had dissolved and the solution then was kept for a further 70 hours at room temperature. The reaction mixture was then poured onto an excess of ice-water and the product was isolated with ethyl acetate. One crystallization from methanol afforded Δ^2-allopregnene-3,17α,21-triol-11,20-dione triacetate (XXII) (3.91 g.), m.p. 171–176°, raised by several crystallizations from methanol to 178–179°, $[\alpha]_D$ +49°; lit.[40] m.p. 175–181°, $[\alpha]_D$ +46°.

Anal. Calcd. for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43; O, 26.20. Found: C, 66.52; H, 7.45; O, 26.03.

2α-Bromoallopregnene-17α,21-diol-3,11,20-trione Diacetate (XXIIIa).—A solution of the enol acetate XXII (1.94 g.) in methylene dichloride (40 cc.) together with N-bromoacetamide (602 mg.) were added to a mixture of anhydrous hydrogen fluoride (9.1 g.) and tetrahydrofuran (16.0 g.) at −80°. After 3 hours at −80° and 16 hours at 0° the mixture was added to an excess of sodium carbonate in ice-water. Isolation of the product with methylene dichloride and one crystallization from acetone afforded 2α-bromoallopregnane - 17α,21 - diol - 3,11,20 - trione diacetate (XXIIIa) (1.37 g.), m.p. 238–242°, raised by several crystallizations from acetone to 245–247°, $[\alpha]_D$ +51°; lit.[40] m.p. 230–232°, $[\alpha]_D$ +45°.

Anal. Calcd. for $C_{25}H_{33}O_7Br$: C, 57.14; H, 6.33; Br, 15.21. Found: C, 57.40; H, 6.29; Br, 15.01.

2α - Iodoallopregnane - 17α,21 - diol - 3,11, 20 - trione Diacetate (XXIIIb).—A solution of the enol acetate XXII (500 mg.) in methylene dichloride (25 cc.) together with N-iodosuccinimide (217 mg.) were added to a mixture of anhydrous hydrogen fluoride (5.2 g.) and tetrahydrofuran (9.15 g.) at −80°. After 2 hours at −80° and 16 hours at 0° the mixture was added to an excess of sodium carbonate in ice-water. Isolation of the product with methylene dichloride and one crystallization from methylene dichloride–hexane gave 2α-iodoallopregnane-17α,21-diol-3,11,20-trione diacetate (XXIIIb) (310 mg.), m.p. 193–197°, raised by several crystallizations from the same solvent system to 197–199° dec., $[\alpha]_D$ +63°.

Anal. Calcd. for $C_{25}H_{33}O_7I$: C, 52.44; H, 5.81; I, 22.17. Found: C, 52.66; H, 5.93; I, 21.41.

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

Steroids. CXLII.[1] New Fluorination Procedures. Part 2.[2] The Abnormal Addition of I–F to Δ^5-Steroids

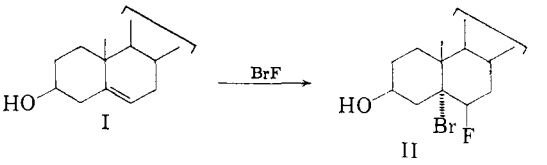
BY A. BOWERS, E. DENOT AND R. BECERRA[3]

RECEIVED DECEMBER 28, 1959

Contrary to expectation, the addition of I–F (N-iodosuccinimide–hydrogen fluoride) to Δ^5-3β-hydroxy steroids afforded the corresponding 6β-iodo-5α-fluoro dihalides. Evidence is presented to support the stereochemical assignments. The mechanism of halogen type addition to Δ^5-double bonds is discussed.

A recent development in steroid hormone chemistry has been the demonstration that the introduction of a fluorine atom into the C-6α position of a wide variety of progestational[4–8] and cortical hormones[5,6,9–14] has had a beneficial effect on their biological activity.

Recently a new route to these compounds was described[15] *via* the *trans* addition of Br–F (N-bromoacetamide and hydrogen fluoride) to a 3β-hydroxy-Δ^5-steroid olefin (I → II). Subsequent manipulation of II led to the biologically important 6α-fluoro-Δ^4-3-ketone system in good over-all yield.[15]



In addition, it has been reported that in the presence of a proton acceptor, cyclohexene readily undergoes addition of I–F (N-iodosuccinimide–hydrogen fluoride) to furnish *trans*-1-fluoro-2-iodocyclohexane.[2] This result coupled with our earlier work[15] suggested that an alternate route to C-6-fluorinated steroids might proceed *via* the addition of I–F to a Δ^5-steroid. It was expected that this reaction would follow a stereochemical course analogous to the addition of Br–F (I → II) and afford 6β-fluoro-5α-iodo steroids.

Treatment of pregnenolone (IIIa) (Fig. 1) with N-iodosuccinimide and hydrogen fluoride in the presence of tetrahydrofuran did indeed afford in good yield a product (IVa) which analyzed correctly for the addition of I–F to the Δ^5-double bond. Acetylation of this compound afforded a monoacetate (IVb) which was identical with the product obtained from the reaction of pregnenolone acetate (IIIb) with the N-iodosuccinimide–hydrogen fluoride couple. It was seen that this reaction was not attended by skeletal rearrangement when reaction of IVb with zinc in methanol regenerated pregnenolone acetate (IIIb) in high yield. Similarly zinc and acetic acid

(1) Steroids. CXL1, F. A. Kincl, *Ber.*, **93**, in press (1960).

(2) Part 1, A. Bowers, L. C. Ibáñez, E. Denot and R. Becerra, THIS JOURNAL, **82**, 4001 (1959).

(3) Part of this work represents a section of the professional thesis submitted by R. Becerra to the Facultad de Química Berzelius for the degree "Químico Industrial."

(4) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(5) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958).

(6) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

(7) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

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(9) A. Bowers, E. Denot, M. B. Sánchez and H. J. Ringold, *Tetrahedron*, **7**, 153 (1959).

(10) J. S. Mills, A. Bowers, C. C. Campillo, C. Djerassi and H. J. Ringold, THIS JOURNAL, **81**, 1264 (1959); **82**, 3399 (1960).

(11) J. A. Edwards, A. Zaffaroni, H. J. Ringold and C. Djerassi, *Proc. Chem. Soc.*, 87 (1959).

(12) J. A. Edwards, H. J. Ringold and C. Djerassi, THIS JOURNAL, **81**, 3157 (1959).

(13) W. P. Schneider, F. H. Lincoln, G. B. Spero, H. C. Murray and J. L. Thompson, *ibid.*, **81**, 3168 (1959).

(14) S. Karaday and M. Sletzinger, *Chemistry & Industry*, 1159 (1959).

(15) A. Bowers, THIS JOURNAL, **81**, 4107 (1959).

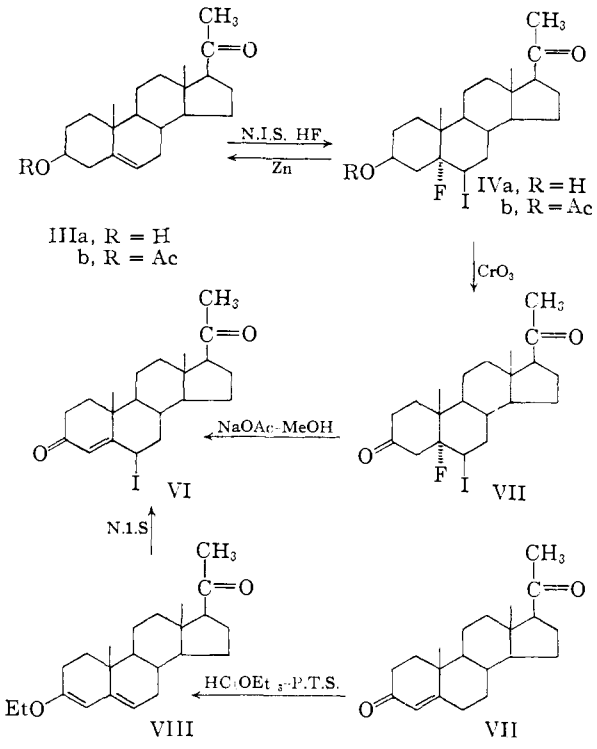


Fig. 1.

treatment of IVa afforded pregnenolone (IIIa). Oxidation of IVa with 8 *N* chromic acid in acetone solution[16] gave the corresponding C-3 ketone V. However, treatment of V with sodium acetate in methanol (β-halo ketone elimination) did not lead to 6β-fluoroprogesterone but instead gave 6β-iodoprogesterone (VI). This compound was identical in every respect with the product obtained by treating progesterone enol ether (VIII) with N-iodosuccinimide in acetone solution containing sodium acetate and acetic acid.[17]

The structure assigned to VI was based on the following observations. Analytical data were in agreement with an empirical formula $C_{21}H_{29}O_2I$. In the ultraviolet it exhibited maximum absorption at 250–252 mμ, ϵ 14,800, and in the infrared it had bands at 1700 (20-ketone), 1670 and 1610 cm.$^{-1}$ (Δ^4-3-ketone). The 6β-configuration was originally assigned to the iodine atom on the basis of the position of maximum absorption in the ultraviolet. The bathochromic shift of 10 mμ[18] caused by introduction of a 6β-iodine atom is in accord with theoretical considerations, whereas a 6α-substituted iodine should not exert any bathochromic shift.[19] A parallel situation exists with 6α- and 6β-bromoprogesterone. The former compound has λ_{max}^{EtOH} 236 mμ,[20a] whereas the 6β-epimer exhibits maximum absorption at 246 mμ.[20b]

It also has been established that the introduction of a 6β-halogen atom into progesterone has a marked levorotatory effect on the molecular optical rotation at the sodium D line. Table I summarizes the contribution of the halogen atom to the molecular rotation of a series of C-6 halogenated progesterone analogs and in accordance with these findings, M_D (6β-iodoprogesterone–progesterone) = −575.

TABLE I

Compound, progesterone	M_D[a]	ΔM_D (6-halo-progesterone − progesterone[b])
6α-Fluoro-[d]	+660	+ 32
6β-Fluoro-[d]	+338	−290
6α-Chloro-[d]	+454	−174
6β-Chloro-[d]	+258	−370
6α-Bromo-17α-acetoxy-[20a]	+189	− 83[c]
6β-Bromo-17α-acetoxy-[20b]	0	−272[c]
6β-Iodo[e]	+ 53	−575

[a] All rotations measured in chloroform. [b] M_D Progesterone = +628; *cf.* J. P. Mathieu and A. Petit, "Tables de Constantes et Données Numeriques 6. Constantes Selectionées Pourvoir Rotatoire Naturel I. Steroides," Masson et Cie., Editeurs, Paris, 1956, p. 36. [c] Calculated for ΔM_D (6-bromo-17α-acetoxyprogesterone-17α-acetoxyprogesterone); M_D 17α-acetoxyprogesterone = +272; *cf.* H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 816 (1956). [d] Private communications from Dr. H. J. Ringold of these laboratories. [e] This paper.

The I–F reaction on Δ^5-steroids then was extended to the androstane series and a suitable starting material was Δ^5-androstene-3β,17β-diol 17-acetate (XIIb) a compound which previously had been prepared by Butenandt and Hanisch[21] by the preferential hydrolysis of the corresponding diacetate XIIa. In our hands this was not the most satisfactory procedure and a more convenient preparation of XIIb began with Δ^5-androstene-3β-ol-17-one (IX). This compound readily formed the C-3 tetrahydropyranyl ether X upon treatment with dihydropyran in benzene solution at room temperature in the presence of *p*-toluenesulfonic acid monohydrate. Sodium borohydride reduction of X followed by acetylation then led to the 17β-acetoxy-C-3-pyranyl ether XI, whence acid hydrolysis with aqueous hydrochloric acid in acetic acid smoothly furnished the diol monoacetate XIIb. In a manner similar to pregnenolone it readily added the elements of I–F to afford the dihalide XIII. Oxidation to the C-3 ketone XIV and a sodium acetate in methanol treatment to eliminate the fluorine atom as hydrogen fluoride led to 6β-iodotestosterone (XV), λ_{max}^{EtOH} 252–254 mμ, ϵ 15,850. An independent synthesis of XV involved treatment of testosterone enol ether (XVI) with N-iodosuccinimide. The product from this reaction was identical in every respect with the product from the elimination reaction with sodium acetate (XIV → XV).

The rotatory dispersion curves of 6 halo-substituted testosterone analogs can be used to define unambiguously the stereochemistry of the halo-

(16) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *ibid.*, 2548 (1953).

(17) C. Djerassi, J. Grossman and G. H. Thomas, THIS JOURNAL, **77**, 3826 (1955), have shown that treatment of $\Delta^{3,5}$-22α,25a-spirostadiene-3-ol acetate with N-iodosuccinimide in dioxane solution afforded 6ϵ-iodo-Δ^4-22α,25a-spirostene-3-one, λ_{max}^{EtOH} 248 mμ, ϵ 12,050.

(18) Progesterone exhibits λ_{max}^{EtOH} 241 mμ; *cf.* L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(19) For a detailed theoretical discussion of the ultraviolet spectra of 6α- and 6β-substituted Δ^4-3-ketones *cf.* H. J. Ringold and A. Bowers, manuscript in preparation.

(20) (a) H. J. Ringold, E. Batres, A. Bowers, J. A. Edwards and J. A. Zderic, THIS JOURNAL, **81**, 3485 (1959). (b) Private communication from Dr. J. A. Edwards of these laboratories.

(21) A. Butenandt and G. Hanisch, *Ber.*, **68B**, 1859 (1935).

gen atom.[22] It has been shown that 6α-halo-substituted testosterones have rotatory dispersion curves very similar to that of testosterone, whereas a 6β-halogen substituent has a very marked effect on the nature of the curve.[23] Figure 3 clearly illustrates the marked difference between the rotatory dispersion curve of testosterone and 6β-iodotestosterone. This result, taken into consideration with the evidence discussed above, clearly establishes that addition of I–F to a Δ^5-double bond leads to a 6β-iodo-5-fluoro dihalide. If the reasonable assumption is made that diaxial addition of I–F occurs *via* the energetically favorable co-planar transition state the fluorine atom must have the 5α-configuration.[24]

It was noted above that the analogous addition of Br–F to a Δ^5-double bond proceeds in exactly the opposite way to afford the 6β-fluoro-5α-bromo steroid. Although the latter result represented a reverse Markownikoff addition of Br^+F^- to the double bond, it was in accord with expectation and it is the addition of I^+F^- in the "electronically correct manner" which must be considered unusual.

The stereochemistry of the addition of Br^+X^- to a Δ^5-double bond is known where X = Br,[25] Cl,[26] OH[27] and F[15] and the results are summarized in Fig. 4.

In each case transient formation of the α-orientated bromonium ion XVIII is followed by attack of the nucleophile X^- to afford the 6β-substituted 5α-bromo compound XIX. Stereochemical factors clearly control the approach of the bromonium ion (or its equivalent). The 1,3-diaxial non-bonded interaction between the C-19 methyl group and an entering 6β-bromine atom is sufficient to inhibit this approach even though the polarization of the Δ^5-double bond would direct the entering cation to this position. The over-all result, therefore, is anti-Markownikoff addition of BrX^+ to the double bond.

In contrast the conjugate acid of N-iodosuccinimide must approach the Δ^5-double bond from the sterically more hindered β-face of the molecule. At first sight this is a puzzling reaction. Iodine being more bulky than bromine is even more susceptible to steric factors and only if I^+ is *considerably more electrophilic* than Br^+ would it be possible to entertain the idea that the direction of polarization of the double bond is the governing factor. This is not in accord with current views and this possibility was rejected. It was necessary therefore to seek an alternate explanation.

(22) In the progesterone series the effect of the C-20 ketone is so great that it renders any interpretation based on the shape of the rotatory dispersion curves of 6-halo derivatives ambiguous. We are grateful to Dr. Carl Djerassi for a helpful discussion on this point.

(23) (a) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, THIS JOURNAL, **80**, 1216 (1958); (b) C. Djerassi, "Optical Rotatory Dispersion Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 129–131.

(24) For an excellent discussion of diaxial addition to cyclic olefins *cf.* D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(25) (a) L. F. Fieser, *Experientia*, **6**, 312 (1950); (b) D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

(26) J. B. Ziegler and A. C. Shabica, THIS JOURNAL, **74**, 4891 (1952).

(27) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

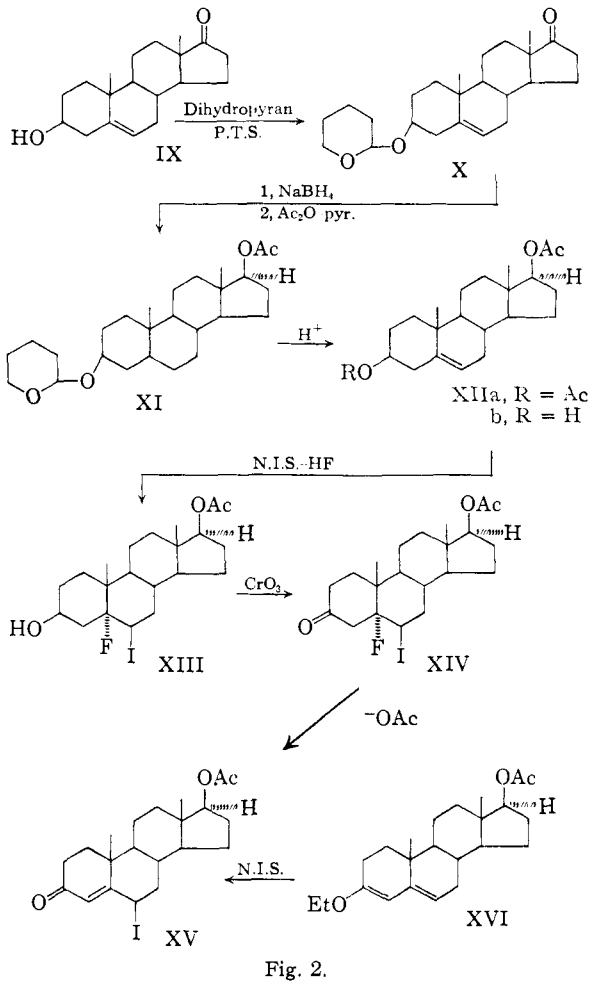


Fig. 2.

Assuming diaxial addition of I–F to the double bond the two possible products are XXII and XXIV (Fig. 5). From a consideration of the non-bonded interactions involved the latter compound would appear to be the thermodynamically more stable arrangement. The relevant non-bonded interactions are summarized

Compound XXII: four iodine–hydrogen 1:3-diaxial interactions; hydrogens at 1α, 3α, 7α and 9α; *two* iodine–hydrogen 1:2-axial–equatorial interactions; hydrogens at 4α and 6α.

Compound XXIV: one iodine–methyl 1:3-diaxial interaction; C-19 methyl group; *two* iodine–hydrogen 1:3-diaxial interactions; hydrogens at 4β and 8β; *one* iodine–hydrogen 1:2-axial–equatorial interaction; hydrogen at 7β.

Cancelling out equal non-bonded interactions the balance is: *compound XXIV:* one iodine–methyl interaction (diaxial); *compound XXII:* two iodine–hydrogen interactions (diaxial); one iodine–hydrogen interaction (axial–equatorial).

Although quantitative data are not available, these results suggest that XXIV is a more stable arrangement than XXII. In addition the greatly increased "back strain"[28] associated with an iodine substituent at a bridgehead as compared to a secondary iodide is an additional factor which makes XXIV a more stable system than XXII.

It is then possible to rationalize that the addition of I–F to the double bond proceeds with a

(28) See a series of papers by H. C. Brown and his colleagues. THIS JOURNAL, **75**, 1 (1953), and references cited therein.

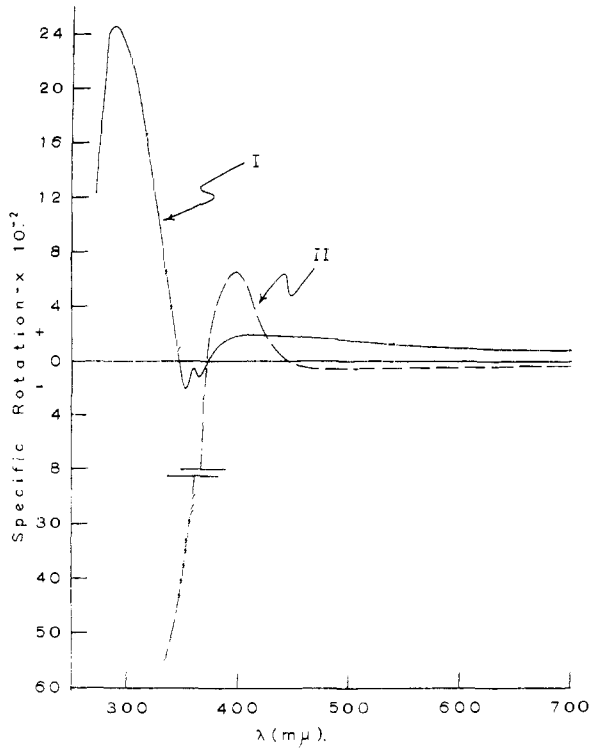
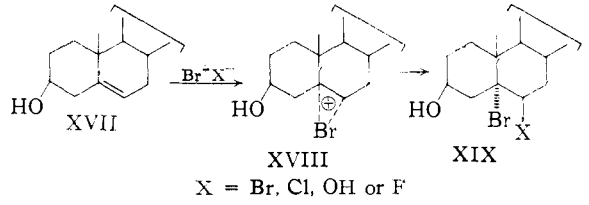


Fig. 3.—Testosterone (I) (*cf.* E. W. Foltz, A. E. Lippman and C. Djerassi, THIS JOURNAL, 77, 4359 (1955)); 6β-iodotestosterone acetate (II).



X = Br, Cl, OH or F

Fig. 4.

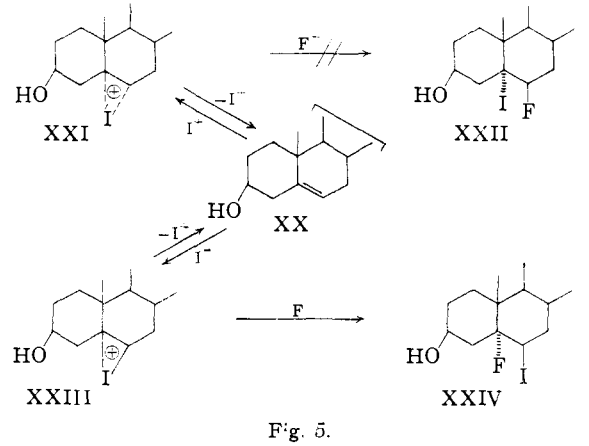


Fig. 5.

measure of thermodynamic control if the basic assumption is made that formation of the iodonium ion is a reversible process such that an equilibrium is set up between the olefin XX and the two possible iodonium ions XXI and XXIII. The kinetically favored iodonium ion will be XXI since, as was mentioned above, Br^+ preferentially approaches the Δ^5-double bond from the α-side of the molecule. Similarly OH^+ (peracid) is well known to attack Δ^5-3β-hydroxy steroids to afford predominantly 5α,6α-epoxides.[29]

However the reaction of XXI with F^- would lead to the thermodynamically less stable of the two possible products. The alternate reaction which proceeds *via* the kinetically less favored iodonium ion XXIII but affords the thermodynamically more stable end product XXIV thus seems to be the preferred pathway.[30]

Experimental[31]

6β-Iodo-5α-fluoropregnane-3β-ol-20-one (IVa).—A suspension of pregnenolone (IIIa) (25 g.) and N-iodosuccinimide (19.85 g.) in methylene dichloride (200 cc.) was added with stirring over 5–10 min. to a mixture of anhydrous hydrogen fluoride (100 g.) and tetrahydrofuran (176 g.) at −80° (acetone–solid carbon dioxide-bath). After 2 hours at −80° and 12 hours at 0° it was then added cautiously to an excess of sodium carbonate in ice-water. The product was extracted with methylene dichloride and the combined methylene dichloride solutions were washed successively with water, sodium thiosulfate solution and water. The dried solution (Na_2SO_4) then was adsorbed onto alumina (700 g.). Elution with methylene dichloride–acetone (98:2, 2.5 l.) afforded 6β-iodo-5α-fluoropregnane-3β-ol-20-one (IVa) (19.0 g.,) m.p. 116–118° dec., raised by crystallizations from acetone–hexane to 121–122° dec.; the m.p. varied greatly with the method of determination and a m.p. as high as 141–143° was recorded; [α] −3°, λ_{max}^{EtOH} 262 mμ, ε 426.

Anal. Calcd. for $C_{21}H_{32}O_2FI$: C, 54.54; H, 6.98; F, 4.11; I, 27.45. Found: C, 54.76; H, 6.89; F, 3.87; I, 27.75.

Treatment of IVa with Zinc.—Zinc dust (2.0 g.) was added to a solution of IVa (500 mg.) in acetic acid (15 cc.) and heated under reflux for 3 hours. Filtration and addition of ice-water to the filtrate afforded a precipitate (270 mg.), m.p. 146–156°, raised by chromatography over alumina to 192–194° (175 mg.). The m.p. was undepressed upon admixture with an authentic sample of pregnenolone and the two infrared spectra were identical.

6β-Iodo-5α-fluoropregnane-3β-ol-20-one Acetate (IVb).—(a) Acetic anhydride (5.0 cc.) was added to a solution of IVa (1.5 g.) in pyridine (20 cc.) at room temperature. After 18 hours at room temperature addition of ice-water and filtration afforded 6β-iodo-5α-fluoropregnane-3β-ol-20-one acetate (IVb) (1.4 g.), m.p. 176–179° dec., raised by several crystallizations from methanol to 187–189° dec. The m.p. was not a reliable criterion of purity and varied from 175–177° to 187–189° for the same sample; $[\alpha]_D$ −11°.

Anal. Calcd. for $C_{23}H_{34}O_3FI$: C, 54.76; H, 6.79; F, 3.77; I, 25.17. Found: C, 54.48; H, 6.84; F, 3.43; I, 24.89.

(b) **Addition of I–F to Pregnenolone Acetate (IIIb).**—Pregnenolone acetate (IIIb) (25 g.) in methylene dichloride (200 cc.) was added with stirring over 10 min. together with N-iodosuccinimide (17.3 g.) to a mixture of anhydrous hydrogen fluoride (100 g.) and tetrahydrofuran (176 g.) at −80°. After 2 hours at this temperature and 5 hours at 0° the mixture was added cautiously to an excess of sodium

(29) *Cf.* ref. 25a.

(30) A similar situation should not prevail with the addition of Br^+–X^- to a double bond since (a) a tertiary bromide has much less "back strain" than a tertiary iodide and (b) three-membered ring bromonium ions are intrinsically more stable than iodonium ions and as such are not likely to enter into a reversible equilibrium of this type.

(31) Melting points were determined on a Fisher–Johns hot stage and are uncorrected. Rotations were measured in chloroform, and ultraviolet light absorption spectra in 95% ethanol. The rotatory dispersion measurements were obtained with a Rudolph spectropolarimeter in dioxane solution using a xenon arc lamp (250–350 mμ) and a zirconium arc lamp (350–700 mμ). We are grateful to Dr. J. Mathews and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by Dr. A. Bernhardt, Mulheim (Ruhr), Germany.

carbonate in ice-water. The product was isolated as described above for IIIa → IVa and then adsorbed from hexane–benzene (80:20) onto alumina (750 g.). Elution with benzene–hexane (50:50, 4.2 l.) afforded 6β-iodo-5α-fluoropregnane-3β-ol-20-one acetate (IVb) (16.0 g.), m.p. 169–175°, raised by one crystallization from methanol to 178–182° dec., undepressed on admixture with a sample prepared as in method a; $[\alpha]_D$ −10°. The infrared spectra of the two samples were identical in every respect.

Treatment of IVb with Zinc and Methanol.—Zinc dust (500 mg.) was added to a solution of IVb (500 mg.) in methanol (20 cc.) and heated under reflux for 3 hours. Filtration, elimination of the solvent and crystallization of the residue from aqueous methanol afforded pregnenolone acetate (290 mg.), m.p. 144–145° undepressed upon admixture with an authentic sample, $[\alpha]_D$ +30°.

Alkaline Hydrolysis of IVb.—A solution of IVb (500 mg.) in methanol (25 cc.) containing potassium hydroxide (250 mg.) was heated under reflux for 45 min. The solution was then neutralized with acetic acid and concentrated to a small volume. Addition of ice-water and filtration afforded 6β-iodo-5α-fluoropregnane-3β-ol-20-one (IVa) (390 mg.), m.p. 136–139° dec., undepressed on admixture with an authentic sample; $[\alpha]_D$ −4°. The infrared spectra of the two samples were identical.

6β-Iodo-5α-fluoropregnane-3,20-dione (V).—An excess of 8 *N* chromic acid[16] was added to a solution of 6β-iodo-5α-fluoropregnane-3β-ol-20-one (IVa) (2.57 g.) in acetone (30 cc.) at 0°. After 1–2 min., ice-water was added and the crystalline precipitate was removed by filtration. Crystallization from methanol–chloroform afforded the dione V (1.65 g.), m.p. 124–126° dec.; the m.p. was variable and the analytical sample from methanol–chloroform had m.p. 122–124°, $[\alpha]_D$ −9°; λ_{max}^{KBr} 1710 and 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_2FI$: C, 54.76; H, 6.57; F, 4.13; I, 27.56. Found: C, 54.59; H, 6.51; F, 3.85; I, 27.14.

$\Delta^{3,5}$-Pregnadiene-3-ethyl Ether-20-one (Progesterone Enol Ether (VIII).—Ethyl orthoformate (20 cc.) and *p*-toluenesulfonic acid monohydrate (600 mg.) were added to a solution of progesterone (20 g.) in dioxane (130 cc.). After stirring at room temperature for 1 hour pyridine (16 cc.) was added. Ice-water then was added slowly to the reaction mixture with scratching and the precipitate was removed by filtration. One crystallization from methanol containing a few drops of pyridine afforded progesterone enol ether (VIII) (13.7 g.), m.p. 100–103°, raised by several cyrstallizations from the same solvent to 105–107°, $[\alpha]_D$ −35°, λ_{max}^{EtOH} 240–242 mμ, ε 21,400; λ_{max}^{KBr} 1710, 1660 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.55; H, 10.01; O, 9.44. Found: C, 80.32; H, 9.93; 0, 9.17.

6β-Iodoprogesterone (VI). (a) **By the Sodium Acetate in Methanol Treatment** of V.—A solution of 6β-iodo-5α-fluoropregnane-3,20-dione (V) in methanol (15 cc.) containing sodium acetate (750 mg.) was heated under reflux for 2.5 hours. The solution then was concentrated to a small volume and ice-water was added. Filtration afforded 6β-iodoprogesterone. After drying in a vacuum desiccator over calcium chloride it had m.p. 83–93° dec., wt. 165 mg. One crystallization from methylene dichloride–hexane raised the m.p. to 98–101° dec. The analytical sample from methylene dichloride–hexane had m.p. 105–107° dec., $[\alpha]_D$ +12°, λ_{max}^{EtOH} 250–252 mμ, ε 14,800; λ_{max}^{KBr} 1700, 1670 and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}O_2I$: C, 57.25; H, 6.64; I, 28.81. Found: C, 56.97; H, 6.45; I, 28.40.

(b) **Treatment of Progesterone Enol Ether (VIII) with N-Iodosuccinimide.**—N-Iodosuccinimide (845 mg.) and acetic acid (0.40 cc.) were added to a solution of progesterone enol ether (VIII) (1.0 g.) in acetone (20 cc.) and water (4.0 cc.) containing sodium acetate (400 mg.) at 0–5°. After stirring at 0–5° for 1 hour the excess of reagent was destroyed by the addition of sodium sulfite solution. Addition of ice-water then afforded a precipitate of 6β-iodoprogesterone (VI) m.p. 94–100° dec., raised by one crystallization from methylene dichloride–hexane to 103–105° dec.; (800 mg.), $[\alpha]_D$ +14°. The m.p. was undepressed on admixture with a sample prepared as in method a and the infrared spectra of the two samples were identical.

Δ^5-Androstene-3β-ol-17-one 3-Tetrahydropyranyl Ether (X).—Dihydropyran (50 cc.) and *p*-toluenesulfonic acid (1.0 g.) were added to a solution of Δ^5-androstene-3β-ol-17-one (IX) (25 g.) in anhydrous benzene (550 cc.). After 20 hours at room temperature the solution was washed with 5% sodium carbonate solution and water and then dried over anhydrous sodium sulfate. Removal of the solvent and crystallization from ether–methanol afforded the tetrahydropyranyl ether (X) (21.4 g.), m.p. 183–187°, raised by several crystallizations from methanol–chloroform to 200–201° $[\alpha]_D$ −61°, λ_{max}^{KBr} 1730 cm.$^{-1}$, λ_{max}^{EtOH} 290–294 mμ, ε 63.

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.10; H, 9.48; O, 13.19.

Δ^5-Androstene-3β,17β-diol 3-Tetrahydropyranyl Ether 17-Acetate (XI).—Sodium borohydride (10.0 g.) in water (20 cc.) was added to a stirred solution of the C-17 ketone X (14.8 g., m.p. 183–187°) in tetrahydrofuran (300 cc.). After 2 hours at room temperature addition of ice-water containing acetic acid (20 cc.) afforded a product which was removed by filtration, dried at 100° and then dissolved in pyridine (100 cc.) containing acetic anhydride (20 cc.). After 45 min. at 90° the solution was cooled and diluted with ice-water (1 l.). Filtration afforded crude Δ^5-androstene-3β,17β-diol 3-tetrahydropyranyl ether 17-acetate (XI) (14.3 g.), m.p. 132–134°, raised by crystallizations from methylene dichloride–methanol to 149–150°, $[\alpha]_D$ −80°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; O, 15.90. Found: C, 74.41; H, 9.41; O, 16.06.

Δ^5-Androstene-3β,17β-diol 17-Acetate (XIIb).—Hydrochloric acid (4.8 cc., 2 *N*) was added to a solution of XI (9.5 g., m.p. 132–137°) in acetic acid (240 cc.). After 5 hours at room temperature the solution was poured onto ice-water. Filtration and crystallization of the product from acetone–hexane afforded Δ^5-androstene-3β,17β-diol 17-acetate (XIIb) (5.1 g.), m.p. 143–145°, raised by one additional crystallization from acetone–hexane to 149–151°, $[\alpha]_D$ −75°; lit.[21,32] report m.p. 146–147°, $[\alpha]_D$ −74°.

6β-Iodo-5α-fluoroandrostane-3β,17β,-diol 17-Acetate (XIII).—Δ^5-Androstene-3β,17β-diol 17-acetate (XIIb) (9.0 g., m.p. 143–145°) in methylene dichloride (250 cc.) was added with stirring over 10 min. together with N-iodosuccinimide (10.1 g.) to a mixture of anhydrous hydrogen fluoride (120 g.) and tetrahydrofuran (211 g.) at −80°. After 3 hours at −80° and 16 hours at 0° the solution was added cautiously to an excess of sodium carbonate in ice-water and the product was isolated as described above for a similar experiment in the pregnane series. The crude product was adsorbed from benzene onto alumina (400 g.). Elution with benzene–ether (90:10, 4.2 l.) followed by one crystallization from methylene dichloride–hexane afforded 6β-iodo-5α-fluoroandrostane 3β,17β-diol 17-acetate (XIII) (6.4 g.) m.p. 155–157° dec. raised by crystallizations from acetone–hexane to 159–161° dec. The m.p. depends greatly on the rate of heating; $[\alpha]_D$ −47°.

Anal. Calcd. for $C_{21}H_{32}O_3FI$: C, 52.71; H, 6.74; F, 3.97; I, 26.53. Found: C, 52.52; H, 6.79; F, 3.60; I, 26.62.

6β-Iodo-5α-fluoroandrostane-17β-ol-3-one Acetate (XIV).—An excess of 8 *N* chromic acid[16] was added to a solution of XIII (500 mg., m.p. 155–157°) in acetone (15 cc.) at 0°. After 1–2 min. addition of ice-water and isolation of the product with methylene dichloride followed by one crystallization from hexane afforded 6β-iodo-5α-fluoroandrostane-17β-ol-3-one acetate (XIV) (280 mg.), m.p. 128–129° dec., raised by crystallizations from hexane to 132–134° dec., $[\alpha]_D$ −76°; rotatory dispersion curve (*c* 0.051 in dioxane): $[\alpha]_{700}$ −35°, $[\alpha]_{589}$ −69°, $[\alpha]_{307.5}$ −753°, $[\alpha]_{300}$ +69°.

Anal. Calcd. for $C_{21}H_{30}O_3FI$: C, 52.93; H, 6.35; F, 3.99; I, 26.64. Found: C, 53.22; H, 6.52; F, 3.68; I, 26.41.

6β-Iodotestosterone Acetate (XV). (a) **By the Sodium Acetate in Methanol Treatment of XIV.**—A solution of 6β-iodo-5α-fluoroandrostane-17β-ol-3-one acetate (XIV) (250 mg.) in methanol (15 cc.) containing sodium acetate was heated under reflux for 2.5 hours. Removal of the solvent *in vacuo*, addition of ice-water, filtration and crystallization of the product from methylene dichloride–hexane afforded 6β-iodotestosterone (150 mg.), m.p. 93–98°, raised by crystallizations from methylene dichloride hexane to 106–108° dec., $[\alpha]_D$ −56°, λ_{max}^{EtOH} 252–254 mμ, ε 15,400; λ_{max}^{KBr} 1735,

(32) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949).

1670, 1600 and 1250 cm.$^{-1}$; rotatory dispersion curve (c 0.0675 in dioxane): $[\alpha]_{700}$ −44°, $[\alpha]_{589}$ −50°, $[\alpha]_{500}$ −62°, $[\alpha]_{332.5}$ −5,510°.

Anal. Calcd. for $C_{21}H_{29}O_3I$: C, 55.26; H, 6.40; I, 27.81. Found: C, 55.54; H, 6.39; I, 27.24.

(b) By the Treatment of Testosterone Acetate Enol Ether (XVI) with N-Iodosuccinimide.—N-Iodosuccinimide (845 mg.) and acetic acid (0.4 cc.) were added to a solution of testosterone acetate enol ether[33] (XVI) (1.0 g., m.p. 129–132°, $[\alpha]_D$ −150°, λ_{max}^{EtOH} 240–242, ϵ 20,900) in acetone (20 cc.) and water (4.0 cc.) containing sodium acetate (400 mg.) at 0–5°. After stirring at 0–5° for 1 hour the excess of reagent was destroyed by the addition of sodium sulfite solution. Addition of ice-water and crystallization of the precipitate from methylene dichloride–hexane afforded 6β-iodotestosterone (XV) (770 mg.), m.p. 98–102° dec. raised by one further crystallization from methylene dichloride–hexane to 105–108° dec., $[\alpha]_D$ −52°, λ_{max}^{EtOH} 252–254 mμ, ϵ 15,300. The m.p. was undepressed upon admixture with a sample prepared as in method a and the infrared spectra were identical.

(33) E. Batres and H. J. Ringold, forthcoming publication from these laboratories.

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[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

16β-Methyl Cortical Steroids[1]

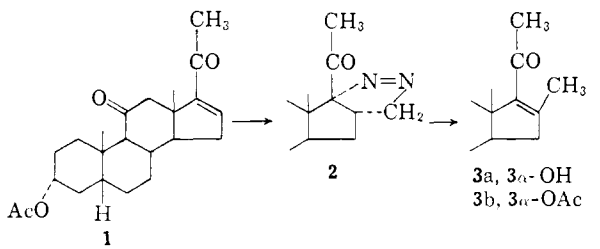
BY D. TAUB, R. D. HOFFSOMMER, H. L. SLATES, C. H. KUO AND N. L. WENDLER

RECEIVED DECEMBER 30, 1959

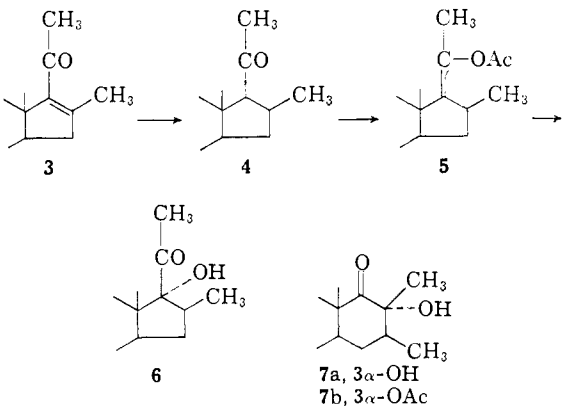
The partial synthesis of a number of 16β-methyl cortical steroids is described.

In this paper we wish to report in detail the preparation of 16β-methyl homologs of cortisone and its congeners. These substances are the first β-substituted cortical steroid derivatives to be described which are more potent anti-inflammatory agents than the corresponding parent steroids. Previously reported potentiating substituents have been attached to the α-face of the steroid nucleus.[2]

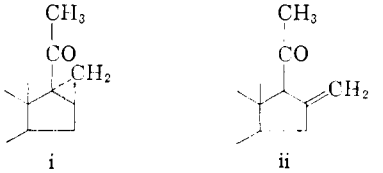
We utilized the readily available 3α-acetoxy-16-pregnene-11,20-dione (1)[3] as starting material, and introduced the 16-methyl substituent by reaction of 1 with diazomethane[4] and pyrolysis of the intermediate pyrazoline (2) followed by treatment with methanolic potassium hydroxide to give 16-methyl-3α-hydroxy-16-pregnene-11,20-dione (3a) in good over-all yield. Omission of the methanolic potassium hydroxide treatment yielded the 3-acetate 3b in somewhat smaller yield.[5] As is shown in the sequel, the 16-methyl-16-pregnene 3 is a versatile intermediate suitable for the preparation of both 16α-methyl- and 16β-methyl-substituted steroids.



Several approaches for the introduction of the 17α-hydroxyl group in the 16β-methyl series were next investigated. Catalytic hydrogenation of the 3α-acetoxy-16-methyl-16-pregnene 3b over palladium-on-calcium carbonate[4] led in excellent yield to 3α-acetoxy-16β-methylpregnane-11,20-dione (4). The β-configuration is assigned to the



C_{16}-methyl group and C-17 side chain in 4 as a consequence of the well established addition of hydrogen and other reactants to the α-side of the methylenepregnane-11,20-dione (ii). Since, as these authors have shown, ii is isomerized to the 16-methyl-16-pregnene (3) under alkaline conditions, the yield of the latter in the pyrolysis step was increased by alkaline treatment of the pyrolysis product before isolation.



(1) (a) A preliminary account of a portion of this work was communicated earlier: D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, THIS JOURNAL, **80**, 4435 (1958). See also (b) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4428 (1958); (c) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 6627 (1958).

(2) For recent discussion and review of structure activity relationships in this field see J. Fried, *Vitamins and Hormones*, **16**, 304 (1958); L. H. Sarett, *Ann. N. Y. Acad. Sci.*, **82**, 802 (1959).

(3) P. L. Julian and W. J. Karpel, U. S. Patent 2,671,794 (1954), H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957).

(4) *Cf.* A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

(5) This sequence is described in detail by H. L. Slates and N. L. Wendler, THIS JOURNAL, **81**, 5472 (1959), who also isolated and characterized the isomeric cyclopropane, 3α-acetoxy-16α,17α-methylenepregnane-11,20-dione (i), and exocyclic olefin, 3α-acetoxy-16-