S, 8.27; CH_3O, 8.01. Found: C, 65.23; H, 6.77; N, 3.92; S, 8.5; CH_3O, 8.30.

The Catalytic Hydrogenation of IX into II (R = O).—A mixture of IX (0.010 g.) and 10% palladium–charcoal (0.005 g.) in ethyl acetate (5.0 ml.) was hydrogenated at room temperature under atmospheric pressure for 5 hr. The compound crystallized from methanol to afford prisms, melting at 226–228°. Its identity with II (R = O) was established by mixture melting point determination and comparison of their infrared spectra.

Acknowledgment.—The authors wish to express their great indebtedness to Dr. Edwin D. Becker of this institute for the interpretation of the n.m.r. spectra and to Mr. Robert B. Bradley for running the spectra. We wish also to thank the Cancer Chemotherapy National Service Center for the supply of valuable starting materials.

Investigations on Steroids. XXXV. Pseudostrophanthidin and Related Compounds[1,2]

TOKUO KUBOTA[3] AND MAXIMILIAN EHRENSTEIN

Division of Steroid Research, The John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Received June 14, 1963

An improved method for the conversion of strophanthidin (I) into pseudostrophanthidin (II) is reported. Old and new evidence in support of the structure of II is discussed. In particular, II has been correlated with a number of steroids previously investigated in this laboratory. The earlier literature in this area has been reviewed and is presented in a revised form, *viz.*, in the light of present concepts. The structure of II appears now firmly established.

As a continuation of our studies on 19:8-lactone analogs of progesterone and cortexone[4] it appeared desirable also to prepare compounds of the 19:8-hemiacetal series. In an early investigation, Jacobs and Collins[5] had demonstrated that, by treatment with concentrated hydrochloric acid, strophanthidin (I) is converted into a crystalline isomer which was named pseudostrophanthidin. Its correct structure (II) was recognized by Fieser and Fieser,[6] and this interpretation is in agreement with our own investigations in this area.

Because of its structural features, pseudostrophanthidin (II) was considered as starting material for the synthesis of a variety of steroids with a 19:8-hemiacetal bridge. As the first task, it appeared necessary to repeat and consolidate some of the early experimental work. Furthermore, since it is cumbersome and sometimes confusing to excerpt and interpret data in the early literature, it was deemed advisable to arrange the pertinent findings in a revised form, *viz.*, in the light of present concepts.

Pseudostrophanthidin (II) was prepared in improved yield by a modified procedure. The deviations from the early literature[5] concerning the melting point and optical rotation are recorded in the Experimental section. Pseudostrophanthidin (II) was characterized by the preparation of several derivatives. Refluxing of II with methanol in the presence of a catalytic amount of hydrochloric acid gave pseudostrophanthidin methylal (III),[7] which could be reconverted into II by treatment with 70% acetic acid. The methylal (III) in turn was characterized as the dinitrobenzoate and acetate, *viz.*, pseudostrophanthidin methylal 3,5-dinitrobenzoate (IV) and pseudostrophanthidin methylal 3-acetate (V), respectively. On demethylating V, pseudostrophanthidin 3-monoacetate (VI) resulted which could be further acetylated at an elevated temperature, yielding pseudostrophanthidin 3,19-diacetate (VII). Acetylation of II at room temperature gave a mixture of the 3-monoacetate (VI) and the 3,19-diacetate (VII).

Pseudostrophanthidin (II) could be correlated with a number of compounds structurally connected with strophanthidinic acid lactone (X) which is prepared from strophanthidinic acid (IX).[8] X recently has served as a starting material for synthetic work in this laboratory.[4] In agreement with earlier observations,[8] oxidation with chromic acid of either II or X gave strophanthidonic acid lactone (XI). In addition, acetylation of X gave strophanthidinic acid 19:8-lactone 3-acetate (XII) which also was obtained by oxidation of VI with chromic acid. Another product belonging to this series is 3-dehydropseudostrophanthidin methylal (VIII) which resulted from the oxidation of III with chromic acid.

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The

(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) from the National Cancer Institute of the National Institutes of Health.

(2) The findings reported in this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein," Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was presented by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

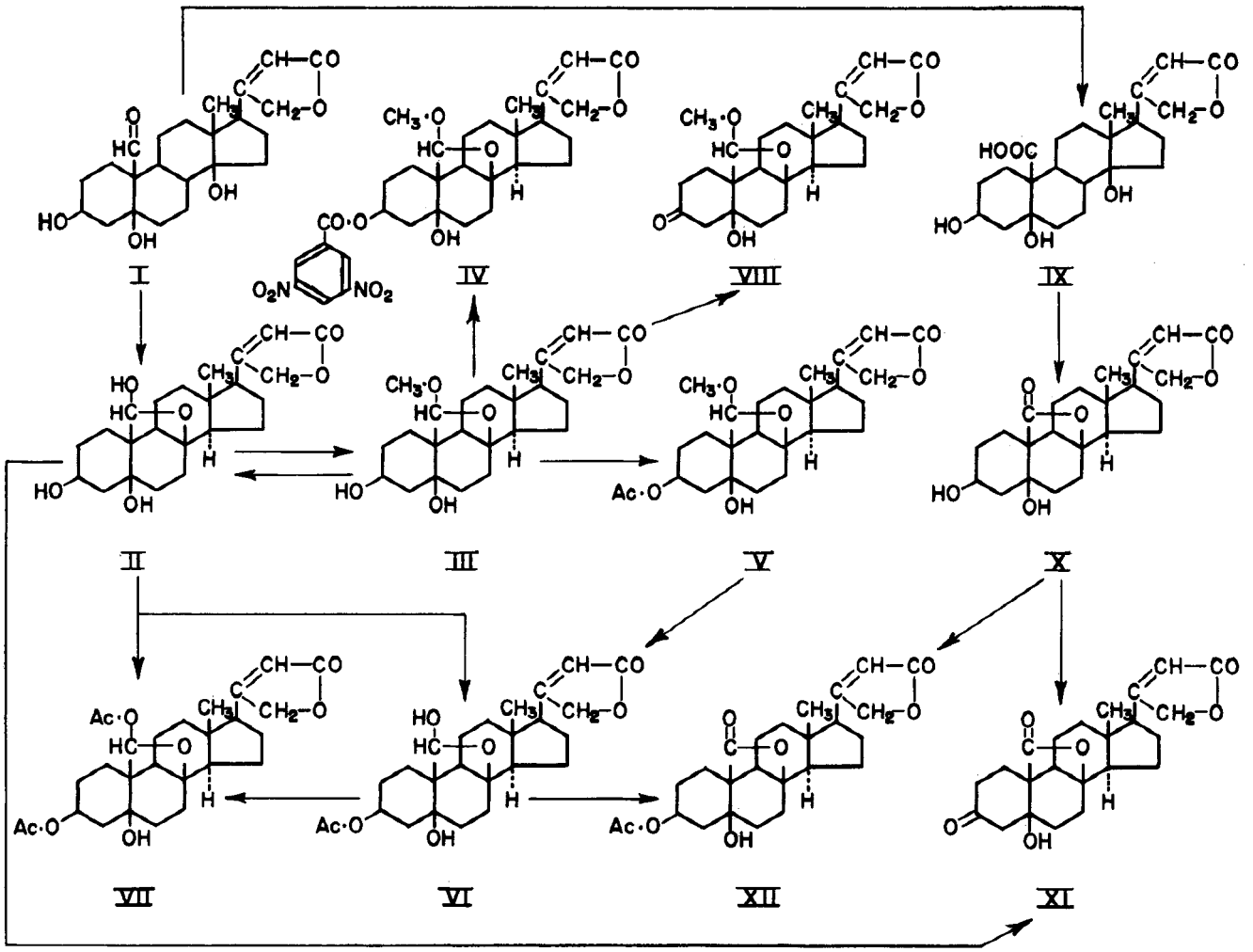
(4) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961).

(5) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **63**, 123 (1925).

(6) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corporation, New York, N. Y., 1949, pp. 523–524; *cf.* also L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 742–744.

(7) From a theoretical point of view, one may consider the existence of two epimeric forms in the series of the C-19 methyals. Only one form was isolated in the present instance.

(8) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **65**, 491 (1925).



true melting points are approximately 3° lower than those reported.

Absorption Spectra.—Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer.

Analyses.—Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide, 80°). The per cent loss of weight on drying is recorded.

Optical Rotation.—No correction for crystal solvent has been made. Unless stated otherwise, the sample was dissolved in chloroform to make 2 ml. of solution and the rotation was determined in a 2-dm. semimicrotube.

Pseudostrophanthidin (II) from Strophanthidin (I).—A solution of 15 g. of I (recrystallized from methanol–water, m.p. 147–160°) in 30 ml. of methanol was evaporated *in vacuo* to give a brittle foam to which 150 ml. of cold concentrated hydrochloric acid was added while cooling in an ice bath. The resulting solution was kept in the ice bath for 4 hr. and was then poured into 1200 ml. of ice–water yielding a white amorphous precipitate (a) which was filtered and washed with water giving the combined aqueous phase (b). The dried precipitate (a), wt., 7.423 g., was taken up in acetone[9] and the solution was evaporated to give a foam which was dissolved in 80 ml. of cold concentrated hydrochloric acid. The mixture was kept in an ice bath for 1 hr. and was then poured into 640 ml. of ice–water, yielding a precipitate (a1), dry wt., 3.883 g., which was filtered from the aqueous phase (a2). Immediately after its isolation, the aqueous phase (b) was extracted with one 500-ml. and six 250-ml. portions of ethyl acetate, and the combined extracts were washed successively with water, 0.5 *N* sodium carbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, evaporation to dryness gave 6.322 g. of a foam (bα). The aqueous phase (a2) was worked up in analogous fashion, yielding 3.006 g. of a foam (a2α). Fractions bα and a2α were combined and crystallized from 60% aqueous acetone yielding 5.654 g. of prisms, m.p. 154–158°. Further recrystallization from aqueous acetone gave 5.142 g. of prisms, m.p. 158–161°. The analytical sample, derived from a repeat experiment, had the m.p. 157–159°, $[\alpha]^{23}D$ +61.5°, $M^{23}D$ +248° (20.8 mg. in 2 ml. of chloroform containing 5 drops of methanol, α +1.28°) [lit.[5] m.p. softening between 123° and 127°, followed by frothing on further heating; $[\alpha]D$ +51° (alcohol)].

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.98. Found: C, 68.63; H, 8.05; wt. loss, 6.0.

Pseudostrophanthidin Methylal (III) from Pseudostrophanthidin (II).—To a solution of 1.000 g. of II, m.p. 156–158°, in 20 ml. of methanol was added 0.2 ml. of concentrated hydrochloric acid. The mixture was refluxed for 30 min. and, after the addition of 30 ml. of water and cooling, the resulting precipitate was collected and dried. Crystallization from methanol gave 0.947 g. of prisms, m.p. 220–226°. Subsequent recrystallization from ethyl acetate yielded plates, m.p. 225–228°. The analytical sample was recrystallized from acetone to yield needles, m.p. 233–235°, Legal test positive, $[\alpha]^{23}D$ +34.0°, $M^{23}D$ +142° (20.1 mg., α +0.68°), λ^{alc}_{max} 217 mμ (ϵ 17,300).

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 68.84; H, 8.28.

Reconversion of Pseudostrophanthidin Methylal (III) into Pseudostrophanthidin (II).—A solution of 20 mg. of III, m.p. 233–235°, in 2 ml. of 70% acetic acid was heated on a water bath (50–80°) for 50 min. and was then concentrated *in vacuo* to leave an oily residue which was dissolved in a small amount of acetone. On adding water, small needles were obtained, 13.9 mg., m.p. 150–152°. This product showed no depression of the melting point on admixture with an authentic sample of II, m.p. 157–159°. Furthermore, the two specimens yielded identical paper chromatograms (system: formamide–chloroform; reagent: *m*-dinitrobenzene, sodium hydroxide).

3,5-Dinitrobenzoate of Pseudostrophanthidin Methylal (IV).—To a solution of 100 mg. of III, m.p. 232–234°, in 1 ml. of pyridine

(9) At this point the use of methanol must be avoided because there is a tendency to form the methylal (III), due to the presence of traces of hydrochloric acid.

was added 200 mg. of 3,5-dinitrobenzoyl chloride and the mixture was allowed to stand at room temperature for 20 hr. After decomposing the excess reagent by the addition of ice, 10 ml. of 2 *N* hydrochloric acid was added and the reaction product was extracted with three 10-ml. portions of ethyl acetate. The combined extracts were washed successively with 10-ml. portions of *N* hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 123.9 mg. of a brittle foam was obtained which crystallized upon the addition of methanol, 76.5 mg. of plates, double m.p. 145–151° and 212–214° dec. After further recrystallization from methanol and drying in a vacuum desiccator, 62.5 mg. of plates resulted, m.p. 211–214° dec., $[\alpha]^{24}D$ +50.9°, $M^{24}D$ +312° (19.8 mg., α +1.01°).

Anal. Calcd. for $C_{31}H_{36}N_2O_{11}$ (612.61): C, 60.77; H, 5.92; N, 4.57. Found: C, 60.87; H, 6.08; N, 4.43.

Pseudostrophanthidin Methylal 3-Acetate (V) from Pseudostrophanthidin Methylal (III).—To 200 mg. of III, m.p. 232–234°, in 2 ml. of pyridine was added 2 ml. of acetic anhydride and the solution was kept at room temperature overnight. After adding ice, the mixture was extracted with ethyl acetate, and the extract was washed twice with 15 ml. of 2 *N* hydrochloric acid, twice with 15 ml. of 5% sodium bicarbonate, and then with 15-ml. portions of water and saturated aqueous sodium chloride. After drying over sodium sulfate and removing the solvent *in vacuo*, the crystalline residue (215.3 mg.) was recrystallized from methanol yielding 178.1 mg. of long prisms, m.p. 204–205°, Legal test positive, $[\alpha]^{23}D$ +50.0°, $M^{23}D$ +230°(20.1 mg., α +1.01°).

Anal. Calcd. for $C_{26}H_{36}O_7$ (460.55): C, 67.80; H, 7.88. Found: C, 68.01; H, 7.94.

Pseudostrophanthidin 3-Monoacetate (VI) from Pseudostrophanthidin Methylal 3-Acetate (V).—A solution of 130 mg. of V, m.p. 204–205°, in 13 ml. of 70% acetic acid was heated at 90° for 45 min. and was then evaporated to dryness *in vacuo*. The residue was completely freed from acetic acid by taking it up in benzene and evaporating the solvent. The resulting brittle foam was crystallized from acetone–hexane yielding 85.8 mg. of prisms, constant m.p. 226–228°, $[\alpha]^{26}D$ +74.5°, $M^{26}D$ +333° (19.20 mg., α +1.43°).

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Found: C, 67.38; H, 7.77; wt. loss, 0.14.

Pseudostrophanthidin 3,19-Diacetate (VII) from Pseudostrophanthidin Monoacetate (VI).—A solution of 50 mg. of VI, m.p. 224–228°, in 1 ml. of pyridine and 1 ml. of acetic anhydride was heated at 83–85° for 1 hr. After cooling, the mixture was treated with ice and was then extracted with two 15-ml. and three 10-ml. portions of ethyl acetate. The extract was washed successively with water, 5% hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, the solvent was removed *in vacuo*, and the oily residue, 53.6 mg., was crystallized from ethyl acetate, yielding 22.5 mg. of needles, m.p. 190–191°. Repeated recrystallization from acetone-hexane gave 18.7 mg. of needles, m.p. 193–194°, $[\alpha]^{24}D$ +81.4°, $M^{24}D$ +398° (11.8 mg., α +0.96°).[10]

Anal. Calcd. for $C_{27}H_{36}O_8$ (488.56): C, 66.38; H, 7.43. Found: C, 65.94; H, 7.52; wt. loss, 0.23.

Acetylation of Pseudostrophanthidin (II). Pseudostrophanthidin 3-Monoacetate (VI) and Pseudostrophanthidin 3,19-Diacetate (VII).—A solution of 300 mg. of II, m.p. 157–159°, in 3 ml. of pyridine and 3 ml. of acetic anhydride was kept at room temperature overnight. After the addition of ice and 15 ml. of 3 *N* hydrochloric acid, the mixture was extracted with five 20-ml. portions of ethyl acetate, and the extract was washed successively with 2 *N* hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 358 mg. of an oily residue resulted which resisted attempts at crystallization. Separation was achieved by chromatography on alumina. Benzene–chloroform, 9:1, eluted 126.3 mg. of material which on crystallization from ethyl acetate gave 60.0 mg. of needles, m.p. 179–180°. Repeated recrystallization from ethyl acetate and from acetone–hexane gave needles, constant m.p. 191–192°. There was no depression of the melting point on admixture with an authentic sample of pseudostrophanthidin 3,19-diacetate (VII). Benzene–chloroform, 4:1 and 1:1, eluted a total of 66.7 mg. of material which on repeated recrystallization did not furnish a uniform product. Elution with chloroform gave 126.9 mg. of material. Crystallization from acetone–hexane yielded 78.5 mg. of crystals, m.p. 216–218°. By repeated recrystallization the melting point was raised to 224–227°. The mixture melting point with an authentic sample of pseudostrophanthidin 3-monoacetate (VI) was not depressed.

3-Dehydropseudostrophanthidin Methylal (VIII) from Pseudostrophanthidin Methylal (III).—To 100 mg. of III, m.p. 233–235°, in 2 ml. of glacial acetic acid was gradually added 0.25 ml. of a solution of 33.3 mg. of chromium trioxide (approximately 100% excess) in 4 *N* sulfuric acid while cooling in an ice bath. After keeping the mixture in the ice bath for 15 min., it was diluted with 30 ml. of water and extracted with two 25-ml. portions of ethyl acetate. The extract was washed successively with water, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, evaporation of the solvent gave 103 mg. of a brittle foam which was crystallized from methanol to yield 63.1 mg. of prisms, m.p. 231–233°. Recrystallization from acetone did not alter the melting point, Legal test positive. The mixture melting point with the starting material (III, m.p. 233–235°) was 220–224°, $[\alpha]^{24}D$ +24.0°, $M^{24}D$ +100° (20.9 mg., α +0.50°).

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.50): C, 69.20; H, 7.74. Found: C, 68.93; H, 7.72; wt. loss, 0.97.

Strophanthidonic Acid 19:8-Lactone (XI). A. From Pseudostrophanthidin (II).—To 100 mg. of II, m.p. 155–159°, in 2 ml. of glacial acetic acid cooled in an ice bath was added 0.25 ml. of a solution of 33.3 mg. of chromium trioxide in 4 *N* sulfuric acid, and the mixture was kept in the ice bath for 20 min. This was followed by the addition of 30 ml. of water which caused the precipitation of lustrous leaflets. The reaction product was extracted with six 25-ml. portions of ethyl acetate and the extract was washed to neutrality as described in the preceding experiment. After drying over sodium sulfate and evaporating the solvent, 89 mg. of crystalline material resulted which was recrystallized from acetone yielding 42.5 mg. of prisms, m.p. 255–263° dec. Further recrystallization from methanol gave 38.3 mg. of prisms, decomposing gradually between 263° and 271° [lit.[8] m.p. 285° with effervescence, after preliminary softening], Legal test positive.

B. From Strophanthidinic Acid 19:8-Lactone (X).—To 100 mg. of X, m.p. 220–224° (effervescence,)[11] in 2 ml. of glacial acetic acid cooled in an ice bath was added 0.25 ml. of a solution of 33.3 mg. of chromium trioxide in 4 *N* sulfuric acid. The mixture was kept in the cold for 20 min. and was then worked up as described under A, furnishing a total of 81 mg. of crystalline material. The product was recrystallized from acetone and from ethanol, yielding 40.8 mg. of prisms, m.p. 269–273° dec., Legal test positive. When compared by paper chromatography in the system formamide–chloroform (reagent: *m*-dinitrobenzene), the products obtained by method A and B gave single spots in the same location.

Strophanthidinic Acid 19:8-Lactone 3-Acetate (XII). A. From Strophanthidinic Acid 19:8-Lactone (X).—A solution of 100 mg. of X, m.p. 220–224° (effervescence), in 1 ml. of pyridine and 1 ml. of acetic anhydride was kept at room temperature overnight. After the addition of ice, the mixture was extracted with four 15-ml. portions of ethyl acetate and the extract was washed successively with *N* hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 102.0 mg. of a crystalline residue, m.p. 245–247° dec., resulted. Recrystallization from methanol gave 76.6 mg. of needles, constant m.p. 265–267°, $[\alpha]^{24}D$ +111.0°, $M^{24}D$ +493° (20.1 mg., α +2.23°).

Anal. Calcd. for $C_{25}H_{32}O_7$ (444.51): C, 67.55; H, 7.26. Found: C, 67.81, 67.94[12]; H, 7.24, 7.19.[12]

B. From Pseudostrophanthidin 3-Monoacetate (VI).—To 20.1 mg. of VI, m.p. 221–223°, in 1 ml. of 90% acetic acid cooled in an ice bath was added 0.05 ml. of a solution of 6.66 mg. of chromium trioxide in 4 *N* sulfuric acid. The mixture was kept in the cold for 20 min. and was then diluted with 15 ml. of water

(10) Determination by Dr. Hiroyuki Ageta.

(11) $[\alpha]^{26}D$ +89.8°, $M^{26}D$ +361° (21.7 mg., α +1.95°). For preparation, *cf.* ref. 4, p. 1239.

(12) Analysis by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

and extracted with four 10-ml. portions of ethyl acetate. The extract was washed successively with water, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 19.7 mg. of crystalline material resulted. Recrystallization from methanol gave 14.9 mg. of needles, m.p. 266–268° dec. There was no depression of the melting point when mixed with the analytical sample, m.p. 265–267° dec., obtained by acetylation of X.

Investigations on Steroids. XXXVI. Conversion of Pseudostrophanthidin into 19-Hydroxy-8,19-epoxycortexone and 8-Hydroxy-19-norcortexone[1,2]

TOKUO KUBOTA[3] AND MAXIMILIAN EHRENSTEIN

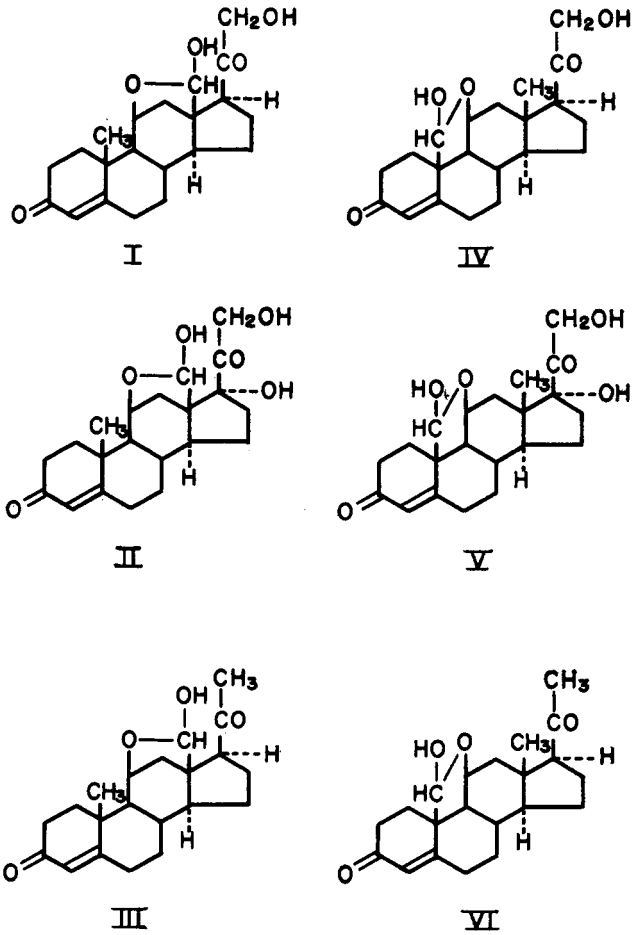
Division of Steroid Research, The John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Received June 14, 1963

The conversion of pseudostrophanthidin (VII) into a structural isomer of aldosterone, *viz.*, 19-hydroxy-8,19-epoxycortexone (XV), is reported. In this procedure VII was first subjected to ozonization, yielding the amorphous 3β,5,19,21-tetrahydroxy-8,19-epoxy-5β-pregnan-20-one (VIII); this was converted into the crystalline methylal (IX) which was characterized as the 3,21-diacetate (X). Selective oxidation of IX with N-bromoacetamide gave 5,21-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (XI) which by demethylation was converted into 5,19,21-trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (XII). Dehydration of XI yielded 19-methoxy-8,19-epoxycortexone (XIII) which was transformed into XV by demethylation. Acetylation of XIII gave 19-methoxy-8,19-epoxycortexone 21-acetate (XIV) which was demethylated to yield 19-hydroxy-8,19-epoxycortexone 21-monoacetate (XVI). Oxidation of XVI with chromic acid gave 19:8-lactocortexone acetate (XVII) which had been described previously. This conversion lends support, especially, to the structures proposed for XIII, XIV, XV, and XVI. The conversion of XI into XIII was associated with an abnormal levorotatory shift, and the products derived from XIII, *i.e.*, XIV, XV, and XVI, show this unexpected feature of optical rotation. On treating either XII or XV with mild alkali, conversion occurred into 8-hydroxy-19-norcortexone (XVIII) which was characterized as the 21-acetate (XIX). Compound XVIII appears to be the first 8-hydroxy analog of a steroid hormone ever prepared.[15c] 19-Hydroxy-8,19-epoxycortexone (XV) produced no mineralocorticoid effects and was found to be inactive as a cortexone inhibitor. 8-Hydroxy-19-norcortexone (XVIII) caused sodium retention of a low order.

Recent investigations in a number of laboratories have opened pathways for the introduction of a functional group at the angular carbon atom 18. Outstanding in this respect is the photolytic approach of Barton and co-workers which resulted in a partial synthesis of aldosterone and of a number of structurally related 3-oxo-Δ^4 steroids. In these synthetic products, we find the C-18:C-11β oxygen bridge present as a lactone, hemiacetal, or ether grouping. By variation of the side chain at carbon atom 17, steroids with the ketol, dihydroxyacetone, and methyl ketone groupings have been prepared. Among the compounds of especial interest may be listed aldosterone (I),[4,5] 17α-hydroxyaldosterone (II),[5] and 21-desoxyaldosterone (III).[6,7]

The photolytic procedure of Barton, as it is applied to an 11β nitrite, not only permits the functionalization of the angular carbon atom 18, but it also results in a functionalization of carbon atom 19. Hence a number of steroids have become available which have a C-19:C-11β, rather than a C-18:C-11β oxygen



(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) from the National Cancer Institute of the National Institutes of Health.

(2) The essential findings of this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein, "Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was reported by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961).

(5) D. H. R. Barton and J. M. Beaton, *ibid.*, **84**, 199 (1962).

(6) R. H. Hesse, H. Kohler, and M. M. Pechet, Abstracts, Division of Biological Chemistry, 141st National Meeting of the American Chemical Society, Washington, D. C., 1962, pp. 22C–23C.

(7) *Cf.* also, K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **45**, 347 (1962).