5α,6β-Dibromo-3β-cholestanyl acetate was prepared according to the general procedure using HBr. From 4.29 g. of cholesteryl acetate there was obtained 4.8 g. of the ordinary cholesteryl acetate dibromide, m.p. 114.5–118°, mixed with an authentic specimen (m.p. 114–116°), m.p. 114–116°.

5α-Bromo-6β-chloro-3-cholestanone.—To a suspension of 5.00 g. of 5α-bromo-6β-chloro-3β-cholestanol in 125 ml. of glacial acetic acid was added a solution of 1.25 g. of chromium trioxide in 2.5 ml. of water and the mixture was warmed at 55° for one hour with occasional stirring. A large excess of water was added, causing crystallization. The crystals were collected on a buchner funnel, washed with water and methanol and air-dried. The product weighed 4.5 g., m.p. 61.5° dec. After recrystallization *in the cold* from chloroform–methanol, the product had m.p. 64.5° dec. A sample was dried for microanalysis for two hours at room temperature *in vacuo* over P_2O_5; $[\alpha]^{23}D$ −45°, [M]D −225°.

Anal. Calcd. for $C_{27}H_{44}OBrCl$: Br + Cl, 23.08. Found: Br + Cl, 23.08.

The melting point of a mixture of this substance with crude 5α,6β-dibromo-3-cholestanone (m.p. 69–70° dec.) was 64–65° dec.

Dehydrohalogenation of 5α-Bromo-6β-chloro-3-cholestanone.—A mixture of 3.00 g. of bromochlorocholestanone, 3.6 g. of anhydrous sodium acetate and 150 ml. of anhydrous ethanol was refluxed for one hour. The supernatant liquid was decanted from the inorganic salt precipitate and water was added to the hot solution to cloudiness. The solution was then cooled under the tap and the crystals were collected on a buchner funnel, washed with a little methanol and air-dried. The crude product so obtained weighed 2.39 g., m.p. 120–124°. After recrystallization from ethyl acetate–methanol in the cold, 1.28 g. of 6β-chloro-4-cholestene-3-one was obtained, fine white crystals, m.p. 128–129°. Vigorous effervescence began at 170°. Recrystallization from the same solvent did not alter the melting point. A sample was dried for microanalysis for two hours at room temperature *in vacuo* over P_2O_5; $[\alpha]^{23}D$ +13°; λ_{max} 241 mμ, ϵ_{max} 11,805 (alc.) [lit.[4] m.p. 129–130° dec.; $[\alpha]D$ +14°, +17°, λ_{max} 241 mμ, ϵ_{max} 15,100 (alc.)].

Anal. Calcd. for $C_{27}H_{43}OCl$: Cl, 8.46. Found: Cl, 8.83, 9.06.

A mixture of another preparation of this substance (m.p. 129–131°) with authentic 6β-chloro-4-cholestene-3-one[4] (m.p. 125–126°) had m.p. 128–130°.

The salt residue from the dehydrohalogenation reaction mixture was combined with the aqueous alcoholic mother liquor from the organic reaction product and the whole was concentrated to small volume *in vacuo*, precipitating a trace of organic matter. The mixture was treated with Norit and filtered. Qualitative tests[10] demonstrated the presence of large amounts of bromide ion but no chloride ion in the filtrate.

6β-Chloro-4-cholestene-3-one.—This substance was prepared according to the procedure of Barton and Miller.[4] After three recrystallizations from ethyl acetate–methanol, the fine, white crystals had m.p. 125–126°. At 200° the melt was pale brown in color with only slight effervescence.

6β-Bromo-4-cholestene-3-one.—This substance was prepared according to the procedure of Dane, *et al.*[11] It has been synthesized by Barton and Miller[1] by a different method.

After recrystallization from ethyl acetate–methanol, the substance had m.p. 129–130°. At about 140° the melt turned blue-black with vigorous effervescence. A mixture of this material with the 6β-chloro-4-cholestene-3-one just described had m.p. 128–133°.

5β,6α-Dibromo-3β-coprostanyl Acetate.—This substance was prepared by acetylation of the corresponding alcohol[1] with acetic anhydride in glacial acetic acid–perchloric acid according to the procedure described above for the acetylation of 5α-bromo-6β-chloro-3β-cholestanol.

From 0.8 g. of the alcohol there was obtained, after recrystallization from ethyl acetate-methanol, 0.67 g. of product in the form of stout, rod-like prisms, m.p. 97–100°. The analytical sample was dried for three hours at 57° *in vacuo* over P_2O_5; $[\alpha]^{24}D$ +36°, [M]D +212°.

Anal. Calcd. for $C_{29}H_{48}O_2Br_2$: C, 59.18; H, 8.22; Br, 27.16. Found: C, 59.27; H, 8.18; Br, 27.32.

(10) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 116.

(11) E. Dane, Y. Wang and W. Schulte, *Z. physiol. Chem.*, **245**, 80 (1936).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

The Transformation of Manogenin to Hecogenin[1]

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RECEIVED APRIL 10, 1952

The transformation of manogenin to Δ^2-22-isoallospirostene-12-one and thence to hecogenin is described.

The isolation of hecogenin from various *Agaves* (*e.g.*, *Agave toumeyana*) generally requires separation from a companion genin manogenin (I), wherein the latter is often present to the major extent.[2] Manogenin isolated by chromatographic methods is very difficult to separate from Δ^9-dehydromanogenin (Ia) which is present with it.[3] In order to obviate complications which would otherwise attend transformation reactions performed on such a mixture as well as to utilize as nearly as possible the total manogenin fraction involved, this mixture was converted by sodium–butanol reduction to the saturated triol, agavogenin (II). The latter in the form of its 2,3-dihemisuccinate derivative (III) was oxidized at position 12 with chromic acid followed by saponification to manogenin (I) in good over-all yield. It was subsequently ascertained that manogenin thus obtained was contaminated with varying amounts of gitogenin (Ib) which, nonetheless, could be easily and completely separated at a later stage (see below).

Manogenin free of Δ^9-dehydromanogenin and containing some gitogenin, was converted in high yield to the dimesylate derivative (IV) from which manogenin dimesylate could be obtained without

(1) Presented in part before the American Chemical Society Meeting-in-Miniature, Newark, N. J., January 28, 1952.

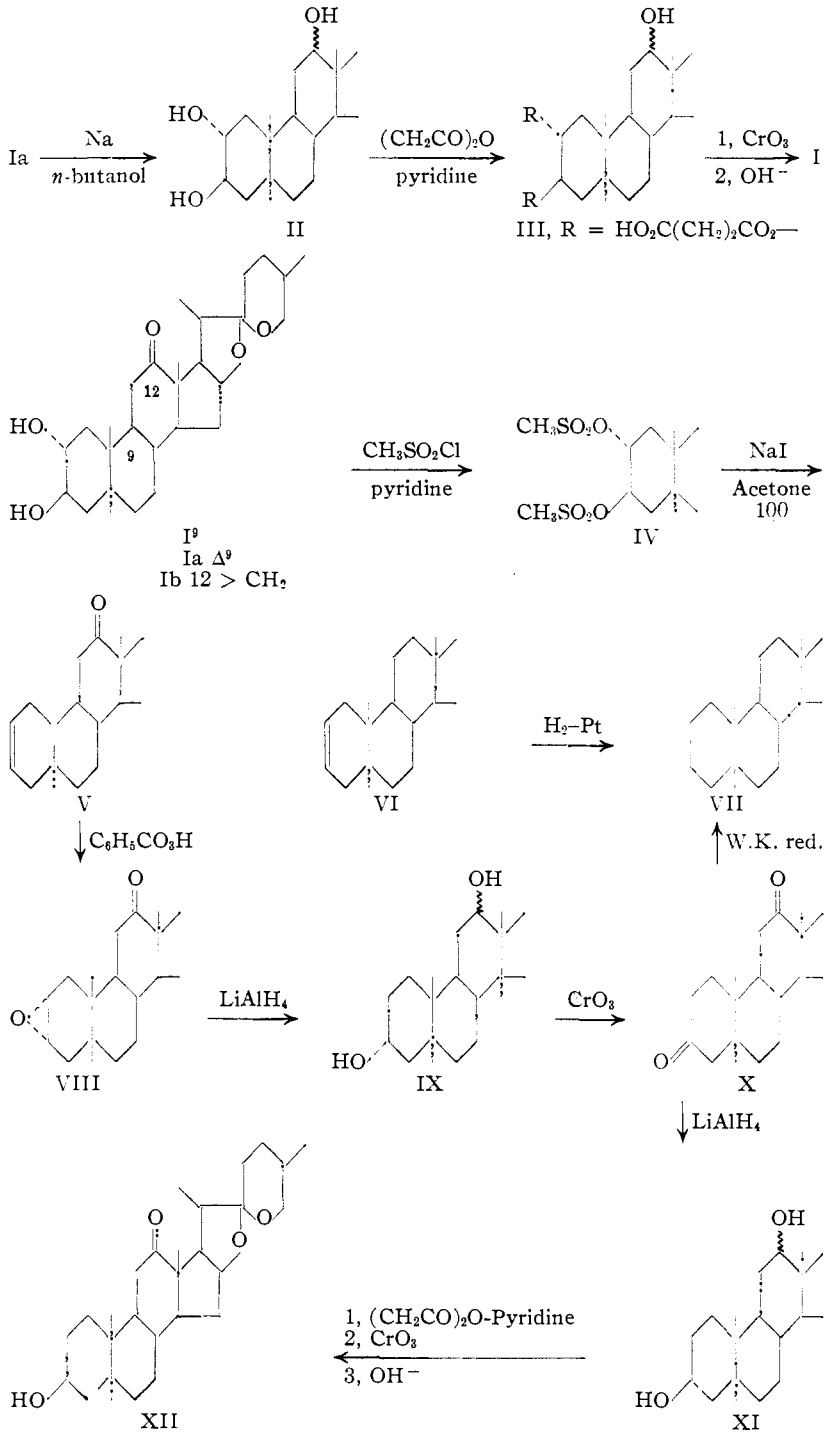
(2) Dr. J. W. Rothrock of these laboratories, to whom we are indebted for our supply of manogenin, has found the ratio of manogenin to hecogenin isolated from many samples of *Agave toumeyana* to average *ca.* 60:40, respectively.

(3) R. B. Wagner, R. F. Forker and P. F. Spitzer (THIS JOURNAL, **73**, 2494 (1951)) have isolated Δ^9-dehydromanogenin by chromatography of manogenin fractions isolated from *Agave huachucensis*. These authors have estimated by ultraviolet absorption measurements that the content of Δ^9-dehydromanogenin in manogenin fractions isolated from various *Agaves* to range from 20–80%. Our own observation, made with certain manogenin fractions isolated from *Agave toumeyana*, indicated a content of Δ^9-dehydromanogenin in the order of 40–50%.

difficulty in analytically pure form by recrystallization from acetone. Treatment of crude IV with sodium iodide in acetone[4] at 100° for 18–20 hours afforded Δ^2-22-isoallospirostene-12-one (V) in good yield mixed with varying amounts of VI. The two olefins V and VI could be separated easily and completely by chromatography. The appearance of VI was due to the presence of gitogenin (Ib) in the original manogenin mixture. Confirmation of the structure of VI was obtained by hydrogenation to the same 22-isoallospirostane (VII)[7] as that obtained by the Wolff–Kishner reduction of hecogenone (X).[5]

Δ^2-22-Isoallospirostene-12-one (V) was converted with perbenzoic acid to the crystalline 2(α),3(α)-epoxide (VIII).[6] The latter was reduced with lithium aluminum hydride to the 3(α),12-diol (IX) which, without isolation, was oxidized with chromic acid to hecogenone (X). Hecogenone obtained in this manner was found to be identical in all respects with hecogenone prepared by the oxidation of hecogenin.[7]

Hecogenone was reduced with lithium aluminum hydride to the 3(β),12-diol (XI)[8] and this in turn was converted without purification to its 3-hemisuccinate derivative; the latter was oxidized with chromic acid at position 12 and subsequently hydrolyzed to hecogenin (XII) in good over-all yield. Hecogenin obtained from this sequence of reactions as well as its acetate derivative were identical in all respects with authentic specimens.



The configurational relationship of the hydroxyl groups of manogenin (see footnote 9) and the stereochemical limitations arising in the elimination reaction will be reported in a forthcoming paper.

Experimental

Agavogenin (II) from Crude Manogenin Fractions.[2]—Crude manogenin containing 40–50% of Δ^9-dehydromanogenin and varying amounts of gitogenin, 37.5 g., was dissolved in 3 l. of refluxing butanol and 75 g. of sodium was added portionwise as rapidly as possible. When all the sodium had reacted (*ca.* 1–2 hours), part of the butanol was removed *in vacuo*, and the remaining butanol removed by

(4) This method has been employed in the sugar series for the production of acyclic olefins. See R. S. Tipson and L. H. Cretcher, *J. Org. Chem.*, **8**, 95 (1943); R. M. Hann, A. T. Ness and C. S. Hudson, THIS JOURNAL, **66**, 73 (1944); P. Karrer, E. Schick and R. Schwyzer, *Helv. Chim. Acta*, **31**, 784 (1948); P. Bladon and L. N. Owen, *J. Chem. Soc.*, 598 (1950).

(5) Since the completion of this work, J. Pataki, G. Rosenkranz and C. Djerassi (THIS JOURNAL, **73**, 5375 (1951)) have reported the preparation of (VI) by treatment of tigogenin *p*-toluenesulfonate with collidine.

(6) The work of A. Fürst and P. A. Plattner (*Helv. chim. Acta*, **32**, 275 (1949)) leaves little doubt that the oxides formed from the epoxidation of Δ^2-*allo*-steroid olefins are configurationally 2(α),3(α). See also ref. 5.

(7) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

(8) It has been demonstrated by C. W. Shoppee and G. H. R. Summers (*J. Chem. Soc.*, 687 (1950)) that 3-keto allosteroids are reduced by lithium aluminum hydride to yield preponderantly (90%) the 3-β-hydroxy epimer.

co-distillation with water. Water was added and the product was collected and washed alkali free on a filter. The dried, crude product amounted to 35.6 g. Two crystallizations from chloroform–ethyl acetate afforded feathery needles of m.p. 240–242°,[9,10] no maximum in the 2400 Å. region.

Anal. Calcd. for $C_{35}H_{44}O_5$: C, 72.27; H, 9.88. Found: C, 72.15; H, 9.87.

The triacetate was prepared by refluxing the triol with acetic anhydride for 1 hour. The product was crystallized twice from methanol, m.p. 221–227°.

Anal. Calcd. for $C_{35}H_{50}O_8$: C, 68.96; H, 8.77. Found: C, 68.48; H, 8.96.

Agavogenin Bis-hemisuccinate (III).—Crude agavogenin obtained directly from the above reduction, 35.5 g., was dissolved in 300 ml. of anhydrous pyridine and treated with 48 g. of succinic anhydride. The reaction mixture was heated at 100° for three hours in an atmosphere of nitrogen. The reaction was cooled and the pyridine was removed *in vacuo* and the residue was shaken with water and chloroform. The aqueous layer was extracted three times with chloroform and the combined organic extracts were washed with 2.5 *N* hydrochloric acid, water, saturated salt solution and finally dried over sodium sulfate. Removal of the solvent *in vacuo* afforded 53 g. of product (III) which was used without further purification in the next step.

Manogenin from Crude Agavogenin Bis-hemisuccinate.—The crude bis-hemisuccinate (III above), 53 g., was dissolved in 500 ml. of acetic acid and oxidized for 16 hr. at room temperature with 5.87 g. of chromic anhydride dissolved in 30 ml. of 30% aqueous acetic acid. The excess oxidizing agent was destroyed by methanol, the solution was concentrated to a small volume *in vacuo*, and water was added. The product was extracted with chloroform–ether and washed with dilute sulfuric acid, water, saturated salt solution, and dried over sodium sulfate. After removal of the solvents *in vacuo*, the residue, 47 g. was dissolved in 1 l. of methanol containing 100 ml. of water and 100 g. of potassium hydroxide. The solution was refluxed for four hours. The methanol was removed *in vacuo* and water was added. The product was extracted with chloroform–ether and the organic extract washed until neutral with water finally with saturated salt solution, and ether–chloroform solution of the product dried over sodium sulfate. Removal of the solvent and crystallization from chloroform–ethyl acetate afforded 20.5 g. of manogenin, m.p. 254–257°, containing some gitogenin.

Manogenin Dimesylate (IV).—A solution of 20 g. of manogenin obtained above was dissolved in 200 ml. of pyridine, cooled to 0–5° and treated with 20 ml. of methanesulfonyl chloride. After standing at 0–5° for 16 hours the reaction mixture was poured with stirring onto ice-water. The crystalline product was filtered, washed with water, dried *in vacuo* and crystallized from acetone–water to afford 21.7 g. of material which was not purified further for subsequent transformation.

A sample for analysis was recrystallized three times from acetone to give manogenin dimesylate as long slender needles, m.p. 241° dec., $[\alpha]^{24.5}D$ −44.2 (chf.).

Anal. Calcd. for $C_{29}H_{46}O_9S_2$: C, 57.81; H, 7.64; S, 10.63. Found: C, 58.03; H, 7.61; S, 11.00.

Δ^2-22-Isoallospirostene-12-one (V).—A solution of 6.1 g. of crude manogenin dimesylate, m.p. 239° dec., in 250 ml. of dry acetone containing 15.25 g. of sodium iodide was heated at 100° for 24 hr. in a glass-lined autoclave. The sodium methanesulfonate formed in the reaction was filtered off and washed with ether and chloroform. The combined organic extracts were concentrated *in vacuo*, diluted with chloroform and ether, washed with 5% aqueous sodium thiosulfate, water, and dried over sodium sulfate. The residue, after removal of the solvents *in vacuo*, was crystallized from acetone affording needles, m.p. 173–175°; wt. 2.55 g. An additional 1.2 g. of material of somewhat higher melting point was obtained from the mother liquors. The material of m.p. 173–175°, 2.0 g., was dissolved in petroleum ether and chromatographed on 100 g. of acid washed alumina, elution being effected with 1 l. of petroleum ether followed by petroleum ether–benzene mixtures. The crystalline material corresponding to 20 through 50% benzene–petroleum ether was crystallized from acetone–water to afford 800 mg. of Δ^2-isoallospirostene-12-one as mica-like plates, m.p. 199–200°, $[\alpha]^{24.5}D$ +39.1 (chf.).

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.54; H, 9.75.

This same olefin was also obtained directly from hecogenin mesylate, on treatment with sodium iodide in acetone at 100° for 24 hr. The two samples showed no depression on admixture. **Hecogenin mesylate** was prepared in the same manner as manogenin dimesylate. It had a m.p. of 178° dec.

Anal. Calcd. for $C_{28}H_{44}O_6S$: C, 66.14; H, 8.66. Found: C, 66.58; H, 8.89.

Δ^2-22-Isoallospirostene (VI).—The crystalline material from the petroleum ether eluates in the chromatographic isolation of Δ^2-22-isoallospirostene-12-one (see above) was crystallized from acetone to afford Δ^2-22-isoallospirostene as needles, m.p. 186–187°; wt. 950 mg. This substance gave a yellow color with tetranitromethane and did not exhibit a carbonyl band in the infrared.

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.55; H, 10.79.

22-Isoallospirostane (VII).[7]—In a 100-ml. flask equipped with a thermometer and condenser were placed 500 mg. of hecogenone (m.p. 239–241°), 6.0 g. of potassium hydroxide, 60 ml. of ethylene glycol and 0.6 ml. of 85% hydrazine hydrate. The reaction mixture was heated cautiously to 140° and held at this temperature for one hour after the condenser was removed, the temperature was raised to 190–195° for one hour and a slow stream of nitrogen was passed over the surface of the liquid. The reaction mixture was poured into water and the precipitate washed free of alkali with water and dried *in vacuo;* wt. 350 mg. Two crystallizations from acetone afforded 22-isoallospirostane as plates of m.p. 173–174°, $[\alpha]^{24.5}D$ −61.8 (chf.).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.87; H, 11.10.

(b).—A solution of 200 mg. of Δ^2-22-isoallospirostene, in 15 ml. of ethyl acetate and 50 mg. of Adams catalyst was hydrogenated. The hydrogenation stopped abruptly after the uptake of 1 mole of hydrogen. The mixture was filtered and evaporated *in vacuo*. Crystallization of the residue from acetone gave 22-isoallospirostane as plates, m.p. 173–174°. The mixed m.p. with an authentic sample (see above) was not depressed.

2(α),3(α)-Oxido-22-isoallospirostane-12-one (VIII).—To a solution of 1 g. of Δ^2-22-isoallospirostene-12-one (V), in 15 ml. of benzene at 5° was added 5 ml. of benzene containing 0.3 g. of perbenzoic acid. The mixture was kept at *ca.* 5° for 24 hours; at the end of this time titration indicated complete reaction. The reaction mixture was diluted with 100 ml. of ether and washed free of peroxide with cold aqueous 5% soda solution. After washing with water and drying over sodium sulfate, the solvents were removed *in vacuo* to yield 1.1 g. of crude epoxide. This material was used directly without further purification in the succeeding step. From a similar preparation the crude epoxide was chromatographed on basic (Merck) alumina and the crystalline material, after two crystallizations from ether, melted at 210–213°; $[\alpha]^{25}D$ +22 (chf.).

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.70; H, 9.35. Found: C, 76.02; H, 9.35.

Hecogenone (X).—A solution of 1.1 g. of crude epoxide (VIII) in 20 ml. of benzene was diluted with 40 ml. of dry ether and added dropwise to a vigorously stirred solution of lithium aluminum hydride, 400 mg., in 100 ml. of dry ether. The reaction mixture was stirred at room temperature for 45 minutes and then refluxed for 10 minutes. The excess hydride was decomposed with water and dilute hydrochloric acid was added to dissolve the aluminum salts. The aqueous layer was separated and extracted with ether. The combined ether extracts were washed free of acid with water and saturated salt solution and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the crude 3(α),12-diol (IX); wt. 1.05 g. This material was dissolved in 20 ml. of acetic acid and oxidized at room temperature overnight

(9) The 2α,3β orientation of the hydroxyl groups in manogenin is derived from work which will be reported in a forthcoming paper. With regard to a similar assignment in related 2,3-dihydroxylated genins see ref. 5.

(10) Marker, *et al.* ref. 9, report a m.p. 240–242° for this substance.

with 358 mg. of chromic anhydride in 15 ml. of 80% aqueous acetic acid. After the excess oxidizing agent had been destroyed with methanol the mixture was concentrated *in vacuo* and water was added. The product was extracted with ether–chloroform and the organic solution washed with 5% aqueous sodium hydroxide and finally water. The solution was dried over sodium sulfate and evaporated to a small volume to afford 350 mg. of hecogenone. The m.p. and mixed m.p. of this material with authentic hecogenone prepared by chromic anhydride oxidation of hecogenin was 238–241°. The infrared spectra of both samples were identical in all respects; $[\alpha]^{24.5}D$ +23.8° (chf.).

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.70; H, 9.35. Found: C, 75.44; H, 9.09.

An additional 200 mg. of hecogenone was obtained from the mother liquors, giving a total yield of 550 mg.

Hecogenin (XII).—A solution of 1.7 g. of hecogenone in 75 ml. of anhydrous tetrahydrofuran was added to a well-stirred solution of 1.5 g. of lithium aluminum hydride in 100 ml. of dry ether. After the mixture had stirred at room temperature for two hours, water and dilute hydrochloric acid were added and the aqueous layer was separated. The aqueous layer was concentrated *in vacuo* to remove the tetrahydrofuran and then extracted with chloroform. The combined organic extracts were washed with water, saturated salt solution, dried and evaporated to give crude XI which was employed as such in the next step.

The crude reduction product (XI) was dissolved in 20 ml. of anhydrous pyridine containing 3.0 g. of succinic anhydride and heated on a steam-bath for 3 hr. in an atmosphere of nitrogen. After the reaction mixture had been concentrated *in vacuo*, water was added and the product was extracted with chloroform and ether. The organic layer was washed with dilute hydrochloric acid, water, saturated salt solution, and finally dried over sodium sulfate. The solvents were evaporated *in vacuo* to give 2.4 g. of the crude 3-hemisuccinate derivative of (XI) which was employed without further purification in the succeeding step.

The above hemisuccinate derivative, 2.4 g., was dissolved in 50 ml. of acetic acid and oxidized at room temperature for 16 hr. with 350 mg. of chromic anhydride in 10 ml. of 80% aqueous acetic acid. The oxidation product was worked up as previously described (see above) to give *ca.* 2.16 g. of crude hecogenin hemisuccinate. Saponification of the latter was effected directly by dissolving it in 75 ml. of methanol containing 4.0 g. of potassium hydroxide and refluxing for 4 hours in an atmosphere of nitrogen. The methanol was removed *in vacuo*, water was added, and the product extracted with chloroform. The chloroform extract was washed with water, saturated salt solution, and dried over sodium sulfate. The residue obtained on removal of the solvent was crystallized from chloroform–ethyl acetate to yield hecogenin as small plates, m.p. 263–266°. A mixed m.p. of this material with an authentic sample was 263–266°; wt. 350 mg. An additional 300 mg. of somewhat lower melting material was obtained from the mother liquors; $[\alpha]^{24.5}D$ +13.5° (chf.).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.35; H, 9.77. Found: C, 75.48; H, 9.94.

The acetate was prepared and crystallized from chloroform–ethyl acetate, m.p. and mixed m.p. with authentic hecogenin acetate was 247–50°, $[\alpha]^{24.5}D$ +92° (chf.).

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.73; H, 9.37. Found: C, 73.52; H, 9.32.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. X. Some 1,3-Oxazolo(5,4-d)pyrimidines

BY ELVIRA A. FALCO, GERTRUDE B. ELION, ELIZABETH BURGI AND GEORGE H. HITCHINGS

RECEIVED MAY 1, 1952

A series of 1,3-oxazolo(5,4-d)pyrimidines has been prepared by treatment of 5-amido-4-hydroxypyrimidines with phosphoryl chloride. With a 5-amido-6-amino-4-hydroxypyrimidine both a purine and an oxazolopyrimidine usually are formed. The relative proportion of the oxazolopyrimidine is increased when a reagent prepared by mixing water with the phosphoryl chloride is used for the cyclization. The latter reagent is superior to phosphoryl chloride in the formation of some other oxazolopyrimidines. The conversion of representative oxazolopyrimidines to purines by heating with amines could be demonstrated. The ultraviolet absorption spectra of the oxazolopyrimidines aid in the differentiation of these substances from certain oxazinopyrimidines previously described.

The preparation and study of some 1,3-oxazolo-5,4-d)pyrimidines in this Laboratory were undertaken for several reasons. Derivatives of condensed pyrimidine systems bearing functional groups in the pyrimidine ring analogous to those of the natural purines are of interest as antimetabolites,[1,2] as are the 5-mono- and 5,7-diamino derivatives.[3] Furthermore, certain derivatives were desired for comparison with the isomeric *p*-oxazino(2,3-d)pyrimidines,[4] to add support to the assignment of the structure of the latter through the elimination of a possible alternative formulation.[4]

Several 1,3-oxazolo(5,4-d)pyrimidines have been reported in the literature. Biltz[5] prepared some acyl and alkyl derivatives of 5,7-dihydroxy-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine by heating uramil and 1-methyluramil with an excess of benzoyl chloride. It appeared possible that the desired derivatives could be obtained by chlorination of the dihydroxy derivative followed by various transformation reactions analogous to those employed by Fischer in the purine series.[6] However, in several attempts a satisfactory preparation of the 5,7-dichloro-2-phenyl-1,3-oxazolo(5,4-d)pyrimidine from the dihydroxy derivative could not be achieved.

Attention was then turned to the method of preparation of Johnson,[7] which involved cyclization of a 5-amido-4-hydroxypyrimidine by treatment with phosphoryl chloride. The only oxazolopyrimidine prepared by Johnson, 5-ethylmercapto-2-phenyloxazolo(5,4-d)pyrimidine, was found unsatisfactory for the present purposes. When it was heated with alcoholic ammonia solution, it was recovered unchanged at temperatures below 170°,

(1) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).

(2) G. B. Elion, G. H. Hitchings and H. VanderWerff, *ibid.*, **192**, 505 (1951).

(3) G. H. Hitchings, G. B. Elion, H. VanderWerff and E. A. Falco, *ibid.*, **174**, 765 (1948).

(4) P. B. Russell, G. B. Elion and G. H. Hitchings, THIS JOURNAL, **71**, 474 (1949).

(5) H. Biltz, K. Strufe and J. Karte, *Ann.*, **404**, 180 (1914).

(6) E. Fischer, *Ber.*, **30**, 2226 (1897).

(7) T. B. Johnson, *Am. Chem. J.*, **34**, 191 (1905).