Nor Steroids. VI. Kinetic Studies on the Favorskii Rearrangement[1,2]

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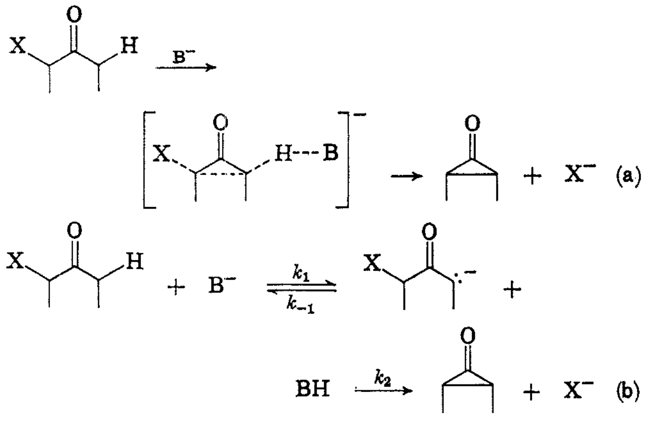
2α-Chloro-, bromo-, and iodocholestan-3-one were prepared and subjected to Favorskii rearrangement conditions. Product analyses were performed and the rates of the reactions were determined. They showed that the order of reactivity was iodo > bromo > chloro. The corresponding deuterated halides were prepared. The rates of their reactions showed a primary deuterium isotope effect, indicating that loss of a proton was involved in the rate-determining step. Interruption experiments on the deuterated halides showed that the hydrogen on the halogen-carrying carbon was rapidly lost prior to the rearrangement reaction.

The mechanism of the Favorskii rearrangement of α-halo ketones has been a subject of considerable interest in recent years.[4]

To date the evidence indicates that the reaction proceeds through a cyclopropanone intermediate,[4a] although a "zwitterion intermediate" has been invoked in certain cases.[4c] The mode of formation of the intermediate, however, has not been investigated. The reasonable assumption has been made that the role of the base is to extract a proton from the α′ position (the carbon atom without the halogen), but experimental verification of this point is lacking. Formation of the symmetrical intermediate could then occur synchronously with this attack of base or in a second step (Scheme I, a and b, respectively).[5]

SCHEME I



In order to clarify the mechanism of the Favorskii rearrangement, the following data were gathered.

1. 2α-Chloro- (Ia), bromo- (Ib), and iodocholestan-3-one (Ic) were prepared and subjected to Favorskii rearrangement conditions. Product analyses were performed and the rates of the reactions were observed.
2. The corresponding deuterated halides were prepared and their rates of reaction measured to obtain values of k_H/k_D.
3. The deuterated compounds were subjected to Favorskii rearrangement conditions and recovered after one half-life. The recovered halo ketones were then examined by infrared, nmr, and deuterium analyses to determine the fate of the α and α′ deuterons.
4. The deuterated bromo ketone was run to completion under Favorskii rearrangement conditions and the deuterium content of the product esters was determined.

Experimental Section[6]

Cholestan-3-one-2,4-d_4 (IIa).—To a suspension of 760 mg of sodium in 100 ml of purified anhydrous dioxane was added slowly 10 ml of deuterium oxide (more than 99.5% pure, obtained from Liquid Carbonics Division, General Dynamics Corp.) After the sodium had dissolved, 15.0 g (38.9 mmoles) of cholestan-3-one (mp 129.5–130.5°, $[\alpha]_D$ +41.2°) was added and the reaction mixture was warmed on a steam bath for 48 hr. After cooling, the water layer was removed and the dioxane was evaporated under reduced pressure. The residue was taken up in chloroform and washed with dilute nitric acid, and the solvent was removed under reduced pressure. The crude product was treated twice more in the same manner to yield 14.1 g (93%) of product. Recrystallization from 95% ethanol gave an analytical sample: mp 131–132°; $[\alpha]_D$ +41.1°. Infrared analyses (see below) showed that no deuterium was lost during recrystallization (lit.[7] mp 129–129.5°; D, 3.69 atoms/molecule).

Anal. Calcd for $C_{27}H_{42}D_4O$: D, 8.70 atom % excess. Found: D, 8.54, 8.48 atom % excess (97.8% exchange or 3.91 atoms/molecule).

While most of the physical properties of the starting material and the product were indistinguishable, the infrared and nmr spectra showed significant differences. In its infrared spectrum the product showed three bands, missing in the starting material, at 4.51, 4.66, and 4.73 μ and the band at 7.1 μ in the starting material was missing in the product.

In the nmr spectrum of the starting material, two apparent doublets are visible in the region of 120 cps, one at 118 (J = 3

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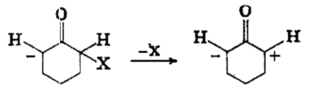
[1] Previous paper in the series: H. R. Nace and D. H. Nelander, *J. Org. Chem.*, **29**, 1677 (1964).

[2] This research was supported in part by the National Science Foundation, Research Grant NSF-G5926. This support is gratefully acknowledged.

[3] Abstracted from the Ph.D. Thesis of B.A.O., Brown University, 1964. Metcalf Fellow, 1961–1962; Eastman Kodak Co., Fellow, summer 1962.

[4] (a) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951); (b) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (c) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 164 (1963), and previous papers cited therein; (d) E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Am. Chem. Soc.*, **88**, 334 (1966).

[5] An alternative view is that halide ion is lost from the enolate anion to form a zwitterion. The zwitterion can be considered as a resonance form of

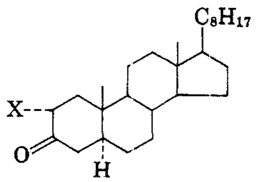


the cyclopropanone which may or may not make an appreciable contribution to the structure of the intermediate. The two interpretations cannot be distinguished on the basis of the present work.

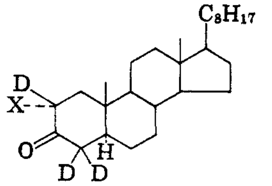
[6] Melting points are corrected and were determined with a Hershberg apparatus and Anschutz thermometers. The analyses for carbon and hydrogen were done by Dr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology, and for deuterium by Dr. J. Nemeth, University of Illinois, Urbana, Ill. Optical rotations were determined on 1% solutions in chloroform. Tlc analyses were made on silica gel G or silica gel G containing uranine water soluble. The former were developed by spraying with 2,4-dinitrophenylhydrazine reagent and the latter were examined under ultraviolet light. Potentiometric titrations for halide ion were done with a Leeds and Northrup pH indicator equipped with a silver electrode, a salt bridge, and a standard calomel electrode. Nmr spectra were determined with a Varian HR-60 using tetramethylsilane as an external standard with solutions of steroids in benzene (concentration 150–200 mg/ml). Infrared spectra were obtained on a Perkin-Elmer Infracord using potassium bromide disks. Analytical determinations were made on 5% solutions in carbon tetrachloride with matched 1.0-mm sodium chloride cells.

[7] B. Nolin and R. N. Jones, *Can. J. Chem.*, **30**, 727 (1952).

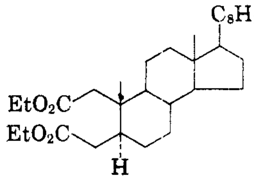
Chart I



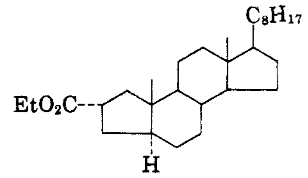
Ia, X = Cl
b, X = Br
c, X = I
d, X = H



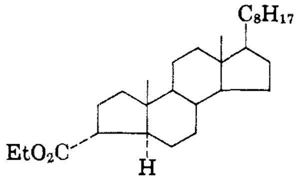
IIa, X = D
b, X = Cl
c, X = Br
d, X = I



III



IV



V

cps) and one at 128 (J = 2 cps). These peaks are not present in the deuterated compound.

2α-Chlorocholestan-3-one (Ia).—Cholestan-3-one was treated with *t*-butyl hypochlorite according to the procedure of Beereboom, Djerassi, Ginsburg, and Fieser.[8] Chromatography of the crude product was carried out on silica gel. Elution with 70% petroleum ether (bp 30–60°)–30% benzene gave 2,2-dichlorocholestan-3-one; with 50% petroleum ether–50% benzene, 2,4-dichlorocholestan-3-one; with 40% petroleum ether–60% benzene, 2α-chlorocholestan-3-one; and with ether, starting material. The monohalide fraction was recrystallized from ethanol-chloroform to give white crystals of Ia: mp 180.5–181.5°; $[\alpha]_D$ +50.6° (lit.[8] mp 178–179°; $[\alpha]_D$ +52°).

2α-Chlorocholestan-3-one-2,4-*d*₃ (IIb).—A solution of 787 mg (11.1 mmoles) of chlorine in 20 ml of carbon tetrachloride was added dropwise with stirring to a solution of 4.33 g (11.1 mmoles) of cholestan-3-one-2,4-d_4 in 100 ml of carbon tetrachloride. Rapid decolorization of the reaction mixture took place, the solvent was removed under reduced pressure, and the residue was dried under reduced pressure and chromatographed on silica gel. Elution with 50% petroleum ether–50% benzene and recrystallization of the residue from ethanol-chloroform gave 1.12 g (24%) of deuterated chloride: mp 182.5–183.5°; $[\alpha]_D$ +45.4°.

Anal. Calcd for $C_{27}H_{42}D_3ClO$: D, 6.6 atom % excess. Found: D, 6.23 atom % excess (93.4% exchanged or 2.80 atoms/molecule).

Treatment of cholestan-3-one under identical conditions gave 2α-chlorocholestan-3-one. The infrared spectrum of the deuterated compound showed absorption at 4.5 μ, not shown in the undeuterated compound. The band at 7.06 μ in the latter compound, attributed[9] to a CH_2 group adjacent to a carbonyl group, was absent. The nmr spectra of these and the other halo ketones are described and discussed below.

2α-Bromocholestan-3-one (Ib).—The crude reaction mixture resulting from the bromination of cholestan-3-one in the usual manner[10] was chromatographed on silica gel. Elution with 40% petroleum ether–60% benzene, followed by recrystallization of the residue from ethanol-chloroform, gave white crystals: mp 173.5–174.5°; $[\alpha]_D$ +43.6° (lit.[11] mp 174–174.5°; $[\alpha]_D$ +46°).

2α-Bromocholestan-3-one-2,4-*d*₃ (IIc).—To a solution of 6.33 g (16.2 mmoles) of cholestan-3-one-2,4-d_4 in 100 ml of carbon tetrachloride was added dropwise with stirring 16.3 ml (16.3 mmoles) of 1 M bromine in carbon tetrachloride. The uptake of bromine was rapid, as evidenced by the fading of the color. The solvent was removed and the residue was dried under reduced pressure and chromatographed on silica gel. Elution with 50% petroleum ether–50% benzene followed by recrystallization of the residue from ethanol-chloroform gave 2.70 g (36%) of the deuterated bromide IIc: mp 176.5–177.0°; $[\alpha]_D$ +44.6°.

Anal. Calcd for $C_{27}H_{42}D_3BrO$: D, 6.66 atom % excess. Found: D, 5.93 atom% excess (88.9% exchanged or 2.67 atoms/molecule).

The infrared spectrum was essentially identical with that of the deuterated chloro compound. Treatment of cholestan-3-one under identical conditions gave 2α-bromocholestan-3-one.

2α-Iodocholestan-3-one (IIc) was prepared as described[12] and recrystallized from ethanol-chloroform to give white needles, homogeneous by tlc: mp 139–140°; $[\alpha]_D$ +30.2° (lit.[12] mp 125–127° dec, 133–136° (Kofler); $[\alpha]_D$ +40°).

2α-Iodocholestan-3-one-2,4-*d*₃ (IId).—A solution of 1.45 g (3.10 mmoles) of 2α-bromocholestan-3-one-2,4-d_3 and 1.84 g of sodium iodide in 40 ml of anhydrous acetone was boiled under reflux for 11 hr. The work-up was analogous to that used for the iodo compound with special emphasis placed on only brief contact with water. Recrystallization of the product from ethanol-chloroform gave 1.22 g (76%) of white crystals: mp 137–138°; $[\alpha]_D$ +29.4°.

Anal. Calcd for $C_{27}H_{42}D_3IO$: D, 6.66 atom % excess. Found: D, 5.73 and 5.70 atom % excess (85.7% exchanged or 2.51 atoms/molecule).

The infrared spectrum was essentially identical with those of the deuterated chloro and bromo compounds.

Favorskii Rearrangements. Standard Conditions.—The following conditions were adopted for all kinetic runs. A weighed amount of freshly cut sodium was dissolved in a measured amount of anhydrous ethanol[13] and cooled to 0°. The concentration of the resulting sodium ethoxide solution was adjusted so as to be approximately 0.21 M after addition to the solution of halo ketone. The compound to be rearranged was warmed in anhydrous ethanol on a steam bath to facilitate solution and then transferred to a volumetric flask. The volume of the steroid solution (adjusted so as to be 0.0043 M after addition of base) was adjusted to a previously marked level. The solution was cooled to 0° in an ice bath and its volume readjusted to the mark. At time zero a measured aliquot of the ethoxide solution was added to the steroid solution *via* a rapid delivery pipet and the reaction solution was thoroughly shaken and returned to the ice bath. In the rearrangements a 50-fold excess of sodium ethoxide over steroid was used to give pseudo-first-order rate conditions. The concentration of iodo steroids was halved owing to lesser solubility; the base concentration remained the same. In a typical run, 1.004 g (2.16 mmoles) of 2α-bromocholestane-3-one was treated with sodium ethoxide (from 2.468 g, 107.3 mg-atoms, of sodium) in 500 ml of anhydrous ethanol.

In each run eight 50-ml samples plus an infinity sample were obtained from the reaction mixture. Samples were withdrawn with a 50-ml syringe and quenched at the designated times into previously prepared mixtures of 50 ml of distilled water, 10 ml of 2 N nitric acid, and 20 ml of reagent grade benzene. The resulting two-phase mixtures were titrated potentiometrically with approximately 0.10 M silver nitrate solution. End points were taken as the point of maximum inflection in a plot of potential against milliliters of silver nitrate added. Log (ml − ml_t) was plotted against time and the slope was used to define k_1, the pseudo-first-order rate constant for the reaction. In each run approximately three half-lives were followed. In all cases

Table I

Rate Data for the Reaction of 2α-Halocholestan-3-ones under Standard Favorskii Rearrangement Conditions

Cholestan-3-one	$k_1 \times 10^3$,[a] sec^{-1} H	D	Relative rate H	D	$t_{1/2}$, sec H	D	k_H/k_D
2α-Chloro-	1.56	0.388	1.00	1.00	444	1787	4.0
2α-Bromo-	9.32	2.22	5.97	5.72	74	312	4.2
2α-Iodo-	10.64	2.08	6.82	5.36	65	333	5.1

[a] Pseudo-first-order rate constants (±5%) under conditions where base concentration is 0.200 M.

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(8) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953).

(9) R. N. Jones and A. R. H. Cole, *ibid.*, **74**, 5648 (1962).

(10) A. Butenandt and A. Wolf, *Ber.*, **B68**, 2091 (1935).

(11) H. R. Nace and R. N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964).

(12) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).

(13) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, 3rd ed, 1955, p 285.

the calculated value for $\log (\mathrm{ml} - \mathrm{ml}_t)$ at time $t = 0$, assuming $\mathrm{ml}_{t0} = 0$, lay on the line defined by the experimental points. Values obtained for k_1 are listed in Table I, p 3439.

Product Analysis.—After approximately ten half-lives, the standard reaction mixture was quenched and extracted with chloroform. The solvent was evaporated and the residue dried under reduced pressure and chromatographed. In each case the mixture of A-nor esters IV and V was separated cleanly from other products and vpc analysis showed the esters to be present in approximately equal amounts.[14] No other materials eluted from the column were isolated, but tlc showed that at least four other compounds were present. The presence of diethyl 2,3-secocholestane-2,3-dioate was indicated by both tlc and vpc, but the amount was too small to permit isolation. The results from the product analysis are given below.

1. **2α-Bromocholestan-3-one.**—Chromatography on alumina and elution with 90% petroleum ether–10% benzene gave the mixed A-nor esters in 66% yield.

2. **2α-Chlorocholestan-3-one.**—Chromatography as above gave a 66% yield of the mixed esters.

3. **2α-Iodocholestan-3-one.**—Chromatography on silica gel gave a 78% yield of the mixed esters.

4. **2α-Bromocholestan-3-one-2,4-*d*$_3$.**—Chromatography on silica gel and elution with 30% petroleum ether–70% benzene gave a 33% yield of mixed esters. The mixed esters were dried under reduced pressure before analysis.

Anal. Calcd for $C_{29}H_{49}DO_2$: D, 2.00 atom % excess. Found: D, 1.79 atom % excess (0.90 atoms/molecule).

Exchange of Deuterated Halides.—The three deuterated halides were subjected to the standard conditions for approximately one half-life, then quenched into dilute nitric acid and the mixture extracted with chloroform. The chloroform extract was evaporated and the residue was chromatographed on silica gel. Elution with 35% petroleum ether–65% benzene, followed by recrystallization of the residue from ethanol–chloroform, gave pure recovered starting material, as follows.

1. 2α-Bromocholestan-3-one-2,4-*d*$_3$ after 240 sec had mp 171.0–171.5°, $[\alpha]_D$ +44.9°.

Anal. Calcd for $C_{27}H_{42}D_3BrO$: D, 6.66 atom % excess. Found: D, 4.04 atom % excess (1.82 atoms/molecule).

2. 2α-Chlorocholestan-3-one-2,4-*d*$_3$ after 1730 sec had mp 183–185°, $[\alpha]_D$ +49.8°.

Anal. Calcd for $C_{27}H_{42}D_3ClO$: D, 6.66 atom % excess. Found: D, 3.32 atom % excess (1.50 atoms/molecule).

3. 2α-Iodocholestan-3-one-2,4-*d*$_3$ after 309 sec had mp 137–138°, $[\alpha]_D$ +31.4°.

Anal. Calcd for $C_{27}H_{42}D_3IO$: D, 6.66 atom % excess. Found: D, 4.17 atom % excess (1.88 atoms/molecule).

Nmr Spectra.—The nmr spectra of 2α-halocholestan-3-ones have been described by Bhacca and Williams[15] and the spectra of the halo ketones described here are in agreement with the reported ones. The 1-axial, 1-equatorial, and 2-axial protons give rise to an ABX (or AMX) system and two sets of quartets are visible, one in the region 4–5 ppm and the other in the region 2–2.8 ppm. Both quartets have disappeared in the deuterated halo ketones, providing additional evidence for the assignments. In place of the quartet in the 2–2.8-ppm region, in the deuterated bromo compound two peaks are present at 2.1 and 2.4 ppm. Presumably these are the two protons at C-1, the peak at 2.1 due to the axial α proton and the one at 2.4 due to the more deshielded equatorial β proton.

Discussion

Previous studies[16–19] of the Favorskii rearrangement of 2α-bromocholestan-3-one have shown the major products to be a 1:1 mixture of the rearranged esters, 2α- and 3α-carbomethoxy-A-norcholestane,[19] and dimethyl 2,3-secocholestane-2,3-dioate in 72 and 5% yield, respectively. Under the conditions[20] of Smith and Nace,[18] which initially appeared to offer the optimum amount of rearrangement products, 2α-bromo-, 2α-chloro-, and 2α-iodocholestan-3-one gave essentially the same product ratio as shown in Table II. This also appears to be the first example of the successful use of an α-iodo ketone in the Favorskii rearrangement.

TABLE II

PRODUCT ANALYSIS FOR THE FAVORSKII REARRANGEMENT OF 2α-HALOCHOLESTAN-3-ONES

	Conditions of Smith and Nace[d]		Kinetic conditions
Compd	Mixed A-nor esters, %	Seco ester, %	Yield of mixed A-nor esters,[c] %
2α-Chloro	67	7	66
2α-Bromo	48,[a] 72[b]	9,[a] 6[b]	66
2α-Iodo	65	5	78

[a] Tlc showed starting material contaminated with about 10% cholestan-3-one. Also, the reaction mixture was boiled under reflux for 2 hr after stirring at room temperature for 24 hr. [b] Yield reported by Smith and Nace. [c] Tlc and vpc indicated that some seco ester was also formed in these reactions, but insufficient amounts were formed to permit isolation and direct comparison. [d] See ref 18, 20.

The experimental procedure selected for the rate measurements employed dilute solutions at 0° with a 50-fold excess of base to approximate pseudo-first-order rate conditions. After ten half-lives the reactions were quenched and a product analysis was performed.[21] Table II shows that the yields of A-nor esters were again nearly identical, indicating that for the 2α-halocholestan-3-ones, contrary to findings for other halo ketones,[4b] the nature of the halogen has little effect on the yield of rearranged products. Table I shows the relative rates for the three halo ketones to be I > Br > Cl in the ratio of 7:6:1.

In order to obtain the deuterated halides, cholestan-3-one was subjected to three consecutive basic exchanges with sodium deuteroxide in deuterium oxide–dioxane solution. Cholestan-3-one-2,4-*d*$_4$ (IIa) was obtained in 93% yield and contained 3.91 atoms of deuterium/molecule, or 98% exchange. Although the physical properties of Id and IIa were virtually identical, the infrared spectra were quite different. As reported by Jones, Cole, and Nolin,[22] the deuterated ketone showed three bands in the 4.5-μ region (4.51, 4.66, and 4.73 μ). The first two were assigned to the CD_2 groups adjacent to the C-3 carbonyl group. The third band was not assigned, but it was suggested that it might be due to C–D stretching vibrations in CHD groups since

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[14] Vpc conditions: column temperature, 220°; detector temperature, 250°; injection port temperature, 315°; bridge power, 150 mamp; flow rate, 150 ml/min. Retention times: V, 64 mm; IV, 68 mm; and III, 113 mm at a chart speed of 4 min/in. The identity of the peaks was established by enriching the ester mixture with an authentic sample of IV. Attempts to find column conditions to give complete separation of IV and V were unsuccessful. Vpc of the methyl esters gave similar results.

[15] N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 46, 75, 144.

[16] F. Winternitz and A. C. dePaulet, *Bull. Soc. Chim. France*, [5] **21**, 288 (1954); **22**, 1393 (1955).

[17] D. E. Evans, A. C. dePaulet, C. W. Shoppee, and F. Winternitz, *Chem. Ind.* (London), 355 (1955); *J. Chem. Soc.*, 1451 (1957).

[18] B. B. Smith and H. R. Nace, *J. Am. Chem. Soc.*, **76**, 6119 (1954).

[19] M. P. Cava, P. M. Weintraub, and E. J. Glambowski, *J. Org. Chem.*, **31**, 2015 (1966).

[20] Reaction of the halo ketone with sodium ethoxide in anhydrous ethanol stirred overnight at room temperature, followed by hydrolysis, methylation of the acidic fraction, and chromatography.

[21] 2α-Iodocholestan-3-one was treated with base. Half of the product mixture was quenched into acidic water and extracted with chloroform. The other half was treated under Smith and Nace's conditions. Vpc analysis showed both product mixtures to be identical. Hence, hydrolysis did not occur during work-up and the yield of esters obtained is a direct measure of the amount of rearrangement.

[22] R. N. Jones, A. R. H. Cole, and B. Nolin, *J. Am. Chem. Soc.*, **74**, 5662 (1952).

the deuterated ketone used analyzed for only 3.69 atoms of deuterium, or 92% exchange. In the present work only 2% of the starting ketone has not been exchanged and the third band, therefore, must also be attributed to vibrations of the CD_2 group.

Each C–D bond should exhibit an asymmetric and a symmetric stretching vibration. In most deuterated steroids only two bands are visible in the 4.5-μ region,[19] and the third band in cholestan-3-one-2,4-d_4 and other deuterated 3-keto steroids is atypical. The ratios of the absorbance of the three peaks is 2:1:1 and a possible explanation attributes the first band to a symmetric vibration and the second two to a split asymmetric vibration, or *vice versa*. The splitting of one of the stretching frequencies into two equivalent peaks is then caused by interaction with the adjacent carbonyl group.[23]

The deuterio ketone was treated with chlorine in carbon tetrachloride to produce 2α-chlorocholestan-3-one-2,4-d_3 (IIb) in 24% yield and with bromine in carbon tetrachloride to give 2α-bromocholestan-3-one-2,4-d_3 (IIc) in 36% yield. Treatment of the deuterio bromo ketone with sodium iodide in anhydrous acetone gave 2α-iodocholestan-3-one-2,4,-d_3 (IId) in 76% yield. Each of the three deuterated halides analyzed for better than 85% exchange of deuterium for hydrogen in the three available α and α' positions. Melting points and optical rotations agreed well with the undeuterated analogs and established that the halogens were in the 2α conformation. The infrared spectra of the three were nearly identical between 2.5 and 4.5 μ. The 7.06-μ band, attributed to a CH_2 group adjacent to a carbonyl group by Jones and Cole,[24] was absent as expected. The absorption at 4.5 μ due to C–D stretching vibrations was not as well defined as that of cholestan-3-one-2,4-d_4.

The rate data for the deuterated halo ketones, obtained using the standard conditions, are given in Table I. Also given are the values for the k_H/k_D ratios. The observed rate constants for each of the deuterated halides represent a maximum value since the compounds are not completely exchanged at the 2 and 4 positions.

Next each of the deuterated halides reacted for approximately one half-life under standard Favorskii rearrangement conditions. After isolation and purification by chromatography and recrystallization the recovered halides were analyzed to determine the location and amount of deuterium remaining.

2α-Bromocholestan-3-one-2,4-d_3, containing 2.67 deuterium atoms/molecule prior to this treatment, retained 1.82 atoms/molecule for a loss of approximately one deuterium atom. The melting point and optical rotation of the recovered bromide agreed well with the starting bromide, but marked differences were present in the infrared and nmr spectra. The latter showed two quartets of similar intensity and position to those found in the spectrum of 2α-bromocholestan-3-one which arise from the 2α and 1α and β protons. The infrared spectrum is also consistent with the loss of deuterium at C-2 rather at C-4, in that there is no trace of the peak at 7.06 μ, assigned to the C-4 methylene group adjacent to the carbonyl group. Equilibration and washing out of the deuterium at C-2 is in accord with the known preference of 5α-cholestan-3-one to enolize toward C-2 and with the expected increase of acidity of the proton at C-2 due to the presence of the electronegative bromine atom.

2α-Iodocholestan-3-one-2,4-d_3, containing 2.51 atoms of deuterium/molecule prior to the above treatment, contained 1.88 atoms after recovery. The infrared and nmr spectra were similar to those for recovered bromide and showed that the deuterium loss again was at C-2.

2α-Cholorocholestan-3-one-2,4-d_3, containing 2.80 atoms of deuterium, was treated as above and after recovery showed 1.50 atoms of deuterium, for a loss of 1.30 atoms. The nmr spectrum showed the presence of the two quartets due to the C-1 and C-2 protons and in the infrared spectrum the deuterium band at 4.50 μ was less intense than it was in the recovered bromide spectrum. No spectral evidence could be found for the presence of a CH_2 group adjacent to a carbonyl group. Assuming complete loss of the deuterium at C-2, 20% of the deuterium at C-4 must also have been lost.

In one experiment, a sample of the deuterated bromide was allowed to rearrange completely under standard conditions. The mixed esters, isolated in 33% yield, were found to contain 0.90 atom of deuterium/molecule, or retention of one deuterium atom/molecule.

From these data several points stand out clearly. The primary deuterium isotope effect found for all three halides shows that an α' proton is lost in the rate-determining step.

The half-life (or interruption) experiment on the chloro ketone shows that deuterium exchange on the α'-carbon occurs and that therefore the C–H bond is broken before the C–Cl bond. The C–H bond breaking in this case is rate determining since a primary isotope effect is observed for the chloro ketone.

In the case of the bromo and iodo ketones, no deuterium exchange was observed at the α' carbon in the half-life experiments and it is not possible to determine whether the C–H and C–X bonds are broken simultaneously or in separate steps. Either of the above mechanisms, a or b, is consistent with these data.

Mechanism b accounts for the primary deuterium isotope effect, provided $k_2 >> k_{-1}$ and under these conditions the effect of changing the halogen is also accounted for, since the differences in electronegativity will affect k_1 and k_{-1} in the ionization step. In the case of the chloro ketone, it is necessary to postulate that $k_2 \cong k_{-1}$ and, since chloride is a poorer leaving group than bromide or iodide, this is reasonable. The partial exchange of deuterium at C-4 in the interruption experiment with the chloro ketone is then also accounted for.

Mechanism a represents a concerted process in which loss of hydrogen from the α'-carbon atom would be involved in the rate-determining step, as well as loss of halogen, and a rate difference for the different halo ketones would be expected. However, it is not possible to account for the observed deuterium exchange at C-4 of the chloro ketone and it then becomes necessary to postulate that mechanism b only operates in

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[23] We are indebted to Professor William T. King, III, Brown University, for suggesting this interpretation.

[24] R. N. Jones and A. R. H. Cole, *J. Am. Chem. Soc.*, **74**, 5648 (1952).

this case while a or b is possible for the bromo and iodo ketones. Actually, as k_2 becomes larger and larger, mechanisms a and b merge and are essentially the same.

Finally, the complete loss of deuterium at the α carbon in all of the interruption experiments shows that the hydrogen on the halogen-carrying carbon is much more acidic than the ones on the α' carbon. This is as expected since the electronegative halogen should increase the acidity of the proton.

Registry No.—Ia, 2516-50-9; Ib, 1452-34-2; Ic, 2516-55-4; IIa, 13976-58-4; IIb, 13976-59-5; IIc, 13976-60-8; IId, 13976-61-9.

Citrus Bitter Principles. VII.[1] Rutaevin

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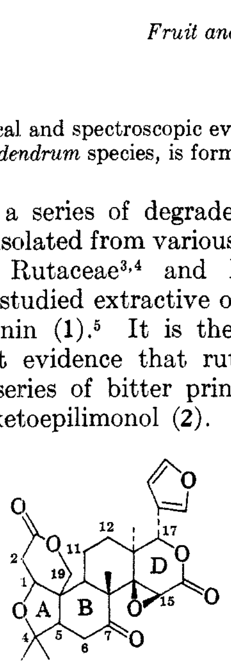
Chemical and spectroscopic evidence is presented which shows that rutaevin, a limonoid isolated from *Evodia* and *Calodendrum* species, is formulated as 6-ketoepilimonol (2).

Limonoids are a series of degraded C_{26} triterpenes which have been isolated from various plants belonging to the families Rutaceae[3,4] and Meliaceae.[4] The most extensively studied extractive of this type in the Rutaceae is limonin (**1**).[5] It is the purpose of this article to present evidence that rutaevin, a further member of this series of bitter principles, should be formulated as 6-ketoepilimonol (**2**).



1

Rutaevin was apparently first isolated by Fujita, *et al.*,[6] from the dried fruit of *Evodia rutaecarpa* Benth and Hook. Fujita and Akatsuka[7] later showed that rutaevin was nonidentical with limonin and co-occurs with limonin (**1**)[8] and limonin diosphenol (**6**).[8,9] A further study[10] on the extractives of *E. rutaecarpa* reported the isolation of three limonoids whose physical properties corresponded to **1**, rutaevin, and limonin diosphenol (**6**) and showed that rutaevin is converted to **6** with base. A previous communication[3] from this laboratory described the isolation of rutaevin from *Evodia hupenhensis*. It has now been found that seeds of Cape Chestnut, *Calodendrum capense* (L.f.) Thumb. (Rutaceae),[11] a native of South Africa, are a good source of rutaevin and also contain **1** and **6**. The isolation of rutaevin from *Calodendrum* is a much more practical matter than from *E. rutaecarpa*. In the latter, rutaevin is sometimes difficult to free from ultraviolet-adsorping impurities.

Rutaevin, analyzed for $C_{26}H_{30}O_9$, illustrated physical properties that were generally similar to those of **1** and was identical with material isolated from *E. rutaecarpa*, It gave a positive Ehrlich's test, indicating the presence of a furan ring.[12,13] This was further confirmed by the ultraviolet spectrum. The infrared spectrum showed bands assigned to a hydroxyl group, three different carbonyl groups, and a β-substituted furan ring. Rutaevin formed a monoacetate, a monobenzoate, and an oxime. The nmr spectra of rutaevin and its acetate (Table I) showed many features in common with those of **1**.[14] Thus, resonances were present for a β-substituted furan ring, H-17, an epoxy H-15, and a C-19 methylene group. The spectra showed three normal C-methyl resonances and one very broad resonance displaced relatively far upfield. The broadness, upfield position, and inconclusive integrations of this resonance lead initially to its assignment as a cyclopropyl methylene.[3] However, the relative stability of rutaevin to strong acids and the failure to observe deuterium incorporation in one of the C-methyl groups upon conversion of rutaevin to limonin diosphenol with NaOD–D_2O made the cyclopropyl grouping unlikely. A 100-Mc nmr spectrum of rutaevin showed that this resonance was clearly due to a C-methyl group. Thus, rutaevin contains four C-methyl groups and must be closely related to **1**. The nmr spectrum of rutaevin further showed a poorly resolved triplet corresponding to H-1 in **1** and a one-proton singlet which shifted downfield in rutaevin acetate (**3**) and benzoate (**4**). Thus, rutaevin is a secondary alcohol.

Although limonin gives a slight test with 2,3,5-triphenyltetrazolium chloride, rutaevin gives a strong positive test with this reagent,[15] indicating the presence of an α-ketol group. As has been observed previously,[10] treatment of rutaevin with base gave limonin diosphenol (**6**). This reaction indicates that both the

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[1] Part VI: D. L. Dreyer, *J. Org. Chem.*, **31**, 2279 (1966).

[2] A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

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