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Lactones Prepared from Dehydroisoandrosterone

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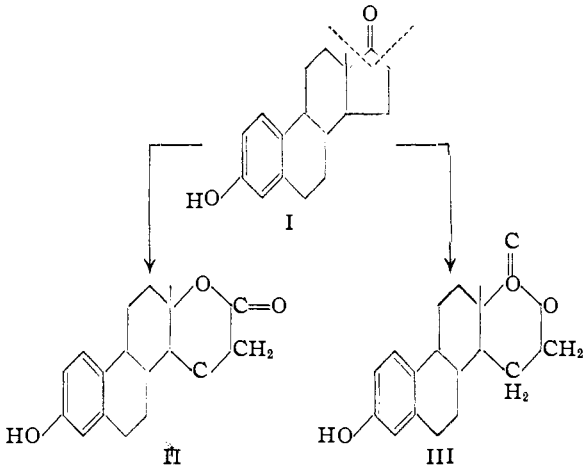
The oxidative cleavage of ring D in a 17-keto-steroid with subsequent lactonization of the hydroxy-acid postulated as intermediate has first been described by Westerfeld,[1] who oxidized estrone (I) with alkaline hydrogen peroxide obtaining a lactone $C_{18}H_{22}O_3$ which formed an acetate and a methyl ether. Westerfeld was unable, however, to formulate an exact structure for his lactone, and he proposed the alternative possibilities of cleavage of ring D between C_{13} and C_{17} or between C_{16} and C_{17}, with lactones of the structure II or III as the end-products of his reaction. He also advanced some evidence which induced him to prefer to ascribe structure II to his lactone.

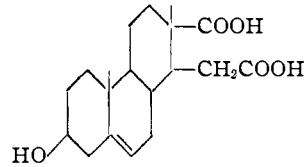


The biological properties of this lactone were subsequently investigated.[2,3,4]

A promising approach to the problem of the synthesis of similar lactones with known structure seemed to be offered through the use as starting materials of the dibasic acids obtained from certain 17-keto-steroids by oxidative opening of ring D. The present investigation relates to the synthesis and characterization of two such lactones derived from esters of 3(β)-hydroxy-$\Delta^{5,6}$-etiobilienic acid.[5-9] as obtained from dehydroisoandrosterone.

(1) Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).
(2) O. W. Smith, *Endocrinology*, **35**, 146 (1944).
(3) O. W. Smith, *Proc. Soc. Exptl. Biol. Med.*, **59**, 242 (1945).
(4) O. W. Smith and G. V. S. Smith, *J. Clin. Endocrinol.*, **6**, 483 (1946).
(5) Kuwada, *J. Pharm. Soc. Japan*, **56**, 75 (1936); *C. A.*, **31**, 2224 (1937).
(6) Kuwada, *J. Pharm. Soc. Japan*, **56**, 631 (1936); *C. A.*, **31**, 2224 (1937).
(7) Kuwada and Nakamura, *J. Pharm. Soc. Japan*, **58**, 841 (1938); *C. A.*, **33**, 2530 (1939).
(8) Kuwada and Nakamura, *J. Pharm. Soc. Japan*, **58**, 835 (1938); *C. A.*, **33**, 2531 (1939).
(9) Butenandt, Schmidt-Thomé, Weiss, Dresler and Meinerts, *Ber.*, **72**, 417 (1939).

A most convenient preparation of some functional derivatives of this acid has been described by Miescher and his co-workers,[10] who oxidized dehydroisoandrosterone acetate with potassium hypoiodite. Its constitution as $\Delta^{9,14}$-2,13-dimethyl-7(β)-hydroxydodecahydrophenanthryl-1-acetic acid-2-carboxylic acid (IV) was established by Kuwada.[5-8]



IV

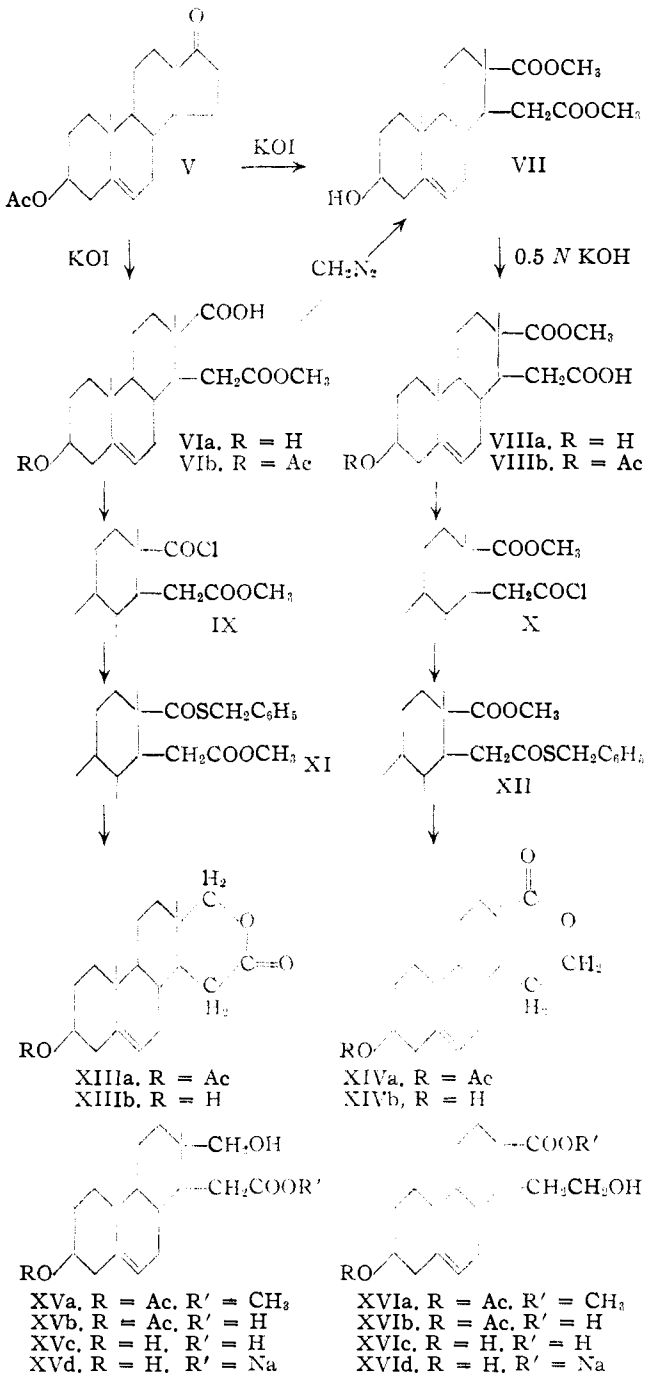
The sequence of reactions we employed to obtain lactones from the above dibasic acid IV consisted essentially of two steps: (1) protection of one of the two carboxylic acid groups by selective esterification and (2) reduction of the remaining free carboxyl to the corresponding alcohol through the half-ester acid chloride, the benzylthiol ester and Raney nickel reduction.[11]

Selective esterification had been achieved by Kuwada,[5,7] who described the two isomeric monomethyl-half-esters of IV, the primary or α-monomethyl ester VIa and the tertiary or β-monomethyl ester VIIIa.

The method of preparing the tertiary or β-monoesters by partial hydrolysis of the diesters as first employed in this series by Kuwada[5,7] follows the general rule relating to the ease of hydrolysis of primary as against tertiary carboxylic acid esters. It has given consistently reliable results in the hands of Miescher and his co-workers[12] and the constitution of such compounds seems to be well established.

The preparation of the primary α-monoester which had hitherto required the esterification of the free dibasic acid IV with the alcohol and a catalyst has been considerably improved by the finding that the crude hypoiodite oxidation mixture of V yielded on acidification a mixture consisting of about four-fifths α-monoester VIa and one-fifth diester VII. From this mixture the α-monoester VIa could be isolated by alkali extraction, while the β-monoester VIIIa could be prepared in quantity by treating the above mixture with diazomethane to form the diester VII, followed by partial hydrolysis to the β-monoester VIIIa.

(10) Wettstein, Fritzsche, Hunziker and Miescher, *Helv. Chim. Acta*, **24**, 332E (1941).
(11) Jeger, Norymberski, Szpilfogel and Prelog, *ibid.*, **29**, 684 (1946).
(12) *E. g.*, Heer and Miescher, *ibid.*, **28**, 156 (1945); Heer, Billeter and Miescher, *ibid.*, **28**, 991 (1945); Heer and Miescher, *ibid.*, **29**, 1895 (1946), and **30**, 786 (1947).



The half-esters VIa and VIIIa were acetylated with acetic anhydride–pyridine and the acetyl derivatives VIb and VIIIb allowed to react in benzene solution with oxalyl chloride[13] to yield the corresponding ester acid chlorides IX and X.[14]

Condensation of the acid chlorides IX and X in benzene solution with benzyl mercaptan under the influence of pyridine gave the thiolbenzyl esters XI and XII, respectively. The ester XI, which was not obtained in crystalline form, on hydrolysis with one normal aqueous methanolic potassium hydroxide consumed three equivalents of alkali to yield IV, while XII, because of the tertiary nature of its carbomethoxy group, was hydrolyzed by only two equivalents of alkali to yield VIIIa.

Treatment of the thiolbenzyl esters XI and XII in methanolic solution at room temperature with Raney nickel according to the method mentioned above[12] yielded not the expected δ-hydroxyacid esters $C_{22}H_{34}O_5$ (XVa and XVIa), but rather two neutral compounds of the composition $C_{21}H_{30}O_4$, which proved to be the acetoxy-lactones XIIIa and XIVa. The neutral substances, which could not be acetylated, while insoluble in cold dilute alkali, dissolved under reflux, consuming two equivalents of alkali to yield sparingly soluble sodium salts. Acidification of the saponification mixtures yielded the unacetylated lactones[15] XIIIb and XIVb.

While reduction of the thiolbenzyl esters XI and XII with Raney nickel may at first have produced the δ-hydroxyacid esters XVa and XVIa, one molecule of methanol was apparently eliminated with the concomitant formation of the lactone ring.

This unusual reaction might be explained by the inordinately strong tendency toward lactonization of compounds of the type of XVc and XVIc, which seemed to be only stable in the form of their sodium salts $C_{19}H_{29}O_4Na$ (XVd and XVId), both of which were isolated and identified by analysis. Acidification of XVd and XVId at room temperature proved to be sufficient to close the lactone rings with the formation of XIIIb and XIVb, and the usual heating with strong acids to effect lactonization was not required.

Finally, we were able to show that the double bond between C_5 and C_6 of the original sterol was still present in the two acetoxy-lactones XIIIa and XIVa, as well as in the two lactones XIIIb and XIVb. All four compounds gave positive color reactions with tetranitromethane. In addition we prepared the dibromides $C_{21}H_{30}O_4Br_2$ of the acetoxy-lactones XIIIa and XIVa in the usual manner, which could be debrominated with zinc to yield again the parent compounds XIIIa and XIVa.

Levy and Jacobsen[16] have reported the preparation of a lactone obtained by oxidation of dehydro-

(13) Oxalyl chloride was employed at this point (see Ställberg-Stenhagen, THIS JOURNAL, 69, 2568 (1947)), to obviate the isomerization of the ester acid chlorides as found to occur with thionyl chloride by Cason (*ibid.*, 69, 1548 (1947)).

(14) Heer and Miescher, *Helv. Chim. Acta*, 30, 786 (1947).

(15) For reasons of convenience we designated the lactones derived from the α-monomethyl ester VIa as α-lactones, and those derived from the β-monomethyl ester VIIIa as β-lactones.

(16) Levy and Jacobsen, *J. Biol. Chem.*, 171, 71 (1947).

isoandrosterone with peracetic acid. This lactone, dehydroisoandrololactone, is undoubtedly different from either our α-lactone XIIIb or our β-lactone XIVb. However, it may be that our α-lactone XIIIb is the same as that of Huffman, *et al.*[17], and that our β-lactone XIVb is perhaps identical with the compound recently reported by Hershberg, *et al.*[18]

Acknowledgment.—We are indebted to Mr. W. Turnbull and Mr. P. Morozovitch for their technical assistance, and to Mrs. D. Jewitt, Miss C. Jockel and Mrs. K. George for the numerous microanalyses and determinations of optical rotations.

Experimental[18a]

$\Delta^{9,14}$-2,13-Dimethyl-7(β)-hydroxydodecahydrophenanthryl-2-carboxylic Acid-1-acetic Acid Methyl Ester (α-Monomethyl Ester VIa).—To a solution of 10 g. of dehydroisoandrosterone acetate (m. p. 167–168°) in 800 ml. of methanol there were added, with vigorous stirring at room temperature, a solution of 35 g. of iodine in 800 ml. of methanol and a solution of 25.4 g. of potassium hydroxide in 800 ml. of 50% aqueous methanol. Both solutions were added from separate tap funnels over a period of five hours in such a manner that a slight excess of free iodine was maintained at all times. Stirring was then continued until the mixture had decolorized from a dark brown to a light yellow. Two such runs were combined, the bulk of the methanol removed *in vacuo* at bath temperatures below 40°, the residual solution (700–800 ml.) diluted with two volumes of ice-water and extracted with ether. This ether extract contained about 2 g. of dimethyl ester VII and was worked up separately (see below). The alkaline aqueous phase was acidified with five normal sulfuric acid and extracted with ether. The spent aqueous layer contained about 1 g. of a dibasic acid, which was probably an isomer of IV and which was made the subject of a separate study. The ether extract was washed with water, then repeatedly with a 10% solution of sodium thiosulfate to remove all iodine, then again with water until neutral to litmus, and extracted with seven 200-ml. portions of 1 *N* sodium bicarbonate. The combined bicarbonate extracts were strongly acidified, extracted with ether, the ether washed neutral, dried with anhydrous sodium sulfate and evaporated to dryness. The dry residue was taken up in boiling acetone, crystallized by addition of boiling hexane in repeated small portions, the crude crystals filtered after cooling and washed with some ice-cold hexane; yield 10.3 g. (48.8%); m. p. 182–184°; $[\alpha]^{27}D$ −51.6° (in methanol); mixed m. p. 182–184°.[7]

Dimethyl Ester VII.—The ether extract containing the dimethyl ester VII (see above) obtained from the oxidation of 20 g. of dehydroisoandrosterone acetate was washed with water, 10% sodium thiosulfate, then again with water until neutral to litmus, dried with anhydrous sodium sulfate and evaporated. The oily residue was extracted several times with boiling hexane, decanting from the insoluble impurities each time, and then crystallized by concentration. A small additional amount was obtained by recrystallizing the oily residues from acetone–hexane; yield of crude VII 2.1 g., m. p. 103–104°.

The ether extracts containing the α-monomethyl ester VIa obtained from the same oxidation run were washed as described above, dried, treated with diazomethane prepared from 12 g. of nitrosomethylurea for one hour and evaporated. The residual oil was repeatedly extracted with boiling hexane, and the dimethyl ester VII crystallized upon concentration and cooling, m. p. 102–104°, yield 8.6 g., combined yield from both fractions 10.7 g. (48.3%). Recrystallized from hexane m. p. 111–112°, identical with dimethyl ester obtained from IV with diazomethane.

Acetate of Dimethyl Ester VII.—A sample of 210 mg. of VII in 6 ml. of pyridine and 2 ml. of acetic anhydride was worked up as usual and purified by chromatographic adsorption on alumina and elution with benzene–hexane 2:1 followed by recrystallization from hexane; m. p. 150.5°,[5] $[\alpha]^{27}D$ −68.34° (in methanol). *Anal.* Calcd. for $C_{23}H_{34}O_6$ (406.5): C, 67.95; H, 8.43. Found: C, 67.70, 67.79; H, 8.69, 8.81.

$\Delta^{9,14}$-2,13-Dimethyl-7(β)-hydroxydodecahydrophenanthryl-1-acetic Acid-2-carboxylic Acid Methyl Ester VIIIa (β-Monomethyl Ester).—Ten and one-tenth grams of dimethyl ester VII was refluxed for two hours with 510 ml. 0.5 *N* potassium hydroxide in 95% aqueous methanol. About two-thirds of the methanol was then evaporated *in vacuo* and the residual solution was poured into 2 l. of ice-water. A small amount of unchanged dimethyl ester VII separated and was recovered by ether extraction. The clear aqueous phase was acidified with 150 ml. of 2 *N* sulfuric acid and extracted with ether. The ether solution was washed with water, dried and evaporated. The unchanged dimethyl ester recovered above was hydrolyzed in an identical manner with 125 ml. of 0.5 *N* potassium hydroxide in 95% aqueous methanol; combined yield 8.4 g. (86.3%). Recrystallized from aqueous methanol, m. p. 216°.[7]

α-Monomethyl Ester Acetate VIb.—Ten and three-tenths grams of α-monomethyl ester VIa was acetylated as usual with 60 ml. of pyridine and 40 ml. of acetic anhydride. Recrystallized from methanol–water, yield 9.4 g. (81.7%); m. p. 204–205°; $[\alpha]^{27}D$ −63.1° (in methanol); $[\alpha]^{27.7}D$ −74.9° (in chloroform). *Anal.* Calcd. for $C_{22}H_{32}O_6$ (392.5): C, 67.32; H, 8.22. Found: C, 67.36, 67.14; H, 8.05, 7.95. Hydrolysis with potassium carbonate in 80% aqueous methanol yielded IV, identified by mixed m. p.

β-Monomethyl Ester Acetate VIIIb.—Acetylation of 8.4 g. of β-monomethyl ester VIIIa in 100 ml. of pyridine with 60 ml. of acetic anhydride and recrystallization from aqueous methanol yielded 7.6 g. (80.8%) of VIIIb: m. p. 168°[7]; $[\alpha]^{27}D$ −72.28° (in methanol). *Anal.* Calcd. for $C_{22}H_{32}O_6$ (392.5): C, 67.32; H, 8.22; equiv. wt., 392.5. Found: C, 67.44, 67.11; H, 8.56, 8.36; equiv. wt. by electrometric titration in aqueous methanol, 421.

α-Monomethyl Ester Acetate Acid Chloride IX.—Nine and three-tenths grams of α-monomethyl ester acetate VIb was dissolved in 150 ml. of dry benzene, and oxalyl chloride (15 ml., freshly distilled) was added slowly at room temperature during ten minutes with constant shaking. After the initial reaction had subsided the mixture was kept at 65–70° for one and one-half hours with occasional shaking, and then distilled *in vacuo* under nitrogen to a sirupy residue. This was redissolved in 100 ml. of benzene, 8 ml. of oxalyl chloride was added at once and the mixture kept at 65–70° for one-half hour, then at 75° for fifteen minutes. Benzene and excess oxalyl chloride was then removed *in vacuo* under nitrogen. The resulting acid chloride IX constituted a yellowish sirup which could not be brought to crystallization. It was kept *in vacuo* over phosphoric anhydride until constant in weight and then used as such in the subsequent condensation with benzyl mercaptan; yield 10.2 g.

β-Monomethyl Ester Acetate Acid Chloride X.—In the same manner, 7.6 g. of β-monomethyl ester acetate VIIIb was dissolved in 125 ml. of benzene and treated first with 12 ml., then with an additional 6 ml. of oxalyl chloride. The reaction mixture was worked up as above and the acid chloride X obtained, in this case, as a crystalline product. It was kept *in vacuo* over phosphoric anhydride until its weight remained constant and then used as such in the subsequent condensation with benzyl mercaptan; yield 8.04 g., m. p. 135–137°. Heer and Miescher[14] obtained the same compound with m. p. 135°.

(17) Huffman, Lott and Ashmore, THIS JOURNAL, **70**, 4268 (1948).

(18) Hershberg, Schwenk and Stahl, *Arch. Biochem.*, **19**, 300 (1948).

(18a) All m. p.'s are corrected.

Thiolbenzyl Ester XI.—The crude acid chloride IX (10.2 g., prepared from 9.3 g. of VIb) was dissolved in 150 ml. of dry benzene, and 15.3 ml. (five moles per mole of VIb) of benzyl mercaptan was added with stirring. Dry pyridine (2.87 ml., 1.5 moles per mole of VIb) was then added with shaking, the flask immediately stoppered and kept at room temperature for forty-eight hours with occasional shaking. The mixture was taken up in 1200 ml. of ether, washed with two 50-ml. portions of water to remove pyridine hydrochloride, then with fifteen 50-ml. portions of 0.5 *N* sodium hydroxide, then with three 50-ml. portions of 0.5 *N* sulfuric acid, and finally with water until neutral. The residue obtained after drying and evaporating the ether *in vacuo* was taken up in hot hexane, filtered, the hexane evaporated and the resulting oily thiolbenzyl ester XI dried to constant weight *in vacuo;* yield 11.75 g., used without further purification in the subsequent reduction. A sample purified by repeated solution in hot hexane and cooling had $[\alpha]^{25}D$ −63.3° (in chloroform). *Anal.* Calcd. for $C_{29}H_{38}O_5S$ (498.6): C, 69.85; H, 7.68; S, 6.43. Found: C, 67.81, 67.25; H, 7.90, 7.65; S, 7.28, 7.65.

Hydrolysis of XI.—A sample of 203.6 mg. was refluxed for three hours with 5 ml. of 1 *N* potassium hydroxide in 90% aqueous methanol with occasional addition of 1-ml. portions of water and simultaneously distilling off 1 ml. of methanol, and the mixture back-titrated against phenolphthalein indicator after addition of 5 ml. of water. Calcd. for consumption of three equivalents: 12.25 ml. 0.1 *N* alkali. Found: 12.25 ml. Acidification of the titrated solution yielded IV, identified by mixed m. p.

Thiolbenzyl Ester XII.—In the same manner, 8.04 g. of the acid chloride X dissolved in 125 ml. of benzene was treated with 11.2 ml. of benzyl mercaptan and 2.3 ml. of pyridine for forty-eight hours at room temperature and the mixture worked up as described above. The oily residue obtained upon evaporation of the washed and dried ether solution *in vacuo* crystallized after some standing *in vacuo* and was twice recrystallized from methanol; yield 8.85 g. (91.7%); m. p. 111–112°; $[\alpha]^{26}D$ −57.00° (in methanol). *Anal.* Calcd. for $C_{29}H_{38}O_5S$ (498.6): C, 69.85; H, 7.68; S, 6.43. Found: C, 68.42, 68.46; H, 7.28, 7.21; S, 6.28, 6.21.

Hydrolysis of XII.—A sample of XII (52.2 mg.) was refluxed for one hour with 5 ml. of 1 *N* potassium hydroxide in 90% aqueous methanol and the mixture back-titrated after addition of 10 ml. of water with 0.1 *N* acid as above. Calcd. for consumption of two equivalents: 2.09 ml. 0.1 *N* alkali. Found: 2.1 ml. Acidification yielded the β-monomethyl ester VIIIa, identified by mixed m. p.

Lactone of $\Delta^{9,14}$-2,13-Dimethyl-2-hydroxymethyl-7(β)-acetoxy-dodecahydrophenanthryl-1-acetic Acid XIIIa (α-Lactone Acetate).—A Raney nickel catalyst was prepared following the general outline of procedure given by Mozingo[19] with the following modifications: Addition of the Raney nickel-aluminum alloy to the solution of sodium hydroxide was carried out at temperatures below 17°, and the mixture was then kept at 50° overnight. After washing by decantation with water and digesting with 10% sodium hydroxide the catalyst was continuously washed with distilled water until the *p*H of the effluent had dropped to 7.2–7.6. It was then centrifuged and repeatedly washed with anhydrous methanol. The catalyst prepared in this manner seemed to be similar in activity to the W-5 Raney nickel described by Adkins and Billica.[20]

Ten and seven-tenths grams of XI was dissolved in 800 ml. of anhydrous methanol and approximately 100 g. of the above Raney nickel catalyst, twice washed immediately before use with anhydrous methanol, was added. The mixture was vigorously stirred at room temperature for six hours, using a seal filled with methanol. The catalyst was centrifuged off, repeatedly washed with methanol, the combined methanolic solutions boiled shortly to coagulate colloidal catalyst, filtered, evaporated *in vacuo* under nitrogen, and the α-lactone acetate XIIIa recrystallized from aqueous methanol; yield 5.81 g. (79%, 76–87% in other runs); m. p. 176–177°; $[\alpha]^{30}D$ −110.6° (in chloroform). *Anal.* Calcd. for $C_{21}H_{30}O_4$ (346.4): C, 72.88; H, 8.74. Found: C, 72.56, 72.57; H, 9.02, 8.70. The compound gave a strongly positive color reaction with tetranitromethane.

Titration of XIIIa.—A sample of 95.0 mg. was refluxed with 5 ml. of 1 *N* aqueous sodium hydroxide with occasional addition of 1-ml. portions of water to keep in solution the sodium salt XVd, and back-titrated with 0.1 *N* acid against phenolphthalein. Calcd. for consumption of two equivalents: 5.48 ml. 0.1 *N* alkali; mol. wt., 346.4. Found: 5.4 ml.; mol. wt., 352. Acidification yielded the free α-lactone XIIIb.

Dibromide of XIIIa.—A sample of 41.6 mg. in 2 ml. of glacial acetic acid was treated with a solution of 19.2 mg. of bromine (one mol) in 0.25 ml. of glacial acetic acid. The initial yellow color disappeared after a few minutes, and after standing at room temperature for two hours the dibromide was isolated by dropwise addition of water (8 ml.) and recrystallized three times from aqueous methanol, m. p. 179–180° (dec.). *Anal.* Calcd. for $C_{21}H_{30}O_4Br_2$ (506.2): Br, 31.57. Found: Br, 30.96, 30.79.

Debromination of 12.1 mg. of the above dibromide in 1.5 ml. of glacial acetic acid with zinc dust (0.5 g.) in the conventional way yielded, after working up as usual and recrystallization from aqueous methanol, the α-lactone acetate XIIIa, identified by mixed m. p.

Lactone of $\Delta^{9,14}$-2,13-Dimethyl-1-hydroxyethyl-7(β)-acetoxydodecahydrophenanthryl-2-carboxylic Acid XIVa (β-Lactone Acetate).—The procedure described above for the reduction of XI was followed. The thiolbenzyl ester XII (8.85 g.) was dissolved in 700 ml. of anhydrous methanol, stirred for six hours with approximately 90 g. of Raney nickel catalyst, and the mixture worked up in the same manner as described for the reduction of XI. The crude β-lactone acetate XIVa (5.96 g.) was recrystallized first from aqueous, then from anhydrous methanol; yield 2.4 g. (39.1%); an additional 3.53 g. was recovered from the mother liquors and used for the preparation of the free β-lactone XIVb—see below); m. p. 188–189.8°; $[\alpha]^{27}D$ −73.7° (in chloroform). *Anal.* Calcd. for $C_{21}H_{30}O_4$ (346.4): C, 72.88; H, 8.74. Found: C, 72.93, 72.97; H, 8.96, 8.78. It gave a strongly positive color reaction with tetranitromethane.

A sample of XIVa (100.0 mg.) was refluxed with aqueous alkali and back-titrated as described above for XIIIa. Calcd. for consumption of two equivalents: 5.77 ml. 0.1 *N* alkali; mol. wt., 346.4. Found: 5.8 ml.; mol. wt., 345. Acidification yielded the free β-lactone XIIIb.

Dibromide of XIVa.—A sample of 100.0 mg. in 6 ml. of glacial acetic acid was stirred for thirty minutes at 20°, then for another thirty minutes at 30°, with a solution of 46.2 mg. of bromine (one mole) in 0.15 ml. of glacial acetic acid. The dibromide was isolated from the almost colorless solution by dropwise addition of water (30 ml.) and recrystallized first from aqueous methanol, then from aqueous acetic acid; yield 86%; m. p. 153–154° (dec. 156°). *Anal.* Calcd. for $C_{21}H_{30}O_4Br_2$ (506.2): Br, 31.57. Found: Br, 31.64, 31.70.

Debromination of 24.5 mg. of the above dibromide in 3 ml. of glacial acetic acid with zinc dust (1 g.) in the conventional manner yielded, after working up as usual and recrystallization from aqueous methanol, the β-lactone acetate XIVa, identified by mixed m. p.

α-Lactone XIIIb.—The crude α-lactone acetate XIIIa (5.81 g.) was refluxed for one hour with 150 ml. of 1 *N* aqueous sodium hydroxide, water (100 ml.) was added to dissolve the sodium salt XVd, and the solution was extracted with two 100-ml. portions of ether. The aqueous layer was filtered through sintered glass, acidified with 75 ml. of 5 *N* sulfuric acid, the precipitate filtered after standing in the cold for forty-eight hours and washed neutral with ice-water. Repeated recrystallization from aqueous methanol yielded 4.54 g. (89%) of α-lactone XIIIb, m. p. 205–207°, $[\alpha]^{27}D$ −92.2° (in methanol). *Anal.*

(19) Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943).

(20) Adkins and Billica, *ibid.*, **70**, 695 (1948).

Calcd. for $C_{19}H_{28}O_3$ (304.4): C, 74.96; H, 9.27. Found: C, 74.69, 74.67; H, 9.69, 9.48. The compound gave a strong depression of the m. p. when mixed with the β-lactone XIVb (see below), and showed a positive color reaction with tetranitromethane. A sample of 11.7 mg. was recovered unchanged after two hours of refluxing with 7 ml. of 1 *N* sulfuric acid and identified by mixed m. p.

A sample of XIIIb (59.5 mg.) was refluxed with aqueous alkali and back-titrated as described above for XIIIa. Calcd. for consumption of one equivalent: 1.95 ml. 0.1 *N* alkali; mol. wt., 304.4. Found: 1.95 ml.; mol. wt., 304.4. Acidification gave a quantitative yield of the unchanged α-lactone XIIIb, identified by mixed m. p.

Sodium Salt of α-Lactone XIIIb (XVd).—A sample of XIIIb (50.5 mg.) was refluxed with 1.7 ml. of 0.1 *N* aqueous sodium hydroxide and 0.9 ml. of water. The clear solution was allowed to stand at −5° for three days, the crystalline sodium salt XVd was separated by centrifuging in the cold, washed with a little ice-water and dried *in vacuo*. *Anal.* Calcd. for $C_{19}H_{29}O_4Na \cdot H_2O$ (362.4): Na, 6.34. Found: Na, 6.12, 6.38.

Acetate of α-Lactone XIIIb (XIIIa).—A sample of the α-lactone XIIIb (150.0 mg.) in 5 ml. of anhydrous pyridine was treated with 3 ml. of acetic anhydride, worked up in the usual way and the α-lactone acetate XIIIa recrystallized three times from aqueous methanol: yield 139 mg., m. p. 176–177°, identified by mixed m. p. and determination of rotation.

β-Lactone XIVb.—The crude β-lactone acetate XIVa (3.53 g., obtained from the mother liquors of the pure XIVa) was refluxed for one hour with 100 ml. of 1 *N* aqueous sodium hydroxide, keeping the sodium salt XVId in solution by addition of 50 ml. of water. Working up as previously described for the hydrolysis of XIIIa there were obtained, after acidification with 50 ml. of 5 *N* sulfuric acid, washing to neutrality, and repeated recrystallization from aqueous methanol, 2.22 g. of β-lactone XIVb: yield 41.3% from XII, m. p. 206–208°, $[\alpha]^{30}D$ −55.5° (in methanol). *Anal.* Calcd. for $C_{19}H_{28}O_3$ (304.4): C, 74.96; H, 9.27. Found: C, 74.82, 75.11; H, 9.02, 9.22. The compound gave a strong depression of the m. p. when mixed with the α-lactone XIIIb, and showed a positive color reaction with tetranitromethane. A sample of 11.1 mg. was recovered unchanged after refluxing for two hours with 10 ml. of 1 *N* sulfuric acid and identified by mixed m. p.

The over-all yield of β-lactone acetate XIVa and β-lactone XIVb obtained from 8.85 g. of thiolbenzyl ester XII was 80.4%.

A sample of XIVb (69.5 mg.) was refluxed with aqueous alkali and back-titrated as described above for XIIIa. Calcd. for consumption of one equivalent: 2.28 ml. of 0.1 *N* alkali; mol. wt., 304.4. Found: 2.30 ml.; mol. wt., 302. Acidification gave a quantitative yield of the unchanged β-lactone XIVb, identified by mixed m. p.

Sodium Salt of β-Lactone XIVb (XVId).—A sample of XIVb (54.5 mg.) was refluxed with 1.79 ml. of 0.1 *N* aqueous sodium hydroxide and 0.7 ml. of water. The clear solution could not be brought to crystallization and was therefore lyophilized. The amorphous sodium salt XVId was washed with a little ice-water and dried *in vacuo*. *Anal.* Calcd. for $C_{19}H_{29}O_4Na \cdot H_2O$ (362.4): Na, 6.34. Found: Na, 6.23, 6.12.

Acetate of β-Lactone XIVb (XIVa).—A sample of XIVb (15.1 mg.) in 1 ml. of dry pyridine was treated with 0.6 ml. of acetic anhydride, worked up in the usual way, the β-lactone acetate XIVa recrystallized from aqueous acetic acid and identified by mixed m. p.

Summary

1. A convenient method for the preparation of the two isomeric monomethyl half-esters of 3(β)-hydroxy-$\Delta^{5,6}$-etiobilienic acid from dehydroisoandrosterone acetate has been described.

2. Conversion of the acetates of the two half-esters to the corresponding half-ester acid chlorides and condensation of the latter with benzyl mercaptan to yield two isomeric methyl-thiolbenzyl esters $C_{29}H_{38}O_5S$, has been carried out, and their constitution established by degradation.

3. Treatment of the latter with Raney nickel at room temperature yielded two isomeric acetoxylactones $C_{21}H_{30}O_4$, which upon alkaline hydrolysis yielded the two isomeric free lactones $C_{19}H_{28}O_3$.

4. One of these, the α-lactone (derived from the α-monomethyl half-ester), was shown to be the lactone of $\Delta^{9,14}$-2,13-dimethyl-2-hydroxymethyl-7(β)-hydroxydodecahydrophenanthryl-1-acetic acid. The isomeric β-lactone (derived from the β-monomethyl half-ester), was shown to possess the structure of the lactone of $\Delta^{9,14}$-2,13-dimethyl-1-hydroxyethyl-7(β)-hydroxydodecahydrophenanthryl-2-carboxylic acid.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. IV.[1a] α-Iodoketones. A Method for the Conversion of *Allo*steroids into Δ^4-3-Ketosteroids[1b]

BY G. ROSENKRANZ, O. MANCERA, J. GATICA AND CARL DJERASSI

Except for 21-iodo-20-ketopregnanes,[2] usually prepared from the corresponding 21-tosylates and not isolated, α-iodoketones of the steroid series appear to be unknown.[2a]

The preparation and reactions, particularly toward dehydrobrominating agents, of brominated derivatives of 3-ketosteroids of both the *allo* (rings A/B *trans*) and *normal* (rings A/B *cis*) series have been studied thoroughly,[3] and it was of interest to extend this work to the corresponding iodo compounds.

The most promising approach appeared to be the well known halogen interchange of bromo compounds by treatment with sodium iodide in acetone solution. When applied to 2-bromo-3-

(1a) Paper III, Rosenkranz, Djerassi, Kaufmann, Pataki and Romo, *Nature*, **165**, 814 (1950).

(1b) A part of the experimental portion of this paper is taken from a thesis to be presented by Srta. Josefina Gatica to the Escuela de Ciencias Químicas de la Universidad Nacional Autónoma de México.

(2) Lardon, *Helv. Chim. Acta*, **32**, 1517 (1949), and references cited therein.

(2a) After submission of this manuscript for publication, an article appeared [Julian and Karpel, THIS JOURNAL, **72**, 362 (1950)] in which the preparation and some reactions of a pure 21-iodo-20-ketosteroid were reported.

(3) See Djerassi, *ibid.*, **71**, 1003 (1949), for a brief review and leading references.