting compound **1** the C-4 proton signals lie beneath the alkane proton envelope and are not discernible.

(4) (a) M. Gorodetsky and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5214 (1964); (b) M. Gorodetsky, E. Levy, R. D. Youssefyeh, and Y. Mazur, *Tetrahedron*, **22**, 2039 (1966).

(5) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, pp 211 ff, and references cited therein.

(6) R. N. Lacey, *J. Chem. Soc.*, 1639 (1960). It is likely that the Δ^1 unsaturation in **4** commands the direction of β-diketone cleavage, since 2-acetylcyclohexanone undergoes preferential ring opening [P. J. Namrick, Jr., C. F. Hauser, and C. R. Hauser, *J. Org. Chem.*, **24**, 583 (1959)].

(7) It is noteworthy that in addition to the normal base-catalyzed β-diketone cleavage mechanism an alternate pathway exists whereby **7** will be formed. The latter proceeds through intermediates i and ii and yields keto aldehyde iii which then undergoes an aldol-type ring closure. Both the



normal and alternate mechanisms have been observed in the base-catalyzed cleavage of 6-acyl-2-cyclohexen-1-ones; see R. N. Lacey, reference cited in footnote 6.

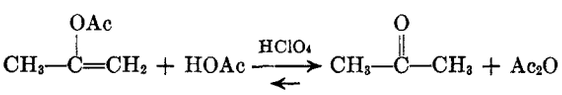
(8) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 50 ff.

(9) Calculation based on assigning the acetyl group the value of an alkyl moiety.

The observed effect must be due to a $\pi \rightarrow \pi^*$ transition involving the conjugated system because the only other absorbing groups present, the acetate and enol acetate functionalities, show Cotton effects considerably below this range.[10] Thus, the predicted[11] and observed strongly negative effect of the M-chiral[12] diene chromophore present in **2** (Figure 1) is completely altered when the system becomes partially conjugated with the C-4 acetyl group in **5**.[13] The structure of **5** was confirmed by treating the compound with 5% hydrochloric acid in methanol, whereby the diketone **4** was obtained.

The compound of unknown structure (**6**) was not obtained in sufficient quantity to allow its complete characterization. The Δ^1-3-keto system appears to be intact from the nmr spectrum—other spectral characteristics and physical properties are recorded in the Experimental Section.

Thin layer chromatographic experiments were conducted in order to gain an insight into the sequence of events which led to the products isolated. These experiments involved a study of the effects of reagent b on compounds **1**, **2**, **4**, and **5** (hereafter called runs A, B, C and D), and the results are shown in Figure 2. After 10 min at room temperature run A contained mainly compound **1**, some **2**, and a small amount of **4**; run B likewise contained mainly **1**, some **2**, and a small amount of **4**; run C contained an equal mixture of **4** and **5**, while run D contained mostly **4** with some **5**. These results clearly indicate that enol acetate formation at the C-3 keto group is rapid and is reversible under the reaction conditions, and are in agreement with the observations of Jeffery and Satchell[14] who reported that the perchloric acid catalyzed acetylation of acetic acid by isopropenyl acetate proceeds in high yield to give acetone and acetic anhydride.



After 2.5 hr at room temperature, the tlc experiments showed that in runs A and B the concentration of **2** had diminished slightly and the amount of **4** present had increased to the extent that it was now present in greater amount than **2**. In addition a slight amount of **5** appeared. Runs C and D showed virtually identical spot patterns, having two spots corresponding to compounds **4** and **5** with **4** predominating. After 3.5 hr, runs A and B showed a predominance of **1**, but also the presence of **2**, **3**, **4**, **5**, and the compound of unknown structure (**6**), whereas runs C and D continued to show two spots corresponding to **4** and **5**, with **4** predominating.

The equilibria and a possible sequence of events leading to products **2**, **3**, **4**, and **5** are shown in Scheme I. However, there are at least three different ways in which the C-4 acetylation can take place. It is generally believed that ketones (*via* their enolic forms) can undergo direct α attack by acetic anhydride in the presence of an acidic catalyst.[15,16] However, it is also possible that **2** undergoes a Friedel–Crafts type of acylation at C-4, and evidence that enol acetates undergo such a reaction has been cited.[17] The product from such a process would be **5**, which in turn forms **4** reversibly as indicated above.

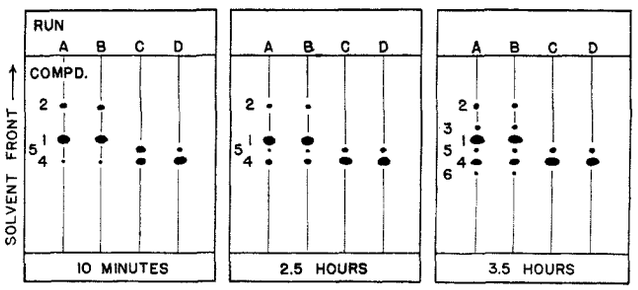
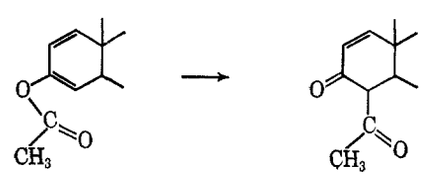


Figure 2.—Thin layer chromatographic studies of the perchloric acid catalyzed reaction of 17β-acetoxy-Δ^1-5α-androstenone-3 with acetic anhydride.

Finally, it is possible that the C-4 acylated product **4** is formed by a Claisen–Haase type of rearrangement of **2**, as depicted in E. Such rearrangements are catalyzed by Lewis acids, as well as basic agents, and the



E

mechanism has been stated to be similar to that of the Fries reaction.[18] In the recent work of Gorodetsky and associates[4b] on the acylation of steroidal ketones (to give β-diketones) using acetic anhydride–boron trifluoride etherate, their findings strongly support the supposition that the corresponding enol acetate is an intermediate in the C-acylation reaction. If this is indeed correct, then it seems highly probable that **4** is formed by a similar mechanism, involving **2** as the intermediate (Scheme I). Unfortunately, the tlc experiments do not allow one to differentiate between these mechanisms, but they do show that C-4 acylation is apparently irreversible under the conditions investigated since no other products were detected in tlc runs C and D. It will be noted that the equilibrium between **4** and **5** is reached more quickly when approached from **4**, the acetolysis of **5** presumably being sterically resisted to a greater extent than is enol acetate formation of **4**.

The tlc experiments showed that under the present conditions the optimum time for preparing enol acetate **2** was about 10 min, and in an actual isolation experi-

(10) A. Yogev and Y. Mazur, *Tetrahedron*, **22**, 1317 (1966); J. P. Jennings, W. Klyne, W. P. Mose, and P. M. Scopes, *Chem. Commun.*, 553 (1966).

(11) U. Weiss, H. Ziffer, and E. Charney, *Tetrahedron*, **21**, 3105 (1965).

(12) For the naming of chiral systems, see R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed., Engl.*, **5**, 385 (1966).

(13) Similar effects of extended conjugation on the n $\rightarrow$ π^* transitions of conjugated ketones have been noted; *cf.* ref 5, p 226.

(14) E. A. Jeffery and D. P. N. Satchell, *J. Chem. Soc.*, 1876 (1962).

(15) See, for example, (a) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 98 (1954); (b) D. P. N. Satchell, *Quart. Rev.* (London), **17**, 196 (1963).

(16) The exact nature of the acetylating species in perchloric acid catalyzed acylations with acetic anhydride apparently remains unresolved. It is probable that the perchloric acid reacts with the acetic anhydride to form acetic acid and acetyl perchlorate. The powerful acylating properties of acetyl perchlorate are well known (*cf.* ref 15b, p 180, and ref 14, p 1882).

(17) C. R. Hauser, F. C. Frostick, Jr., and E. H. Man, *J. Am. Chem. Soc.*, **74**, 3231 (1952); ref 15a, pp 98–101.

(18) D. Kästner in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p 289; F. Gogan, A. E. O'Briain, E. M. Philbin, N. S. O'Connor, R. F. Timoney, and T. S. Wheeler, *Tetrahedron*, **3**, 140 (1958); see, however, F. G. Young, F. C. Frostick, Jr., J. J. Sanderson, and C. H. Hauser, *J. Am. Chem. Soc.*, **72**, 3635 (1950).

ment an 18% yield of **2** was obtained when the reaction was allowed to proceed for this length of time, along with a major portion of starting material **1**. We next studied the effects of reagent a on **1** and tlc experiments established that here, too, enol acetate **2** was formed. These results were confirmed by an isolation experiment, where a 19% yield of the enol acetate was realized.

The results with reagent a were indeed surprising since it will be recalled that Edwards and Rao[2c] had reported that 5α-androst-1-ene-3,17-dione and 17β-hydroxy-5α-androst-1-en-3-one (**7**) were unaffected by this reagent. We therefore treated **7** with reagent b and found by tlc that after 20 min all of the starting material had reacted and the reaction mixture, as expected, contained mostly **1** with some **2**.

Thus, in conclusion, it can be stated that the Δ^1-3-keto system can be converted to the enol acetate derivative but that an equilibrium exists between the two substances with the ketone heavily favored in the present case. Whether this is generally true of all Δ^1-3-keto steroid systems is of course not known at the present time.

Experimental Section[19]

Reagents a and b.—These reagents were prepared exactly as described by Edwards and Rao.[2c] Calculations show that the concentration of perchloric acid are actually 2.3×10^{-3} in reagent a and 1.2×10^{-2} in reagent b.

The Reaction of 17β-Acetoxy-5α-androst-1-en-3-one (1) with Reagent b.—Five hundred milligrams of 17β-acetoxy-5α-androst-1-en-3-one (**1**) was dissolved in 50 ml of reagent b and allowed to react at room temperature for 4 hr. The reaction mixture was then washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. (If any acetic anhydride remained, it was removed by adding several milliliters of methanol containing a trace of pyridine and again removing the solvent under reduced pressure.) The residue (480 mg) showed the presence of six compounds when thin layer chromatographed on silica gel G[20] using an acetone (7 ml)–hexane (30 ml) mixture as eluent. The residue was column chromatographed on silica gel (0.50–0.20 mm),[20] 15-ml fractions being collected. Elution was begun with 200 ml of an acetone–hexane (1:99, v/v) mixture and the acetone concentration was then increased in succeeding 200-ml portions until the last compound emerged from the column. The mixtures used had acetone–hexane ratios of 2:98, 4:96, 8:92, 10:90, and 15:85.

The first product eluted from the column consisted of 50 mg (11%) of 3,17β-diacetoxy-5α-androsta-1,3-diene (**2**). After several recrystallizations from methanol containing a trace of pyridine, it had mp 139–140°; ν_{max} 1755, 1725, 1255, 1215, and 1170 cm^{-1}; λ_{max} 259 mμ (log ε 3.585); nmr 0.80 (3 H, singlet, C-18 CH_3), 0.92 (3 H, singlet, C-19 CH_3), 2.03 (3 H, singlet, C-17 acetate), 2.13 (3 H, singlet, C-3 enol acetate), 4.63 (1 H, triplet, J = 8 cps, C-17 H), 5.10 (1 H, triplet, J = 2 cps, C-4 H), AB quartet with doublets[21] centered at 5.65 (1 H, J = 10 cps, each peak further split into a doublet,[22] J = 2 cps, C-2 H), and 6.13 ppm (1 H, J = 10 cps, C-1 H). The circular dichroism is shown in Figure 1, $[\phi]^{24}_{300}$ 0, $[\phi]^{24}_{261}$ −34,500, $[\phi]^{24}_{236}$ 0 (*C* 0.00086, dioxane).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.30; H, 8.80.

The infrared spectrum and melting point were identical with those of an authentic sample.[23]

The second product eluted from the column was 18 mg of 1-acetoxy-4-methyl-1,3,5(10)-estratrien-17β-ol acetate (**3**), which melted at 135–137° (lit.[24] mp 134–135°) after recrystallization from methanol, mp 135–137°. The infrared spectrum showed major bands at 1755 and 1725 ($\nu_{C=O}$), 1245, 1195 cm^{-1}; the ultraviolet spectrum had bands at λ_{max} 276 mμ (inflection) (log ε 2.477), 266 (2.616), and 219 (3.903); nmr 0.85 (3 H, singlet, C-18 CH_3), 2.03 (3 H, singlet, C-17 acetate), 2.20 (3 H, singlet, C-1 acetate[25]), 2.24 (3 H, singlet, C-4 CH_3[25]), 4.75 (1 H, triplet, J = 7.5 cps, C-17 H), and 6.88 ppm (2 H, AB quartet, J = 8 cps, $\Delta\delta$ = 0.32 ppm,[21] C-2,3 H).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.28; H, 8.30.

A comparison sample for this compound was prepared from the dienone **8** (see below); the mixture melting point and a comparison of the infrared spectra showed the substances to be identical.

The third compound eluted was 230 mg (46%) of unchanged starting material (**1**).

The fourth substance obtained from the column consisted of 22 mg (3.5%) of 3,17β-diacetoxy-4-acetyl-5α-androsta-1,3-diene (**5**) which melted at 165–166° when recrystallized from acetone–hexane. Significant bands in the infrared spectrum appeared at 1755, 1725, 1680, 1260, 1210, and 1180 cm^{-1}; ultraviolet spectrum showed λ_{max} 287 mμ (log ε 3.667). The circular dichroism curve is shown in Figure 1, $[\phi]^{27}_{380}$ 0, $[\phi]^{27}_{324}$ −8680, $[\phi]^{27}_{301}$ 0, $[\phi]^{27}_{290}$ 6170, $[\phi]^{27}_{286}$ 4620, $[\phi]^{27}_{281}$ 6700, $[\phi]^{27}_{252}$ 0, $[\phi]^{27}_{234}$ −3960, $[\phi]^{27}_{226}$ 0 (*C* 0.00063, dioxane); nmr 0.82 (3 H, singlet, C-18 CH_3), 1.01 (3 H, singlet, C-19 CH_3), 2.04 (3 H, singlet, C-17 acetate), 2.16 (3 H, singlet, C-3 enol acetate[25]), 2.24 (3 H, singlet, C-4 acetyl[25]), 4.64 (1 H, triplet, J = 8 cps, C-17 H), AB quartet with doublets[21] centered at 5.73 (1 H, J = 10 cps, C-2 H), and at 6.31 ppm (1 H, J = 10 cps, C-1 H).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.42; H, 8.33.

The fifth compound eluted was identified as 4α-acetyl-17β-acetoxy-5α-androst-1-en-3-one (**4**, 85 mg, 15%) and recrystallization of this substance from acetone–hexane yielded two crystalline modifications: needles, mp 198–199°, and prisms, mp 205–206°. The infrared spectrum showed bands at 1740, 1710, 1665, and 1235 cm^{-1}; the compound exhibited a ultraviolet absorption peak at 231 mμ (log ε 4.033); nmr 0.83 (3 H, singlet, C-18 CH_3), 1.06 (3 H, singlet, C-19 CH_3), 2.04 (3 H, singlet, C-17 acetate), 2.20 (3 H, singlet, C-4 acetyl), 3.43[21] (1 H, unsymmetrical doublet, J = 12.5 cps, C-4 H), 4.65 (1 H, triplet, J = 8 cps, C-17 H), AB quartet with doublets[21] centered at 5.91 (1 H, J = 10 cps, C-2 H), and at 7.26 ppm (1 H, J = 10 cps, C-1 H). The circular dichroism curve is shown in Figure 1, $[\phi]^{27}_{385}$ 0, $[\phi]^{27}_{370}$ −2460 (inflection), $[\phi]^{27}_{353}$ −5640, $[\phi]^{27}_{347}$ −5310, $[\phi]^{27}_{341.5}$ −5840, $[\phi]^{27}_{327}$ −3890 (inflection), $[\phi]^{27}_{304.5}$ 0, $[\phi]^{27}_{282}$ 1430 (*C* 0.00081, dioxane).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.29; H, 8.59.

The last compound (**6**) eluted from the column was obtained in an amount too small (10 mg) to permit its positive identification. When recrystallized from acetone–hexane, the substance melted at 247–249° and had a molecular weight of 403. The infrared spectrum showed bands at 1735, 1655, 1605, 1560, 1420, and 1235 cm^{-1}; nmr 0.81 (3 H, singlet, C-18 CH_3), 0.89 (3 H, singlet, C-19 CH_3), 2.03 (3 H, singlet, C-17 acetyl), 2.19 (3 H, singlet), 2.64 (2 H, broad triplet J = 12 cps), 3.25 [1 H, broad doublet (?), J = 12 cps], 4.66 (1 H, broad triplet, J = 7 cps, C-17 H), AB quartet with doublets[21] centered at 6.04 (1 H, J = 9 cps, C-2 H), and at 6.61 ppm (1 H, J = 7 cps, C-1 H). In addition there is a singlet (1 H) which overlaps the farthest upfield member of the AB quartet, at about 6.0 ppm. An insufficient amount of sample prevented the further characterization of this compound.

(19) All melting points were determined in a heated oil bath and are corrected. The nmr spectra were determined in deuteriochloroform solution (unless specified otherwise) on a Varian A-60 spectrometer and chemical shift values are given in parts per million (ppm) values measured downfield from tetramethylsilane used as an internal standard. The infrared spectra were determined in the solid state in a potassium bromide matrix on a Perkin-Elmer Infracord Model 337. The ultraviolet absorption spectra were determined in methanol on a Beckmann Model DK-2, and the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The circular dichroism curves were determined on a Durrum-Jasco ORD/UV-5 instrument with CD attachment.

(20) E. Merck AG, Darmstadt, Germany; U. S. distributor is Brinkmann Instruments, Inc., Cantiague Road, Westbury, N. Y.

(21) The chemical shift values for all doublets were measured at the geometrical midpoint between the two peaks.

(22) This additional splitting is due to a coupling of the protons at C-4 and C-2, an observation also made by R. Wiechert and G. Schulz.[2a]

(23) We wish to thank Dr. R. Wiechert[2a] for providing a generous sample.

(24) H. Dutler, H. Bosshard, and O. Jeger, *Helv. Chim. Acta*, **40**, 494 (1957).

(25) Tentative assignment.

3,17β-Diacetoxy-5α-androsta-1,3-diene (2). Using Reagent b.—Two hundred milligrams of 17β-acetoxy-5α-androst-1-en-3-one (1) was dissolved in 20 ml of reagent b and the mixture was allowed to stand at room temperature. After 10 min a sample was taken for tlc and the chromatogram showed that the major components in the reaction mixture were compounds 1 and 2, with a small amount of 4. The mixture was worked up as described previously and the residue (180 mg) was chromatographed on silica gel. The first compound eluted from the column was enol acetate 2 (40 mg, 18%). When this substance was recrystallized twice from methanol containing a trace of pyridine, it had a melting point, mixture melting point, and infrared spec identical with those of an authentic sample. The remainder of the material eluted from the column consisted of starting material 1 and a small amount of 4.

Using Reagent a.—When 200 mg of unsaturated ketone 1, dissolved in 20 ml of reagent a, was allowed to stand at room temperature for 10 min and then worked up as described previously, 175 mg of residual products was obtained. This was chromatographed on silica gel, whereby 43 mg (19%) of enol acetate 2, mp 134–136°, was obtained. A recrystallization from methanol containing a trace of pyridine raised the melting point to 139–140°. The remainder of the material recovered was unchanged starting ketone 1.

4-Methylestra-1,3,5(10)-triene-1,17β-diol Diacetate (3).—A solution of 100 mg of 17β-acetoxyandrosta-1,4-dien-3-one (8) in 10 ml of reagent b was allowed to stand at room temperature for 30 min. The reaction mixture was washed with saturated sodium carbonate solution and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue (95 mg) was recrystallized from acetone–hexane, yielding 85 mg of rearranged diacetate 3, mp 134–136° (lit.[24] mp 134–135°).

17β-Hydroxy-5α-androst-1-en-3-one (7).—A solution of 35 mg of diketone 4 in 10 ml of 15% methanolic potassium hydroxide was allowed to stand at room temperature for 30 min. The mixture was diluted with water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid and then with water, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left 20 mg of product which crystallized from methanol. This substance appears to have a double melting point but the lower one could not be definitely established; the higher one was at 152–154° (lit.[26] mp 150°). When ketone 1 was treated in the manner described above, the same product was obtained, as determined by a comparison of their identical infrared spectra and melting points, as well as an undepressed mixture melting point.

Compound 7 was allowed to react for 20 min with reagent b at room temperature. After this time, tlc showed that the major product in the mixture was 1, together with a small amount of enol acetate 2.

4α-Acetyl-17β-acetoxy-5α-androst-1-en-3-one (4) from 3,17β-Diacetoxy-4-acetyl-5α-androsta-1,3-diene (5).—A solution of 20 mg of enol acetate 5 in 7 ml of 5% hydrochloric acid in methanol was allowed to stand at room temperature for 30 min. The reaction mixture was diluted with water and extracted with ether, and the ether extracts were washed with sodium carbonate solution. The ether layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The remaining product (15 mg) was recrystallized from acetone–hexane and identified as diketone 4 by its melting point (198–200°), undepressed mixture melting point, and its infrared spectrum.

The Thin Layer Chromatographic Experiments.—For the time study shown in Figure 2, 1.00 mg of each of compounds 1, 2, 4, and 5 was allowed to react with 0.100 ml of reagent b at room temperature. After the indicated time intervals, the reaction mixtures were spotted in equivalent quantities on 8.5 × 11 cm glass plates coated with silica gel,[20] and the plates were eluted with an acetone (7 ml)–hexane (30 ml) mixture. The plates were dried in an oven at 100° for 10 min, then developed by spraying with chlorosulfonic acid, and again dried at 100° for 1 hr.

The tlc method was calibrated to give semiquantitative, as well as qualitative results. For the semiquantitative calibration chromatograms, 1.00 mg of each of compounds 1, 2, 4, and 5 was dissolved in 0.100 ml of acetone at room temperature. Silica gel coated plates were then spotted, eluted, and developed as described above. The densities of the spots corresponding to the four compounds were identical on visual inspection.

Registry No.—1, 64-82-4; 2, 3941-70-6; 3, 6224-00-6; 4, 10050-97-2; 5, 10050-96-1.

(26) A. Butenandt and H. Dannenberg, *Chem. Ber.*, **73**, 206 (1940).

Cassaine Analogs. I. Intermediate Hydrophenanthrones

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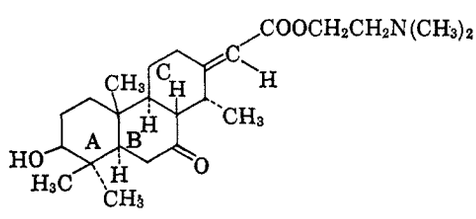
7-Methoxytetrahydrophenanthrone (5) was used to prepare tricyclic ketones required for the synthesis of cassaine analogs. All four possible ring-A-aromatic 7-methoxyoctahydrophenanthrols were prepared, as well as perhydrophenanthrones having *cis-anti-trans*, *trans-anti-cis*, and *trans-anti-trans* configurations.

For years it has been known that the *Erythrophleum* alkaloid cassaine (1) exerts an effect on the heart similar to that of the cardiac glycosides.[1] Recently, Turner, Buchardt, Herzog, Morin, Riebel, and Sanders[2] reported the total synthesis of this complex molecule. Hauth, Stauffacher, Nicklaus, and Melera[3] and, more recently, Clarke, Daum, Shaw, and Kullnig[4] have contributed some additional data to certain aspects of configuration which have more rigorously defined the structure of cassaine.



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It was of interest to determine the effect of various changes in configuration and functional groups of cassaine on its biological activity. This paper is devoted to the synthesis of several tricyclic ketones which were subsequently[5] converted to basic ester analogs of cassaine. A carbonyl group in ring C was essential for attaching the required side chain.

(1) See F. Erjavec and Š. Adamič, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley in "The Alkaloids," Vol. V, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1955, pp 101–107 and references therein.

(2) R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel, and J. M. Sanders, *J. Am. Chem. Soc.*, **88**, 1766 (1966).

(3) H. Hauth, D. Stauffacher, P. Nicklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965).

(4) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kullnig, *J. Am. Chem. Soc.*, **88**, 5865 (1966).

(5) R. L. Clarke, S. J. Daum, and P. E. Shaw, *J. Med. Chem.*, in press.