Anal. Calcd. for methyl *O*-methyl-*O*-methylenerhamnoside, $C_7H_{10}O_3(OCH_3)_2$: OMe, 30.4. Found: OMe, 28.5.

Hydrolysis of this material for one hour gave a partially crystalline material which was dissolved in water, and the solution extracted continuously with ether. Evaporation of the residual aqueous solution gave a sirup (25 mg.) with $[\alpha]_D$ +24° (*c* 1.0) and R_g 0.66. After reaction with ethanolic aniline, it yielded *N*-phenyl-L-rhamnosylamine 2-methyl ether, m.p. and mixed m.p. 150° (from ether). The ethereal extract gave crystalline **5-*O*-methyl-2,3-*O*-methylene-L-rhamnose (XIII)** (130 mg.), which after recrystallization from cyclohexane had m.p. 77–79° and $[\alpha]_D$ +6.4° (init. value, *c* 1.4) → +4.5° (46 hours, equil. value).

Anal. Calcd. for $C_7H_{11}O_4(OCH_3)$: C, 50.5; H, 7.4; OMe, 16.3. Found: C, 50.2; H, 7.4; OMe, 16.3.

Prolonged heating of this compound in *N* sulfuric acid at 100° failed to remove the methylene group. It was therefore oxidized with bromine water for 3 days, and after the usual treatment yielded a crystalline product. Recrystallization from chloroform–light petroleum afforded **5-*O*-methyl-L-rhamnono-γ-lactone** as colorless stubby needles, m.p. 164–166°, $[\alpha]_D$ −36 ± 4° (10 min., showing no significant change in 60 hours; *c* 0.6).

Anal. Calcd. for $C_6H_9O_4(OCH_3)$: C, 47.7; H, 6.8; OMe, 17.6. Found: C, 47.7; H, 6.6; OMe, 16.5.

The lactone (10 mg.) in water (5 cc.) required 5.58 cc. of 0.01 *N* sodium hydroxide for neutralization (screened methyl red), hence equiv. wt. 179 (equiv. wt. of $C_7H_{12}O_5$, 176).

Oxidation of this sodium salt with sodium metaperiodate failed to give any detectable acetaldehyde.[18]

One of us (P.A.) thanks the Directors of Monsanto Chemicals Ltd. for the award of a Fellowship.

(18) B. H. Nicolet and L. A. Shinn, THIS JOURNAL, **63**, 1456 (1941).

BRISTOL, ENGLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE RICE INSTITUTE]

Ouabagenin. II. The Hydroxyl Groups of the A/B Ring System[1]

BY R. P. A. SNEEDEN AND RICHARD B. TURNER

RECEIVED JULY 19, 1954

Of the eight oxygen atoms of the cardiac aglycone, ouabagenin, two are accounted for by an α,β-unsaturated lactone side chain, and one by a tertiary hydroxyl group at C_{14}. The remaining five oxygen functions are all present as hydroxyl groups, of which four can be acetylated by the use of acetic anhydride and pyridine. Selective oxidation of 20,21-dihydroöuabagenin with platinum and oxygen, followed by treatment with base, results in aromatization of ring A with the simultaneous loss of an angular hydroxymethyl group as formaldehyde. Methylation of the phenolic product thus formed yields a phenolic methyl ether, which on subsequent dehydration and rearrangement furnishes a compound possessing typical β-methoxynaphthalenoid absorption in the ultraviolet. Interpretation of these conversions permits assignment of hydroxyl groups at C_1, C_3, C_5 and C_{19} in ouabagenin.

In 1942, Mannich and Siewert[2] suggested structure I[3] for the cardiac glycoside, ouabain. This proposal was based upon the following observations. Ouabain gives a positive Legal test and is converted into an iso compound by the action of methanolic potassium hydroxide.[4] Such behavior suggests that ouabain, like other members of the heart poison group, possesses an α,β-butenolide side chain at C_{17} and a tertiary hydroxyl group at C_{14}, conclusions that have been amply verified by the ultraviolet absorption measurements and degradative studies of Reichstein and his associates.[5,6] On acetolysis, the tetrahydro derivative of heptaacetylanhydroouabain undergoes aromatization with loss of a carbon atom as formaldehyde.[4] This change has been interpreted by Fieser and Newman[7] as evidence for the presence of a hydroxymethyl group at an angular position, probably C_{10}.

Whereas ouabain is cleaved by vigorous acid hydrolysis to rhamnose and resinous conversion products of the genin,[8] treatment with acetone and small amounts of hydrochloric acid under mild conditions affords the aglycone, ouabagenin, in good yield as a monoacetonide derivative.[2] The monoacetonide yields a diacetate, and is readily convertible in weakly acidic media into free ouabagenin, from which a tetraacetyl derivative may be obtained. Since it has been demonstrated by lead tetraacetate titration that no two hydroxyl groups in ouabagenin can occupy adjacent positions,[2] the monoacetonide was formulated as a derivative of a 1,3-glycol, in which both hydroxyl groups are acylable. These groups were tentatively assigned to C_1 and C_3. Formation of a tetraacetate from ouabagenin further suggests the presence in this molecule of a second tertiary hydroxyl group, which was placed at C_5 on the basis of analogy to other cardiotonic substances. The remaining hydroxyl group has been provisionally assigned to C_{11} for reasons that are discussed in a later paragraph.

Since the occurrence of an oxygen function at C_1 in a steroid of natural origin is without precedent,[9] we have undertaken an investigation of ouabagenin with a view toward establishing the details of its structure in an unambiguous manner. In order to avoid complications resulting from epimerization at C_{17}, or from isomerization of the side chain structure in the presence of base, we employed 20,21-dihydroöuabagenin (*II*)[2] as starting material.

After a number of abortive attempts at partial

(1) This investigation was supported by a research grant, H-1084, from the National Heart Institute, of the National Institutes of Health, Public Health Service. A preliminary account of this work appeared in *Chem. & Ind.*, 1235 (1954). For paper I see R. P. A. Sneeden and R. B. Turner, THIS JOURNAL, **75**, 3510 (1953).

(2) C. Mannich and G. Siewert, *Ber.*, **75**, 737 (1942).

(3) The original formulation of Mannich and Siewert contained a β,γ-butenolide side chain at C_{17}. In consideration of more recent work of Reichstein noted below [*cf.* W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941)], an α,β-unsaturated structure has been incorporated in formula I.

(4) W. A. Jacobs and N. M. Bigelow, *J. Biol. Chem.*, **96**, 647 (1932); **101**, 15 (1933).

(5) A. Meyrat and T. Reichstein, *Helv. Chim. Acta*, **31**, 2104 (1948).

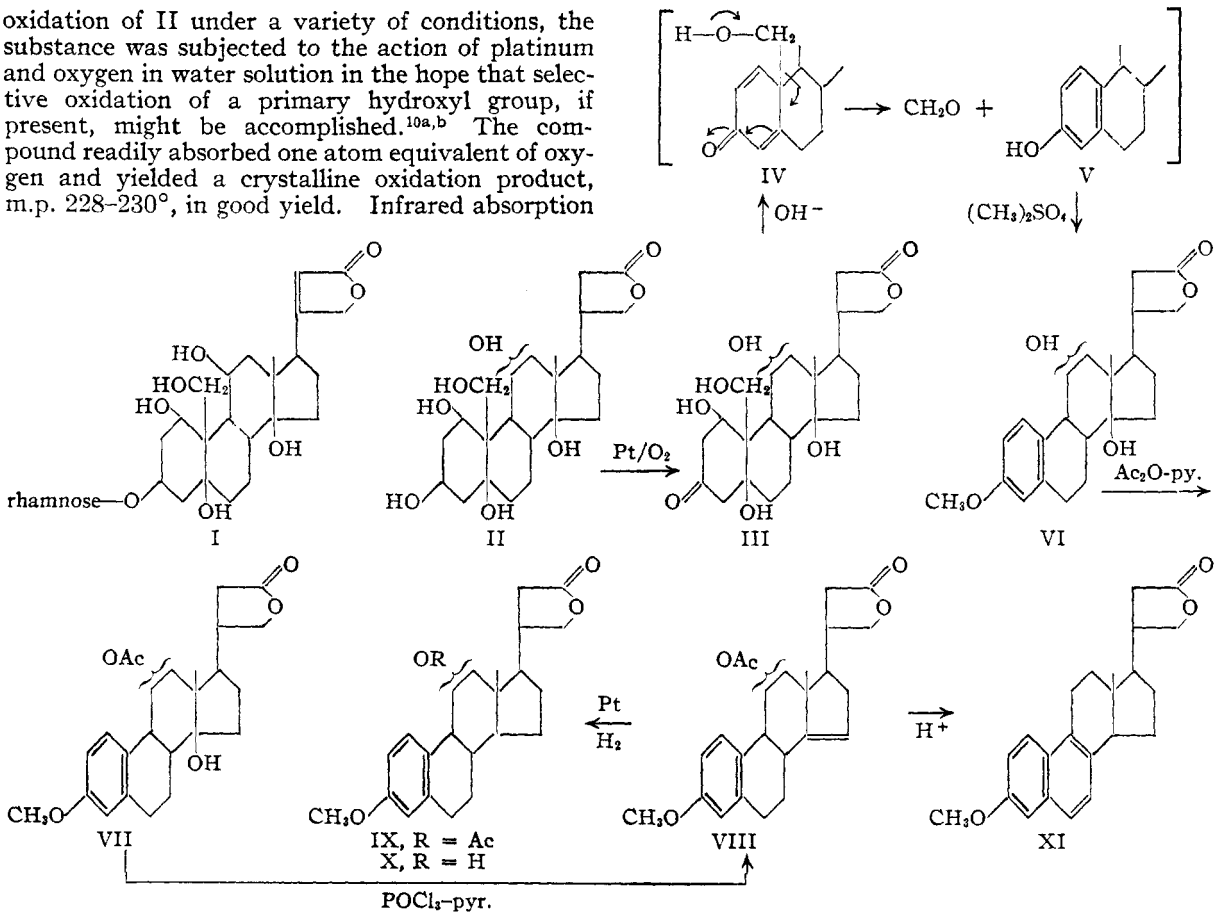
(6) R. F. Raffauf and T. Reichstein, *ibid.*, **31**, 2111 (1948).

(7) L. F. Fieser and M. S. Newman, *J. Biol. Chem.* **114**, 705 (1936).

(8) A. Arnaud, *Compt. rend.*, **126**, 346, 1208 (1898).

(9) The possibility that acovenoside A and abomonoside may possess such a function has been discussed by T. Reichstein and his associates, *Helv. Chim. Acta*, **34**, 1224 (1951); **35**, 2202 (1952).

oxidation of II under a variety of conditions, the substance was subjected to the action of platinum and oxygen in water solution in the hope that selective oxidation of a primary hydroxyl group, if present, might be accomplished.[10a,b] The compound readily absorbed one atom equivalent of oxygen and yielded a crystalline oxidation product, m.p. 228–230°, in good yield. Infrared absorption



measurements established the presence in the latter substance of a new carbonyl function, and the compound gave a strong positive test with Tollens reagent. Polarographic analysis,[11] however, clearly indicated that the carbonyl group in question was not aldehydic in character. The presence of an α-ketol structure could furthermore be excluded in view of the failure of ouabagenin to react to any appreciable extent with lead tetraacetate.[2]

In attempting to account for the positive Tollens test, we were attracted by the thought that selective oxidation of II at C_3 rather than at C_{19} would furnish a product (III),[12] which, under the basic conditions of the Tollens reaction, might be expected to undergo β-elimination (*cf.* IV) and reverse aldol cleavage to yield *formaldehyde* and phenolic derivative (V).[13] On the basis of this reasoning we were led to investigate the action of base on the platinum–oxygen dehydrogenation product, now formulated as III.

A solution of III in aqueous sodium hydroxide accordingly was allowed to stand at room temperature in an atmosphere of nitrogen for two hours. Acidification of the reaction mixture and steam distillation into aqueous dimedon gave crystalline material, m.p. 190–191°, that was identified as the dimedon derivative of formaldehyde by a mixed melting point determination with an authentic sample. In a second experiment the course of the base-catalyzed reaction was followed spectrographically in the ultraviolet. The formation of phenolic material was ascertained readily by the rapid appearance (5 min.) of absorption bands at 239 mμ (ϵ 7700) and 294 mμ (ϵ 2145), corresponding to pheoxide ion (Fig. 1). Acidification gave material with a single band, λ_{max} 278 mμ, ϵ 1664, characteristic of phenol absorption. Purification of the phennolic product proved unsatisfactory, and the substance was converted ordinarily into the corresponding methyl ether VI, λ_{max} 276 mμ, ϵ 1764 (Fig. 1), prior to isolation.

Treatment of VI with acetic anhydride and pyridine afforded a monoacetyl derivative VII, m.p. 183–184°, which was dehydrated with phosphorus oxychloride and pyridine to the corresponding 14,-

(10) (a) H. Wieland, *Ber.*, **45**, 484, 2606 (1912); **46**, 3327 (1913); **54**, 2353 (1921); (b) *cf.* R. P. A. Sneeden and R. B. Turner, THIS JOURNAL, **77**, 190 (1955).

(11) We are indebted to Dr. J. L. Franklin and Mr. J. H. Karchmer of the Humble Oil and Refining Co., Baytown, Texas, for these results.

(12) The compounds referred to in this paper have not been given systematic names for reasons of complexity. The following names are, however, suggested. In cases where two are given the first is preferred on the basis of rules developed by the Committee on steroid nomenclature. It should be pointed out in this connection that the suggestions of this committee do not cover the compounds in question: compound III, 3-ketocardogenan-1β,5β,14β,19,x-pentol; compound VI, β'-[3-methoxy-14β,21,x-trihydroxyestra-1,3,5(10)-trienyl-(17)]-butanolide or 3-methoxy-14β,21-x-trihydroxy-19,24-bisnorchola-1,3,5(10)-trienic acid lactone; compound VII, β'-[x-acetoxy-3-methoxyestra-1,3,5(10),14-tetraenyl-(17)-butanolide or x-acetoxy-3-methoxy-19,24-bisnorchola-1,3,5(10),14-tetraenic acid lactone; compound XI, β'-[3-methoxyestra-1,3,5(10),6,8-pentaenyl-(17)]-butanolide or 3-methoxy 19,24-bisnorchola-1,3,5(10),6,8-pentaenic acid lactone.

(13) Oxidation at C_1 would serve this argument as well, but can be excluded by later evidence.

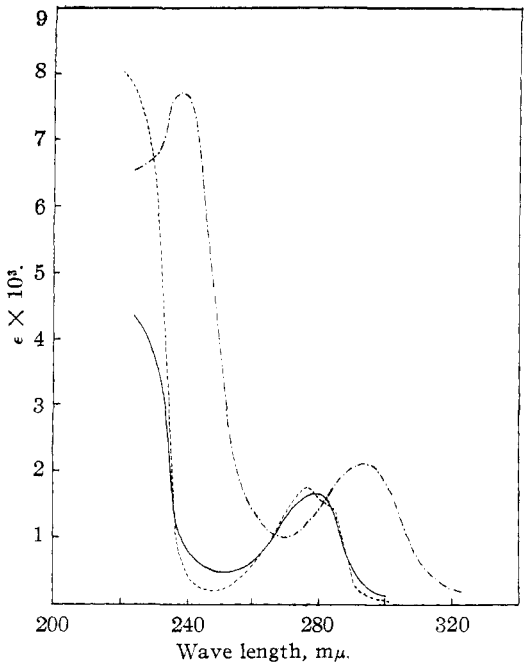
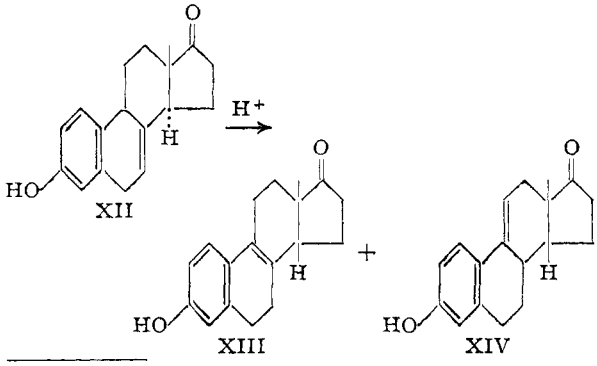


Fig. 1.—Ultraviolet absorption spectra: ———, compound V; –·–·–·–, compound V (in base); - - - - - - -, compound VI.

15-unsaturated product VIII. Catalytic hydrogenation of VIII furnished a difficultly separable mixture, from which a dihydro derivative IX, m.p. 204–205°, could be isolated in poor yield. In addition there was obtained in lesser amount a second substance, m.p. 144–147°, which was not further investigated. In view of the unpromising nature of these results, we turned to a more direct procedure, which led to removal of the remaining hydroxyl function and aromatization to a naphthalenoid system in a single step.

Acid-promoted migration of double bonds in the steroid series is well known and has been studied in considerable detail in connection with migrations involving the 7,8-, 8,9-, 8,14- and 14,15-positions.[14] Of special interest with regard to the present problem is the demonstration of Banes, Carol and Haenni[15] that equilin (XII) is converted by treatment with mineral acid into a mixture of 8-dehydro-14-isoestrone (XIII) and 9-dehydro-14-isoestrone (XIV).



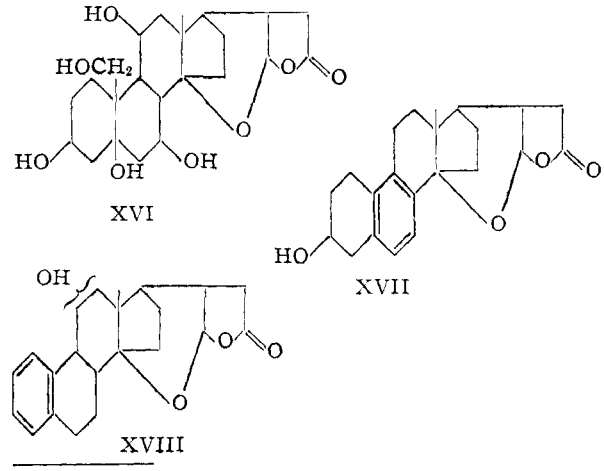
(14) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd. Ed., Reinhold Publishing Corp., New York, N. Y., 1949, pp. 241, 243, 248, 284.

(15) D. Banes, J. Carol and E. O. Haenni, *J. Biol. Chem.*, **187**, 557 (1950).

It seemed likely, therefore, that acid treatment of VIII would initiate a similar change, which would lead to the intermediate formation of an allylic alcohol derivative, irrespective of the precise location of the acetoxyl group in the B or C rings. Elimination of the latter function and rearrangement of the unsaturated system thus produced to a methoxynaphthalene might then be anticipated.

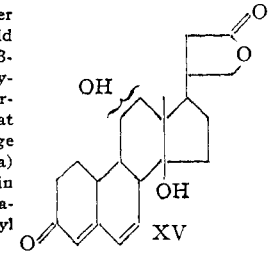
These expectations were fully realized experimentally. On treatment with methanolic hydrochloric acid, VIII afforded a crystalline product XI,[16] m.p. 185–188°, which exhibited ultraviolet absorption characteristic of a **β-methoxynaphthalene** (Fig. 2). The methoxyl group of XI, and hence the keto group of III, must therefore be located at C_2, C_3 or C_7. Positions 2 and 7 are incompatible with the conversion III → VI, in which two acylable hydroxyl groups and one non-acylable hydroxyl group are eliminated, and the groups in question must thus be located at C_3. In view of relationships already established between the keto group of III and the neighboring hydroxyls, these results permit assignment of a hydroxyl group to C_1 in ouabagenin[17] and otherwise confirm the Mannich–Siewert formulation with respect to the A/B system.[17a]

The only remaining point of uncertainty concerns the location of the fourth acylable hydroxyl group. This function was assigned originally to C_{11} by Fieser and Newman[7] in order to rationalize the conversion of isoöuabain, provisionally formulated as XVI, into a trianhydrohydroxylactone,[4] for which structure XVII was proposed.[18] It is



(16) The configuration of the hydrogen atom at C_{14} in this derivative, although probably β, has not been established.

(17) It will be apparent that transfer of the C_1 hydroxyl group to C_7, would render impossible the formation of a 1,3-acetonide involving two *acylable* hydroxyl groups. Position 7 can furthermore be excluded on the grounds that successive β-eliminations and cleavage would furnish a dienone XV, which (a) would not be expected to aromatize in base, and (b) should undergo base-catalyzed elimination of the 14-hydroxyl group as well.



(17a) NOTE ADDED IN PROOF (Nov. 1, 1954).—Since this manuscript was submitted a paper has appeared by K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1174 (1954), in which similar conclusions were reached on the basis of a somewhat different argument.

(18) *Cf.* R. Tschesche and W. Haupt, *Ber.*, **70**, 48 (1937).

now clear that the trianhydrohydroxylactone must have structure XVIII, being formed by elimination of the angular hydroxymethyl group *via* 1,3-glycol cleavage.[19] The question of assignment of a hydroxyl group to C_{11} thus requires re-examination. Experiments directed toward the solution of this problem and toward the synthesis of XI are in progress.

Experimental[20]

Preparation of Dihydroöuabagenin (II).[2]—Pure ouabagenin monohydrate (m.p. 236–239°, 7.2 g.) prepared by the procedure of Mannich and Siewert[2] was dissolved in 100 ml. of methanol and stirred with 400 mg. of platinum oxide catalyst in an atmosphere of hydrogen. After 24 hours 1 molar equivalent of hydrogen had been absorbed, and the catalyst was removed by filtration. The filtrate, on concentration to small volume, deposited 6.0 g. of dihydroouabagenin containing 1 molecule of methanol of crystallization, m.p. 260–262°, lit.[2] 261°.

Oxidation of Dihydroöuabagenin with Platinum and Oxygen (III).—A solution of 2.4 g. of dihydroöuabagenin, obtained in the preceding experiment, in 100 ml. of water was concentrated and finally dried in high vacuum to ensure removal of the methanol of crystallization. The dried material was then taken up in 100 ml. of water and added to a suspension of platinum black (from 300 mg. of platinum oxide) in 40 ml. of water. The air in the system was then replaced with oxygen, and the reaction mixture stirred for 48 hours, at the end of which time 1 atom equivalent of oxygen had been consumed. After removal of the catalyst, the solution was concentrated under reduced pressure and cooled in ice. The product III separated as a monohydrate, m.p. 220–222°, yield 2.0 g. Recrystallization from water furnished the analytical sample, m.p. 228–230°, $[\alpha]_{5460}$ +11.6° (*c* 1.0, pyridine), infrared maxima (Nujol) at 1724 cm.$^{-1}$ (C=O) and at 1788 cm.$^{-1}$ (5-membered lactone).

Anal. Calcd. for $C_{23}H_{34}O_8 \cdot H_2O$: C, 60.58; H, 7.97. Found: C, 60.41, 60.58; H, 7.69, 7.64.

Reaction of III with Base.—A solution of 200 mg. of the above product in 1 ml. of water was placed in a distillation flask fitted with inlets for nitrogen and for steam. Three ml. of 5% aqueous sodium hydroxide was then added, and nitrogen was bubbled through the solution and into a trap containing 30 ml. of 5% aqueous dimedon. After 2 hours at room temperature, the reaction mixture was acidified with dilute sulfuric acid and steam distilled directly into the trap. The precipitate that formed in the dimedon solution was removed by filtration and dried at 100° under diminished pressure; yield 43 mg., m.p. 190–191°. A mixed melting point determination with an authentic sample of the dimedon derivative of formaldehyde showed no depression.

From the residue remaining after steam distillation a white solid, m.p. 280–285°, $\lambda_{max.}$ 278 mμ (ε 1980) was obtained. This material resisted attempts at purification and in subsequent experiments was converted directly into the corresponding phenolic methyl ether.

Conversion of III into VI.—A stream of hydrogen was bubbled through a suspension of 2.0 g. of III in 40 ml. of water in order to remove all traces of air. Solid sodium hydroxide (4 pellets) was then added and the mixture was stirred under hydrogen for 15 min. when a clear solution was obtained. The reaction flask was cooled in an ice-bath, and 10 ml. of dimethyl sulfate was added. Stirring was continued, and sodium hydroxide pellets were introduced from time to time to maintain an alkaline reaction to Alizarin Yellow R (*p*H 10). After a total of 34 pellets (5.2 g.) of sodium hydroxide had been added, the mixture was stirred for a further hour and then acidified to congo red with 5 *N* sulfuric acid. The product was extracted into ethyl acetate and was allowed to stand overnight in the presence of a catalytic amount of *p*-toluenesulfonic acid in order to ensure relactonization. The organic solution was then washed repeatedly with potassium bicarbonate, sodium carbonate and finally with 1 *N* potassium hydroxide. After drying over anhydrous calcium sulfate, the solvent was removed under reduced pressure and the residue crystallized from acetone. By this procedure 1.028 g. of white prisms, m.p. 206–207°, was obtained. Two recrystallizations from acetone afforded the analytical specimen, m.p. 212–213°, $[\alpha]_{5460}$ + 44.8° (*c* 1.3, pyridine), $\lambda_{max.}$ 276 mμ (ε 1764), $\lambda_{inflection}$ 282 mμ (ε 1620).

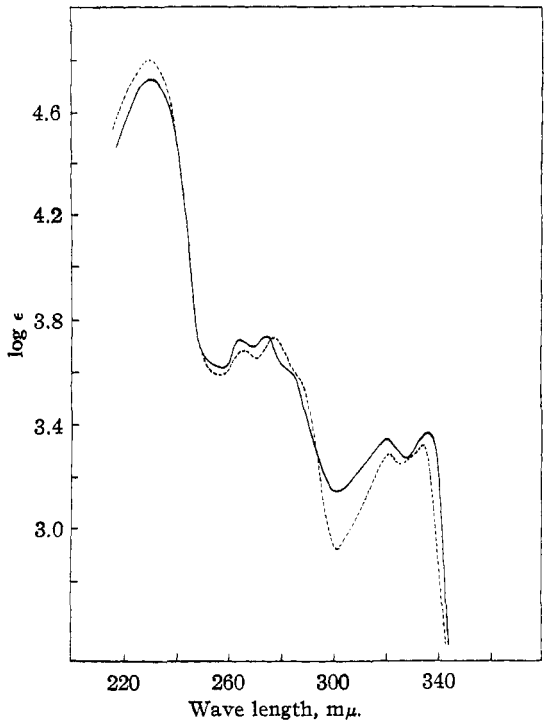


Fig. 2.—Ultraviolet absorption spectra: ———, compound XI; - - - - - -, *trans*-3-methoxyequilen-16-one (plotted from the data of A. L. Wilds, J. A. Johnson and R. E. Sutton, THIS JOURNAL, **72**, 5526 (1952)).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.16; H, 7.93.

From the carbonate wash liquors considerable amounts of amorphous acidic material could be recovered. This material has not been investigated further, but appears to arise from methylation of the lactone hydroxy group.

Acetylation of VI to VII.—The methoxy derivative VI (1.03 g.) after thorough drying was dissolved in 20 ml. of pyridine and 6 ml. of redistilled acetic anhydride was added. After standing for 24 hours at room temperature, the excess acetic anhydride was decomposed with ice-water, and the product was extracted into ethyl acetate. The organic layer was washed with 1 *N* hydrochloric acid and 1 *N* sodium carbonate and dried over anhydrous calcium sulfate. Crystallization from acetone of the material remaining after evaporation of the solvent gave 740 mg. of white prisms, m.p. 183–184°. Two recrystallizations from acetone raised the melting point to 191–193°, $[\alpha]_{5460}$ − 27.2° (*c* 1.8, acetone).

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.18; H, 7.53.

Dehydration of VII to VIII.—The above methyl ether acetate (200 mg.) was dissolved in 6 ml. of pyridine and treated with 1 ml. of redistilled phosphorus oxychloride. After 24 hours, ice was added to the reaction mixture, and the product extracted into ethyl acetate. The organic layer was washed successively with dilute hydrochloric acid, water and dilute sodium hydroxide solution. The solvent was finally removed by evaporation, and the residual material crystallized from acetone. In this way 160 mg. of prisms, m.p. 181–182° (loss of solvent at 80°), containing a molecule of acetone of crystallization, was obtained.

Recrystallization from acetone furnished the analytical sample, m.p. 181–182°, $[\alpha]_{5460}$ + 3.75° (*c* 1.6, acetone), $\lambda_{max.}$ 276 mμ (ε 2000), 280–285 mμ (ε 1000). The infrared

(19) *Cf.* F. V. Brutcher and J. English, THIS JOURNAL, **74**, 4279 (1952).

(20) All melting points are corrected. Microanalyses were carried out by S. M. Nagy, M.I.T., and by G. Weiler and F. Strauss, Oxford University.

absorption spectrum ($CHCl_3$) showed maxima at 1790 cm.$^{-1}$ (5-membered lactone), 1745 cm.$^{-1}$ (acetate), 1612 and 1502 cm.$^{-1}$ (phenyl), 812 cm.$^{-1}$ (—C=C—H). No absorption was observed in the hydroxyl region.

Anal. Calcd. for $C_{25}H_{30}O_5 \cdot C_3H_6O$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.55.

Hydrogenation of VIII.—The anhydro derivative VIII (620 mg.) was dissolved in 70 ml. of methanol and stirred in an atmosphere of hydrogen with 280 mg. of platinum oxide catalyst. After the uptake of hydrogen ceased, the catalyst was removed by filtration, and the filtrate evaporated to dryness. Chromatography of the residual material (550 mg.) on silica gel followed by repeated crystallization from methanol furnished 103 mg. of a substance melting at 204–205°, $[\alpha]_{5460}$ −105° (*c* 1.3, acetone).

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.63; H, 7.75.

A smaller amount of a second substance, m.p. 144–147°, $[\alpha]_{5460}$ + 5.4° (*c* 1.2, acetone) also was obtained. This material was not investigated further.

Hydrolysis of the product melting at 204–205° gave material, m.p. 223–224°, that is presumed to be the free hydroxy derivative X. The amount of this substance available was, however, insufficient for analysis.

Conversion of VIII into XI.—A solution of 110 mg. of the anhydro derivative VIII in 20 ml. of methanol was treated with 10 ml. of concentrated hydrochloric acid, and the resulting mixture was refluxed for 7 hours under hydrogen. On cooling and dilution with 150 ml. of water, a white solid separated, which was purified in the following manner. The product was first dissolved in 60 ml. of methanol and stirred for 2 hours under hydrogen with 100 mg. of platinum oxide to reduce or rearrange non-aromatic unsaturation, the presence of which was suggested by a spurious absorption band in the 305–310 mμ region. The resulting material was then adsorbed from benzene solution on magnesium silicate. A crystalline compound was eluted with methylene chloride, which after recrystallization from methanol gave 30 mg. of fine needles, m.p. 185–188°, $[\alpha]_{5460}$ +48° (*c* 1.0, acetone).

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48; $-OCH_3$, 8.85. Found: C, 78.61; H, 7.44; $-OCH_3$, 8.85.

The ultraviolet absorption data are recorded in Fig. 2.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

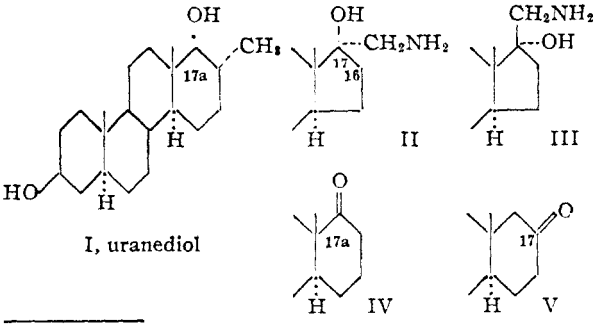
17-Keto-17a-methyl-D-homosteroids from 17α-Hydroxy-20-amino-C_{21} Steroids. Stereochemistry of D-Homoannulation

BY FAUSTO RAMIREZ AND STANLEY STAFIEJ[1]

RECEIVED JUNE 1, 1954

The action of nitrous acid on a 17α-hydroxy-20α-aminosteroid (XVa) has been studied with the view of (a) correlating the configurations at carbons 17 and 20 with the course of deamination and (b) providing a new route to C_{21}-D-homosteroids. It was found that the amino alcohol XVa rearranged exclusively to a 17-keto-17a-methyl-D-homosteroid with migration of the 13–17 bond. This result is interpreted in terms of steric strain in the transition state of the deamination, and is compared with the previously reported D-homoannulation of 17α-hydroxy-17-aminomethylsteroids, in which no steric bias is associated with carbon 20. The amino alcohol studied XVa was obtained—together with a small amount of the 20β-epimer XVIa—from the catalytic hydrogenation of a 17α-hydroxy-20-oxime (XIV). The configurations of the amino alcohols are based on the molecular rotation differences between the 20-epimeric acetamido derivatives (XVb and XVIb) by comparison with previously reported molecular rotation differences of 20-epimeric 20-acetate derivatives of 17α,20-dihydroxysteroids of analogous constitution.

The sequence of events which resulted in the original partial syntheses of D-homosteroids[2] and in the elucidation of the structural changes taking place during these syntheses, has been extensively reviewed.[3] C_{21}-D-Homosteroids (*i.e.*, urane derivatives such as I[3d]) have been isolated from natural sources by several investigators.[4] It has been shown, furthermore,[5] that some D-homoanalogs of steroid hormones are as active or even more active than the corresponding hormones. For these reasons the partial synthesis of C_{20}- and C_{21}-D-homosteroids has received considerable attention. In a recent publication[6] the action of nitrous acid on a 17β-hydroxy-17-aminomethylsteroid (II) was described. The Swiss authors concluded that the D-homoannulation brought about by nitrous acid was stereospecific and led exclusively to a 17a-keto-D-homosteroid IV by migration of the C_{16}-C_{17} bond. It was also suggested[6] that the isomeric 17-keto-D-homosteroid V, previously isolated (together with IV) by Goldberg and co-workers[5b,7] from the action of nitrous acid on a crude mixture of 17-hydroxy-17-aminomethylsteroids,[8] resulted from the rearrangement of III with migration of the C_{13}–C_{17} bond. No satisfactory explanation has been



(1) From part of the Ph.D. Thesis of S. Stafiej.

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(8) Obtained by catalytic hydrogenation of a crude cyanohydrin mixture.