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

Steroids. CXXXIX.[1] New Fluorination Procedures. Part I. The Addition of Br–F and I–F to Cyclohexene and a Variety of Unsaturated Steroids[2]

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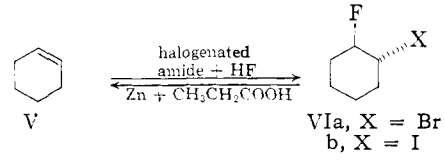
Treatment of cyclohexene with N-bromoacetamide and anhydrous hydrogen fluoride in the presence of an organic proton acceptor such as ether or tetrahydrofuran afforded *trans*-1-fluoro-2-bromocyclohexane. A similar reaction with N-iodosuccinimide led to *trans*-1-fluoro-2-iodocyclohexane. Application of this reaction to a variety of unsaturated steroids led to the preparation of C-6, C-11 and C-16 fluorinated steroids.

The ionic mechanism for the addition of molecular bromine or chlorine to an olefinic double bond in a polar medium is well established[4] and bromination, for example, is known to proceed in two discrete stages: electrophilic attack by bromine to afford a cation (I → II) which then undergoes attack by Br^- to give the *trans*-dibromide (III).

The formation of the cation II has been demonstrated by showing that the second stage of the reaction (II → III) can be diverted by the addition of other anions such as chloride, iodide or nitrate to afford the mixed addition products (IV, X = Cl, I or ONO_2) as well as the dibromide III.[5]

A stereospecific approach to 1,2-*trans*-bromochloro compounds, however, was developed by Buckles and Long[6] who by the use of N-bromoacetamide and hydrogen chloride converted olefins into their respective *trans*-bromo-chloro compounds. The conjugate acid of N-bromoacetamide ($CH_3\overset{+}{C}ONH_2Br$) was the source of electrophilic bromine which reacted with an olefin (I) to give a cation (II) (in the absence of Br^-) and thence by attack of Cl^- afforded a *trans*-bromo-chloro compound (IV, X = Cl). It can be seen that the intermediate cation II retains its steric identity from a consideration of the products formed by this reaction. Cinnamic acid, for example, gave 2-bromo-β-chlorohydrocinnamic acid[6] and in some previous work Buckles[7] had shown that the N-bromoacetamide–hydrogen bromide couple, which mechanistically is an identical system, converted *cis*-stilbene into *dl*-stilbene dibromide. Other investigators who have applied this reaction to steroid olefins[8,9] have also obtained stereospecific *trans* addition of Br–Cl.

It seemed feasible, therefore, that under the proper experimental conditions it should be possible to add Br–F across a double bond by treating a cation such as II with fluoride ion (II → IV, X = F). Recently, it has been shown that the low degree of ionization of hydrogen fluoride can be substantially increased by the presence of an organic proton acceptor such as 5% ethanol in chloroform[10] or tetrahydrofuran[11] and hence a system such as N-bromoacetamide–anhydrous hydrogen fluoride–diethyl ether seemed a logical choice for experimentation with olefins. Indeed, when cyclohexene (V) and 1.1 mols of N-bromoacetamide were added with stirring to a mixture of anhydrous hydrogen fluoride and tetrahydrofuran at −80° and subsequently kept for 2 hours at 0°, *trans*-1-fluoro-2-bromocyclohexane (Vb) was formed in good yield.



V VIa, X = Br
b, X = I

Taken in conjunction with mechanistic considerations the structure assigned to VIa was chosen on the basis of these data. Elemental analysis indicated an empirical formula of $C_6H_{10}BrF$; treatment of VIa with zinc and propionic acid at 90° readily regenerated cyclohexene (V); VIa was remarkably stable to all attempts to displace the bromine atom by magnesium, lithium or *n*-butyllithium under a reasonable variety of experimental conditions. The inert nature of the bromine atom reflects its deactivation by the strong inductive (−I) effect of the nearby fluorine atom.

Cyclohexene then was treated with N-iodosuccinimide[12] and hydrogen fluoride in the presence of diethyl ether when an analogous reaction took place and *trans*-1-fluoro-2-iodocyclohexane (VIb) was formed in 73% yield.[13]

All attempts to remove the iodine selectively from VIb were abortive. The compound resisted Grignard formation and was inert to lithium metal and *n*-butyllithium although, as expected, with zinc and propionic acid at 90° VIb regenerated cyclohexene.

(1) Steroids. CXXXVIII. J. A. Zderic, M. A. Cabezas Rivera and D. Chávez Limón, THIS JOURNAL, **82**, in press (1960).

(2) Presented in part by A. B. at the "International Symposium on Fluorine Chemistry," Birmingham, England, on July 15, 1959, and as a preliminary communication: A. Bowers, *ibid.*, **81**, 4107 (1959).

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

(4) *Cf.* (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, pp. 658–670; (b) P. B. D. de la Mare, *Ann. Repts. Chem. Soc.* (*London*), **47**, 126 (1950), and references therein.

(5) A. W. Francis, THIS JOURNAL, **47**, 2340 (1925).

(6) R. E. Buckles and J. W. Long, *ibid.*, **73**, 998 (1951).

(7) R. E. Buckles, *ibid.*, **71**, 1157 (1949).

(8) J. B. Ziegler and A. C. Shabica, *ibid.*, **74**, 4891 (1952).

(9) C. H. Robinson, L. Finckenor, E. P. Oliveto and D. Gould, *ibid.*, **81**, 2191 (1959).

(10) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

(11) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(12) C. Djerassi and co-workers have shown clearly that the conjugate acid of N-iodosuccinimide is a readily available source of electrophilic iodine; *cf.* C. Djerassi and C. T. Lenk, *ibid.*, **76**, 1722 (1954); C. Djerassi, J. Grossman and G. H. Thomas, *ibid.*, **77**, 3826 (1955).

(13) E. D. Bergmann and I. Shahak, *J. Chem. Soc.*, 1418 (1959), have shown, however, that cyclohexene reacts with iodine and silver fluoride to afford 3-iodocyclohexene.

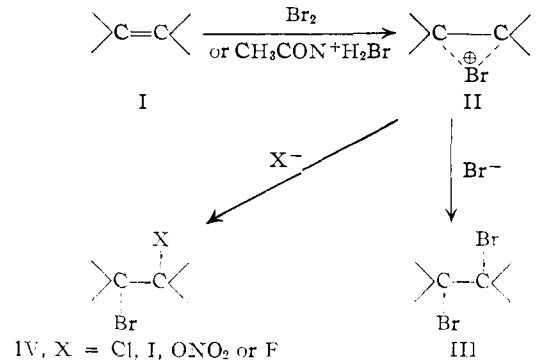


FIG. 1

In view of the current interest in fluorinated steroids it was of considerable interest to extend this reaction to unsaturated steroids and by examining a variety of compounds it was also possible to assess the utility of the reaction and define its scope. Accordingly, two steroid olefins (Δ^5 and $\Delta^{9(11)}$), an α,β-unsaturated ketone (Δ^{16}-20-ketone), a conjugated dienone ($\Delta^{4,6}$-3-ketone) and the enol acetate of a saturated ketone (Δ^2-3-acetate) were each treated with N-bromoacetamide and hydrogen fluoride in the presence of tetrahydrofuran.

The Δ^5-olefin readily added Br–F to afford the corresponding 6β-fluoro-5α-bromo derivative.[2] A full discussion of this reaction and the subsequent conversion of the fluoro-bromo intermediate into

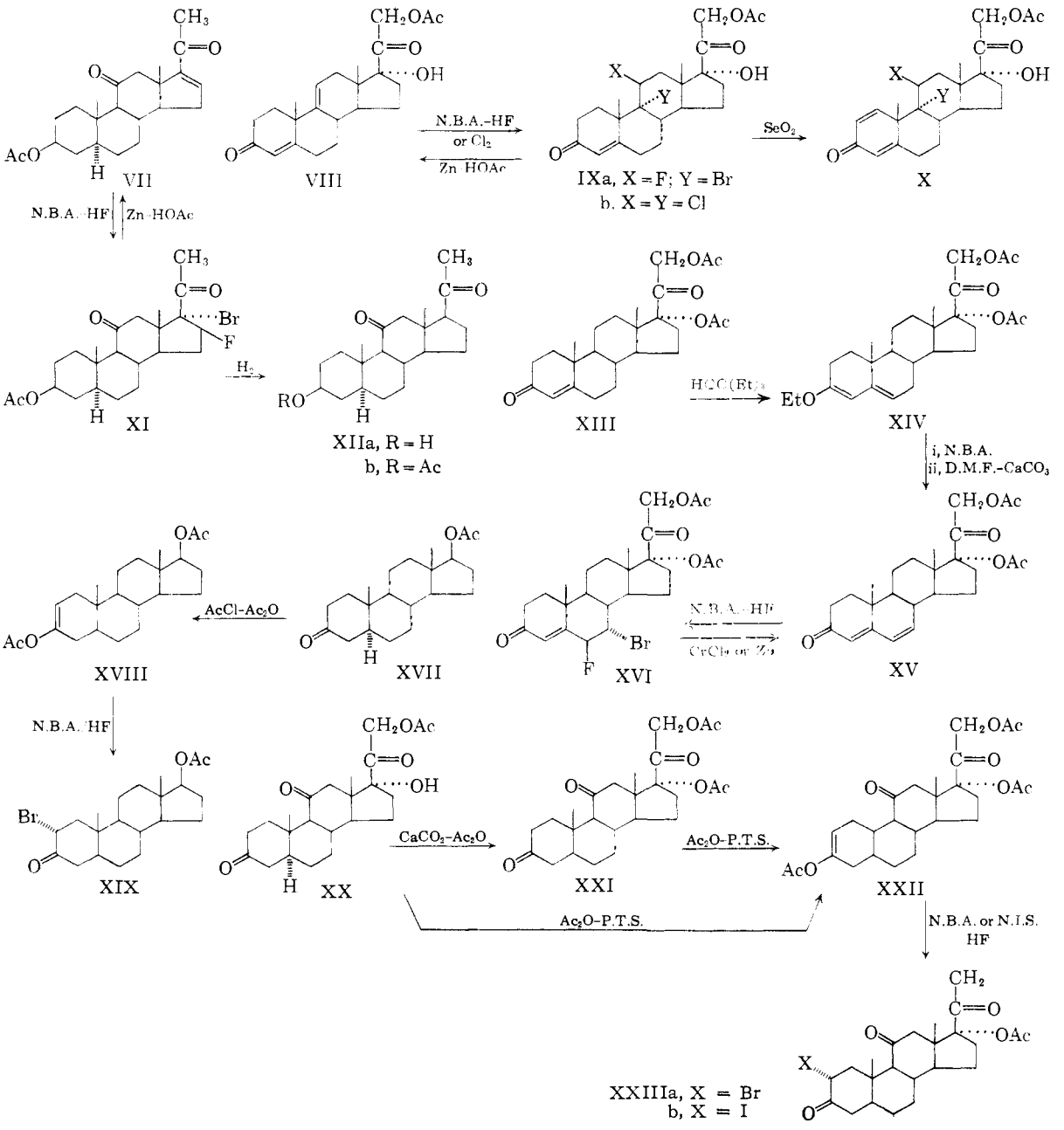


Fig. 2.

the biologically important 6α-fluoro-Δ⁴-3-ketone will be reported in a subsequent publication. The results obtained with the other unsaturated systems are outlined in Fig. 2.

Treatment of $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (VIII) ($\Delta^{9(11)}$-dehydro "Compound S" acetate)[14] with N-bromoacetamide and hydrogen fluoride led to the addition of Br–F to the $\Delta^{9(11)}$-double bond to afford 9α-bromo-11β-fluoro-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (IXa), the reaction being reversed by zinc and acetic acid treatment of the dihalide.

After the completion of this work a paper from the Schering Laboratories[9] reported the preparation of the Δ¹-analog of IX by the direct addition of Br–F to the Δ¹-analog of VIII. The same general method which is described in this paper was utilized, namely treatment of the olefin with N-bromoacetamide and hydrogen fluoride. Our conclusions as to the structure and stereochemistry of the 9,11-dihalide follows the reasoning outlined by Robinson and his colleagues and it is sufficient to note here that our views are in full accord.

Concurrent with the preparation of the 9α-bromo-11β-fluoro compound and as part of our structure–activity studies, the preparation of 9α,-11β-dichloro "Compound S" acetate (IXb) was investigated. Treatment of $\Delta^{9(11)}$-"Compound S" acetate (VIII) with 1.05 mols of chlorine in chloroform at 0° or N-chlorosuccinimide and hydrogen chloride led to the dichloride IXb whence selenium dioxide[15] oxidation afforded the corresponding Δ¹-analog Xb. Subsequent to this work Figdor[16] reported the preparation of IXb and Robinson, *et al.*,[9] the preparation of Xb. In the latter paper the structure and stereochemistry of Xb is discussed in detail and requires no further elaboration.[17]

In Table I are listed the anti-inflammatory activities of IXa, IXb and Xb as determined by the cotton pellet implant method, subcutaneous route in adrenalectomized rats. In this test these compounds show either zero or low order anti-inflammatory activity. Our findings with Xb (anti-inflammatory activity 0.15–0.5 X hydrocortisone) are in sharp conflict with those reported by the Schering workers[9] (4 and 8.5 × prednisolone acetate for the anti-inflammatory activity of Xb and the free 21-alcohol, respectively). This discrepancy presumably lies in the different methods used for the bioassays.[18]

TABLE I

Compound	Anti-inflammatory activity[a]
IXa	Inactive at 2.0 mg.[b]
IXb	0.15–0.5[c]
Xb	0.15–0.5[c]

[a] Cotton pellet implant method, subcutaneous route in adrenalectomized rats. Assays by Endocrine Laboratories, Madison, Wisc., and Dr. R. I. Dorfman, Worcester Foundation, Shrewsbury, Mass. [b] Both IXb and Xb showed a significant response at a dose level of 1.0 mg. [c] Hydrocortisone acetate = 1.0.

Recent interest in C-16 methyl steroids[19] prompted us to try the addition of Br–F across a Δ¹⁶-double bond with a view to obtaining 16-fluorinated steroids. It was found that when Δ¹⁶-allopregnene-3β-ol-11,20-dione acetate[20] was treated with N-bromoacetamide and hydrogen fluoride in the presence of tetrahydrofuran, a product was obtained which no longer exhibited selective absorption in the ultraviolet and which analyzed correctly for $C_{25}H_{36}O_4BrF$. Peracid epoxidation (initial attack by OH^+) of the Δ¹⁶-20-ketone moiety is known to proceed by α-side attack[21] and it is reasonable to expect that electrophilic approach by bromine would proceed in a stereochemically analogous manner to form the transient 16α,17α-bromonium cation. Fluoride ion attack of such an intermediate would then give the 17α-bromo-16β-fluoro dihalide (XI).[22] However, on the available evidence the possibility that this product is the 16α-bromo-17β-fluoride cannot be dismissed completely.

As expected XI readily regenerated the Δ¹⁶-20-ketone VII upon treatment with either zinc and acetic acid or chromous chloride in acetone. Similarly, collidine or sodium iodide in acetic acid treatment of XI led to VII. Hydrogenation of XI with a variety of catalysts invariably led to loss of both halogen atoms and formation of XIIa or XIIb dependent upon whether the reaction was attended with concomitant hydrolysis of the acetate group.

The reaction then was extended to a linearly conjugated diene-one, namely, Δ⁴,⁶-pregnadiene-17α,21-diol-3,20-dione diacetate (XV). This compound was prepared conveniently by converting Compound S-diacetate (XIII)[23] to its corresponding enol ether XIV with ethyl orthoformate and *p*-toluenesulfonic acid,[24] whence subsequent treat-

(14) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(15) (a) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **21**, 239 (1956); (b) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); (c) S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 457 (1956); (d) K. Florey and A. R. Restivo, *J. Org. Chem.*, **22**, 406 (1957).

(16) S. K. Figdor, Amer. Chem. Soc. Meeting, Chicago, Ill., Sept., 1958, Abstracts p. 66-P.

(17) Through the courtesy of Dr. C. H. Robinson we were able to show the identity of Xb with the compound prepared by the Schering workers[9] by a mixture m.p. determination and a direct infrared comparison.

(18) In ref. 9 the reported biological activities were based on results obtained by the granuloma pouch test in rats. ADDED IN PROOF May 4, 1960.—E. M. Glenn, S. L. Richardson and B. J. Bowman, *Metab.*, **8**(3), 265 (1959), recently reported that in the *local* granuloma pouch assay they found significant anti-inflammatory activity for progesterone and Compound "S."

(19) (a) G. E. Arth, J. Fried, D. B. R. Johnston, D. H. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, THIS JOURNAL, **80**, 3161 (1958); (b) E. P. Oliveto, R. Rousser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4431 (1958); (c) J. A. Edwards, H. J. Ringold and C. Djerassi, *ibid.*, **81**, 3156 (1959).

(20) (a) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951); (b) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952).

(21) P. L. Julian, E. W. Meyer and I. Ryden, *ibid.*, **72**, 367 (1950).

(22) Similarly the *trans* addition of HOBr to a Δ¹⁶-C-20-ketone is known to lead to the 16β-hydroxy-17α-bromo compound; *cf.* G. Gansau, Doctorate Thesis, Technische Universität Berlin-Charlottenburg, 1952, and B. Loken, S. Kaufman, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 1738 (1956); and lithium aluminum hydride fission of a 16α,17α-epoxide yields the 17α-alcohol by 16β-attack of the hydride ion; *cf.* ref. 21.

(23) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 820 (1956).

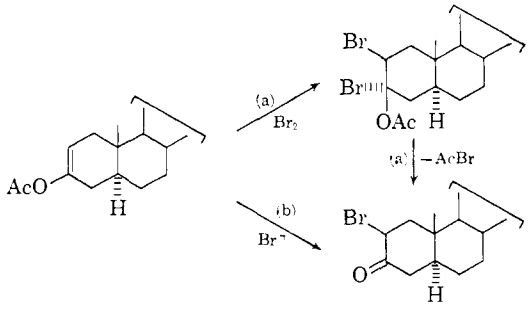
(24) We are grateful to Dr. Howard J. Ringold for making available to us the details of this procedure.

ment with N-bromosuccinimide and acetic acid in an aqueous buffered acetone medium led to the 6β-bromo-Δ⁴-3-ketone which without purification was dehydrobrominated with calcium carbonate in dimethylformamide to afford the diene-one XV.

The N-bromoacetamide–hydrogen fluoride couple then reacted with XV to give a product which was formulated as 6β-fluoro-7α-bromo-Δ⁴-pregnene-17α,21-diol-3,20-dione diacetate (XVI). Initial attack by Br^+ would be expected from the α-face,[25] whence diaxial opening of the bromonium ion[26] would afford the 6β-fluoro-7α-bromo dihalide XVI. It exhibited maximum absorption in the ultraviolet at 234–236 mμ, ε 10,500, in full accord with its assigned structure.[27] Treatment of XVI with zinc and acetic acid, chromous chloride or sodium iodide in acetic acid led to the elimination of both halogen atoms and regeneration of XV.

It is worthy of comment that both VII, VIII and XV were recovered unchanged after treatment with N-iodosuccinimide and anhydrous hydrogen fluoride under conditions where cyclohexene readily gave 1-fluoro-2-iodocyclohexene in good yield. Presumably steric factors inhibit the approach of the conjugate acid of N-iodosuccinimide.

A recent publication by Jones and Wluka[28] has indicated that the bromination of the Δ⁶-enol acetate of a C-7 ketone does not necessarily proceed with stereoelectronic control[29] and an alternate mechanism was proposed. In addition, Barton and Cookson[26] have pointed out that diaxial addition of bromine to the double bond of an enolate followed by the loss of the elements of acetyl bromide would lead (mechanism a) to the same product as that obtained by stereoelectronic control[29] (axial approach of electrophilic bromine, mechanism b).[30]



If mechanism a was operative, then the addition of Br^+ F^- to the enol acetate of a C-3 ketone (5α-allo series) would afford a 2β-fluoro-3-ketone.

Accordingly, two Δ²-enol acetates were prepared and their reaction with N-bromoacetamide and hydrogen fluoride and N-iodosuccinimide and hydrogen fluoride were investigated. Reaction of dihydrotestosterone acetate (XVII) with acetic anhydride and acetyl chloride under reflux smoothly led to the Δ²-enol acetate XVIII. The enol acetate derived from dihydro allocortisone 17,21-diacetate was prepared by one of two methods. Acetylation of dihydroallocortisone acetate (XX) by heating under reflux with acetic anhydride in the presence of calcium carbonate[31] gave the corresponding 17,21-diacetate XXI whence treatment with acetic anhydride and *p*-toluenesulfonic acid hydrate for seventy-two hours at room temperature[32] afforded the enol acetate XXII. More conveniently, XXII was prepared by the direct reaction of XX with acetic anhydride and *p*-toluenesulfonic acid.

Both XVIII and XXII, however, afforded the corresponding 2α-bromo-3-ketones XIX and XXIIIa, respectively, after treatment with N-bromoacetamide and hydrogen fluoride under the usual low temperature conditions. In addition, XXII gave an iodoketone XXIIIb when the N-bromoacetamide was replaced by N-iodosuccinimide. The 2α-stereochemistry of the iodine atom in XXIIIb was assigned by analogy with the results obtained with N-bromoacetamide. These results indicate that diaxial addition of Br–F does not operate for the enol acetate of a C-3-ketone in the allo series.

Experimental[34]

1-Fluoro-2-bromocyclohexane (VIa).—Dry ether (98 g.) was added to anhydrous hydrogen fluoride (54 g.) at −80° (acetone–solid CO_2) in a polyethylene bottle. N-Bromoacetamide (30 g.) and cyclohexene (V) (16 g.) then were added portion-wise and simultaneously over 10 min. After a further 2 hours at −80° with stirring (polyethylene covered magnet) the solution was kept at 0° for 2 hours. The reaction mixture now was added cautiously to an excess of ice-cold sodium bicarbonate solution. Ether extraction and distillation afforded 1-fluoro-2-bromocyclohexane (VIa) (14.95), b.p. 30° (13 mm.), n^{20} 1.4830.

Anal. Calcd. for $C_6H_{10}BrF$: C, 39.78; H, 5.56; Br, 44.13; F, 10.49. Found: C, 39.40; H, 5.57; Br, 44.07; F, 10.16.

1-Fluoro-2-iodocyclohexane (VIb).—Dry ether (270 g.) was added to anhydrous hydrogen fluoride (131 g.) at −80° and N-iodosuccinimide[35] (150 g.) and cyclohexene (V) (45 g.) then were added portionwise and simultaneously over 10 min. with stirring. After a further 2 hours at −80° and 1 hour at 0° the reaction mixture was added cautiously to an excess of ice-cold sodium bicarbonate solution. The product was extracted from the alkaline solution with ether and the iodine-colored ether solution was washed successively with water, sodium thiosulfate solution and water. After drying over anhydrous sodium sulfate the ether was removed *in vacuo*. The product was distilled from finely powdered sodium carbonate (2–3 g.) or calcium carbonate[36] to afford

(25) Peracid epoxidation of a Δ⁴,⁶-3-ketone is known to give the 6α,7α-epoxide; *cf.* A. Nussbaum, G. Brabazon, T. L. Popper and E. P. Oliveto, THIS JOURNAL, **80**, 2722 (1958).

(26) For a full discussion of "diaxial addition" to double bonds *cf.* D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(27) For a discussion of the effect of a 6β-fluorine atom on the ultraviolet spectrum of a Δ⁴-3-ketone *cf.* A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

(28) E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.*, 911 (1959).

(29) E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6269 (1956).

(30) For a full discussion of the mechanism of the halogenation of the enol acetates of C-3 ketones *cf.* forthcoming publication by R. Villotti, H. J. Ringold and C. Djerassi.

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

(32) A. Bowers, L. C. Ibáñez and H. J. Ringold, THIS JOURNAL, **81**, 3709 (1959).

(33) Melting points were determined on a Fisher hot-stage and are uncorrected.

(34) The rotations listed were determined in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. We are grateful to Dr. J. Matthews and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer. The alumina used in this work had been suspended in ethyl acetate for 18 hours, and then dried at 100°. The elemental analyses were carried out by Dr. A. Bernhardt, Mulheim (Ruhr), Germany.

(35) Commercially available from Arapahoe Chemicals, Boulder, Colo.

(36) In the absence of carbonate the distillation was accompanied by some decomposition.

1-fluoro-2-iodocyclohexane (VIb) (90.4 g.), b.p. 64° (9 mm.), n^{20} 1.5314. This product still contained a trace of free iodine. After washing with 10 cc. of 2% sodium thiosulfate it was dried and redistilled over sodium carbonate to afford 76 g. of an almost colorless product, n^{20} 1.5318, unchanged after a further fractional distillation. It was found convenient to store this product at 0–5° in the absence of light. A sample exposed to the sunlight liberated iodine.

Anal. Calcd. for $C_6H_{10}FI$: C, 31.59; H, 4.42; I, 55.63; F, 8.32. Found: C, 31.87; H, 4.44; I, 55.46; F, 7.92.

Treatment of 1-Fluoro-2-bromocyclohexane with Zinc and Propionic Acid.—Zinc dust (10 g.) was added to a solution of 1-fluoro-2-bromocyclohexane (VIa) in propionic acid (15 cc.) and heated at 100° for 1 hour in a distillation apparatus. Cyclohexene (2.5 g.) was collected in the receiver identical (infrared comparison) with an authentic sample.

A similar experiment with 1-fluoro-2-iodocyclohexane (VIb) afforded 1.42 g. of cyclohexene.

$\Delta^{4,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (VIII).—Methanesulfonyl chloride (6.7 cc.) was added to a solution of hydrocortisone acetate (11.27 g.) in dimethylformamide (freshly distilled) (113 cc.) and pyridine (16.2 cc.). After heating at 80° for 1.5 hr. the solution was poured onto ice-water. Filtration afforded a product which was adsorbed from methylene dichloride onto a column of silica (400 g.) intimately mixed with an equal volume of Celite. Elution with methylene dichloride–acetone (90:10, 4.8 l.) and one crystallization from methanol–chloroform afforded $\Delta^{4,9(11)}$-pregnadiene-17α-21-diol-3,20-dione 21-acetate (VIII) (8.27 g.), m.p. 234–236°, $[\alpha]_D$ +117°; lit.[14] m.p. 236–237°, $[\alpha]_D$ +117°.

9α-Bromo-11β-fluoro-Δ^4-pregnene-17α,21-diol-3,20-dione-21-Acetate (IXa).—A suspension of $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (772 mg.) and N-bromoacetamide (300 mg.) in anhydrous methylene dichloride (40 cc.) was added over 2–3 minutes with stirring to a mixture of anhydrous hydrogen fluoride (10.19 g.), and anhydrous tetrahydrofuran (18 g.) in a polyethylene bottle at −80° (acetone–solid CO_2). After 1 hr. at −80° it was kept for a further 1 hr. at 0° and then added cautiously to an excess of an ice-cold solution of sodium carbonate. Extraction with methylene dichloride and crystallization from acetone–hexane furnished 9α-bromo-11β-fluoro-Δ^4-pregnene-17α-21-diol-3,20-dione 21-acetate (IXa) (690 mg.), m.p. 205–208°, raised by several crystallizations from acetone–hexane to 215–217°, $[\alpha]_D$ +142°, λ_{max}^{EtOH} 240–242 mμ, ϵ 15,500.

Anal. Calcd. for $C_{23}H_{30}O_5FBr$: C, 56.90; H, 6.23; F, 3.91; Br, 16.48. Found: C, 56.41; H, 6.14; F, 3.77; Br, 16.40.

Treatment of IXa with Chromous Chloride.—In an atmosphere of CO_2, zinc dust (10.0 g.) and mercuric chloride (0.8 g.) were suspended in water (10 cc.) containing concentrated hydrochloric acid (0.5 cc.) and shaken for 3 min. The aqueous layer was decanted and replaced by *N* hydrochloric acid (22 cc.). Chromic chloride hexahydrate (5.43 g.) was then added in three portions over 5 min. and the suspension shaken for a further 5 min. when it was filtered in an atmosphere of CO_2 to afford a deep blue solution; 5.0 cc. of this solution was added to a solution of IXa (330 mg.) in acetic acid (20 cc.) and kept in a CO_2 atmosphere at room temperature for 30 min. Addition of ice-water and filtration afforded $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (VIII) (270 mg.), m.p. 222–227°, raised by chromatography over alumina to 229–231°, $[\alpha]_D$ +111°. A mixture melting point with an authentic sample gave no depression and the infrared curve was identical with that of VIII.

9α,11β-Dichloro-Δ^4-pregnene-17α,21-diol-3,20-dione 21-Acetate (IXb). (a) By Treatment of VIII with N-Chlorosuccinimide and Hydrogen Chloride.—N-Chlorosuccinimide (177 mg.) was added to a solution of $\Delta^{9(11)}$-Compound S acetate (VIII) (400 mg.) in methylene dichloride (25 cc.) at 0°. Dry hydrogen chloride then was bubbled through the solution for 10 min. The stoppered flask then was kept at 0° for a further 20 min. Addition of water and isolation with methylene dichloride afforded 9α,11β-dichloro-Δ^4-pregnene-17α-21-diol-3,20-dione 21-acetate (IXb) (410 mg.), m.p. 228–233°, raised by one crystallization from acetone–hexane to 234–236° (150 mg.). The analytical sample from acetone–hexane had m.p. 238–240°, $[\alpha]_D$ +192°, λ_{max}^{EtOH} 240 mμ, ϵ 16,050.

Anal. Calcd. for $C_{23}H_{30}O_5Cl_2$: C, 60.46; H, 6.47; Cl, 15.18. Found: C, 60.29; H, 6.59; Cl, 15.56.

(b) By Direct Addition of Chlorine.—Chlorine (423 mg., 1.1 mol) in carbon tetrachloride (10.3 cc.) was added in one portion to a solution of $\Delta^{9(11)}$-Compound S acetate (2.1 g.) in chloroform (50 cc.) at 0°. After one minute at this temperature the solution was washed with sodium bicarbonate solution and then water. Removal of the solvent after drying over sodium sulfate afforded the dichloro compound IXb (2.3 g.), m.p. 195–225°, raised by one crystallization from acetone–hexane to 233–235° (990 mg.) undepressed on admixture with a sample prepared as in method (a). The infrared spectra were identical.

Treatment of IXb with Zinc and Acetic Acid.—Zinc (110 mg.) was added portionwise over 1 hour with stirring to a solution of the 9α,11β-dichloride IXb (110 mg.) in acetic acid (5.0 cc.) at 70°. After a further 15 min. the solution was filtered and evaporated to dryness. Chromatography of the product over silica (5.0 g.) afforded $\Delta^{9(11)}$-Compound S acetate (VIII) (50 mg.), m.p. 229–231°, $[\alpha]_D$ +115°; the m.p. was undepressed upon admixture with an authentic sample; λ_{max}^{EtOH} 240 mμ, ϵ 16,600.

9α,11β-Dichloro-$\Delta^{1,4}$-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (Xb).—Selenium dioxide (516 mg.) was added to a solution of 9α,11β-dichloro-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (IXb) (950 mg.) in tertiary butyl alcohol (45 cc.) containing pyridine (0.2 cc.) and heated under reflux with stirring in an atmosphere of nitrogen for 48 hours. After filtration over Celite to remove the precipitated selenium, the solution was evaporated to dryness, redissolved in ethyl acetate and washed well with water. The dried solution (Na_2SO_4) was evaporated to dryness and the residue adsorbed from methylene dichloride onto silica (38 g.) intimately mixed with an equal volume of Celite. Elution with methylene dichloride–acetone (90:10, 500 cc.) afforded 9α,11β-dichloro-$\Delta^{1,4}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (Xb) (450 mg.), m.p. 234–238°, raised by crystallizations from acetone–hexane to 244–247°, $[\alpha]_D$ +170°, +165°, λ_{max}^{EtOH} 238 mμ, ϵ 14,500. The m.p. was undepressed on admixture with an authentic sample[9,17] and the infrared curves of the two samples were identical.

Anal. Calcd. for $C_{23}H_{28}O_5Cl_2$: C, 60.66; H, 6.20; Cl, 15.57. Found: C, 60.31; H, 6.12; Cl, 15.40.

Enol Ether of Compound S Diacetate (XIV).—Ethyl orthoformate (50 cc.) was added to a suspension of Compound S diacetate[23] (50 g.) in dioxane (380 cc.) containing *p*-toluene sulfonic acid monohydrate (1.6 g.) and stirred at room temperature for 1.5 hr. During this time all the steroid dissolved. Pyridine (40 cc.) then was added and the product was precipitated by the addition of ice-water (3 l.). Filtration afforded the enol ether XIV which was washed with water and dried over calcium chloride in a vacuum desiccator; wt. 39 g., m.p. 123–125°, raised by several crystallizations from methanol containing a few drops of pyridine to 125–126°, $[\alpha]_D$ −123°, λ_{max}^{EtOH} 240–242 mμ, ϵ 20,400.

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35; O, 20.94. Found: C, 70.48; H, 8.34; O, 21.30.

$\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,20-dione Diacetate (XV).—Sodium acetate (21.3 g.) in water (150 cc.) was added to a solution of the enol ether XIV in acetone (1.2 l.). The solution then was cooled to 0° and N-bromosuccinimide (33.49 g.) followed by acetic acid (22.4 cc.) were added. After stirring for 3 hours at 0° addition of water and extraction with ether afforded the crude 6β-bromo-Δ^4-3-ketone which without purification was dissolved in dimethylformamide (170 cc.) (without heating) and added dropwise over 10 min. to a suspension of finely divided calcium carbonate (17.8 g.) in refluxing dimethylacetamide (350 cc.). After heating under reflux for a further 30 min. the solution was cooled and filtered to remove the excess of calcium carbonate. Addition of the filtrate to ice-water (4 l.) and filtration afforded $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione diacetate (XV) (36 g.), m.p. 201–204°, λ_{max}^{EtOH} 284 mμ, ϵ 22,900. After two crystallizations from acetone–hexane it had m.p. 210–212°, λ_{max}^{EtOH} 284 mμ ϵ 27,500, $[\alpha]_D$ + 20°.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53; O, 22.40. Found: C, 69.84; H, 7.43; O, 22.90.

$\Delta^{5,5,7}$-Pregnatriene-3,17α,21-triol-20-one Triacetate.—A solution of $\Delta^{4,8}$-pregnadiene-17α,21-diol-3,20-dione diacetate (XV) (5.0 g.) in acetic anhydride (25 cc.) and acetyl chloride (25 cc.) was heated under reflux in an atmosphere of nitrogen for 2.5 hr. Elimination of the solvent *in vacuo* at 90° gave an oily residue which crystallized from methanol to

afford $\Delta^{3,5,7}$-pregnatriene-3,17α,21-triol-20-one triacetate (1.95 g.), m.p. 140–149°, raised by crystallizations from methanol to 145–147°, $[\alpha]D$ −127°; λ_{max}^{EtOH} 302, 314–316 and 330 mμ, ϵ 15,850, 19,050 and 13,800, respectively.

Anal. Calcd. for $C_{27}H_{34}O_7$: C, 68.91; H, 7.28; O, 23.81. Found: C, 68.57; H, 7.02; O, 23.65.

6β-Fluoro-7α-bromo-Δ^4-pregnene-17α,21-diol-3,20-dione Diacetate (XVI).—A solution of $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione diacetate (XV) (5.0 g.) in methylene dichloride (200 cc.) was added slowly with stirring together with N-bromoacetamide (2.0 g.) to a mixture of anhydrous hydrogen fluoride (21 g.) and dry tetrahydrofuran (37 g.) at −80°. After keeping at −80° for 1.5 hr. and 0° for a further 16 hr. the reaction mixture was added cautiously to an excess of sodium carbonate solution in ice-water. Extraction with methylene dichloride and removal of the solvent at 30° *in vacuo* afforded a non-crystalline product which was adsorbed from benzene onto alumina (250 g.). Elution with benzene and benzene–ether (90:10) afforded 6β-fluoro-7α-bromo-Δ^4-pregnene-17α,21-diol-3,20-dione diacetate (XVI) (2.08 g.), m.p. 120–124°. After several crystallizations from methanol it had m.p. 120–122°, $[\alpha]D$ +7°, λ_{max}^{EtOH} 234–236 mμ, ϵ 12,000.

Anal. Calcd. for $C_{25}H_{32}O_6BrF$: C, 56.93; H, 6.11; Br, 15.16; F, 3.60. Found: C, 56.49; H, 5.93; Br, 15.60; F, 3.32.

Further elution with benzene–ether (80:20) afforded starting material (610 mg.) as shown by a mixture m.p. determination and infrared curve comparison.

Chromous Chloride Treatment of XVI.—Chromous chloride solution (5.0 cc.) (prepared as described above) was added to a solution of XVI (400 mg.) in acetic acid (35 cc.) in an atmosphere of carbon dioxide. After 30 min. addition of ice-water and filtration afforded $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione diacetate (XV) (300 mg.), m.p. 195–200°, raised by chromatography over alumina to 207–209°, undepressed on admixture with an authentic sample; λ_{max}^{EtOH} 284–286 mμ, ϵ 24,400.

Raney Nickel Treatment of XVI.—Raney nickel (approx. 500 mg.) was added to a solution of XVI (300 mg.) in acetone (30 cc.) and heated under reflux for 2 hr. After filtration over Celite the solution was evaporated *in vacuo* and the product chromatographed over alumina to afford the diene-one XV (160 mg.), m.p. 203–205° undepressed on admixture with an authentic sample, λ_{max}^{EtOH} 284–286 mμ, ϵ 23,900.

16β-Fluoro-17α-bromoallopregnane-3β-ol-11,20-dione Acetate (XI).—Δ^{16}-Allopregnene-3β-ol-20-one acetate[20] (25 g., m.p. 179–181°, $[\alpha]D$ +64°) in methylene dichloride (525 cc.) was added together with N-bromoacetamide (10.1 g.) to a mixture of anhydrous hydrogen fluoride (48 g.) and tetrahydrofuran (83.5 g.) at −80°. After 1 hour at this temperature and 16 hours at 0° the reaction mixture was added cautiously to an excess of sodium carbonate in ice-water. Isolation with methylene dichloride gave a product which was adsorbed from hexane–methylene dichloride (90:10) onto alumina (1 k.). Elution with hexane–methylene dichloride (70:30) afforded 16β-fluoro-17α-bromoallopregnane-3β-ol-11,20-dione acetate (XI) (11.8 g.), m.p. 170–177°, and did not exhibit selective absorption in the ultraviolet. One crystallization from methylene dichloride–hexane raised the m.p. to 190–192°, 8.6 g. The analytical sample from the same solvent mixture had m.p. 209–211°, $[\alpha]D$ −4°; λ_{max}^{KBr} 1700, 1730 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_4BrF$: C, 58.59; H, 6.84; Br, 16.96; F, 4.03. Found: C, 58.16; H, 7.15; Br, 17.15; F, 4.35.

Further elution with methylene dichloride–hexane (1:1) afforded starting material (4.05 g.), m.p. 165–170°, raised by one crystallization to 178–180°, λ_{max}^{EtOH} 234–236 mμ, ϵ 8,900. The m.p. was undepressed on admixture with an authentic sample.

Chromous Chloride Treatment of XI.—Chromous chloride solution (5.0 cc.), prepared as described above, was added to a solution of XI (400 mg.) in acetic acid (25 cc.) at 0°. After 45 min., addition of water and filtration afforded the Δ^{16}-20-ketone VII (280 mg.), m.p. 180–185°, raised by crystallization from acetone–hexane to 184–186° (160 mg.), $[\alpha]D$ 64°, λ_{max}^{EtOH} 236 mμ, ϵ 9,100. The m.p. was undepressed on admixture with an authentic sample and the infrared spectra were identical.

Treatment of XI with Sodium Iodide in Acetic Acid.—Sodium iodide (300 mg.) was added to a solution of XI (250 mg.) in acetic acid (25 cc.) and heated under reflux for 4 hr. The cooled solution then was poured onto ice-water. Filtration afforded the Δ^{16}-20-ketone VII, m.p. 178–184°, raised by crystallization from acetone–hexane to 184–186°, $[\alpha]D$ +61°, λ_{max}^{EtOH} 234–236 mμ, ϵ 9,000. The infrared spectrum was identical with that of an authentic sample.

Similarly when XI was heated under reflux in collidine solution for 6 hr. it was converted to VII in good yield.

Hydrogenation of XI.—A solution of 16β-fluoro-17α-bromoallopregnane-3β-ol-11,20-dione (XI) (400 mg.) in methanol (80 cc.) was added to a suspension of 10% palladium-on-carbon (200 mg.) in methanol (10 cc.) and stirred in atmosphere of hydrogen for 5 hours. Filtration and removal of the solvent *in vacuo* afforded a product which was adsorbed from hexane–benzene (30:70) onto alumina (25 g.). Elution with benzene–ether (80:20) afforded allopregnane-3β-ol-11,20-dione (165 mg.), m.p. 185–189°, raised by crystallizations from acetone–hexane to 194–196°, undepressed on admixture with an authentic sample.[37]

The Δ^2-Androstene-3,17β-diol Diacetate (XVIII).—A solution of dihydroallotestosterone (2.0 g.) in acetic anhydride (10 cc.) and acetyl chloride (10 cc.) was heated under reflux in an atmosphere of nitrogen for 4 hours. Removal of the solvent *in vacuo* and crystallization of the residue from methanol afforded Δ^2-androstene-3,17β-diol diacetate (XVIII) (1.53 g.), m.p. 160–163°, raised by several crystallizations from methanol to 168–170°, $[\alpha]D$ +55°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.96; H, 9.09; O, 16.82.

Treatment of XVIII with N-Bromoacetamide and Hydrogen Fluoride.—Δ^2-Androstene-3,17β-diol diacetate (XVIII) (1.3 g.) in methylene dichloride (40 cc.) together with N-bromoacetamide were added simultaneously over 2–3 min. to a mixture of anhydrous hydrogen fluoride (6.0 g.) and tetrahydrofuran (10.5 g.) at −80°. After a further 1 hr. at −80° and 1 hr. at 0° the solution was added to an excess of sodium carbonate in ice-water. Isolation with methylene dichloride and one crystallization of the product from acetone–hexane furnished 2α-bromoandrostane-17β-ol-3-one acetate (XIX) (940 mg.), 170–172°, raised by several crystallizations from the same solvent system to 177–179°, $[\alpha]D$ +23°; lit.[38] m.p. 177–178°, $[\alpha]D$ +35°.

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59; Br, 19.43. Found: C, 61.28; H, 7.58; Br, 18.80.

Stability of XIX to Acid.—Dry hydrogen chloride was bubbled through a solution of XIX (250 mg.) in acetic acid (15 cc.) for 4 hr. at room temperature. Addition of water and filtration afforded unchanged starting material. After one crystallization from acetone–hexane it had m.p. 175–177° (180 mg.), undepressed on admixture with XIX; $[\alpha]D$ +25°.

Dihydroallocortisone Diacetate (XXI).—Finely divided calcium carbonate (2.0 g.) was added to a solution of dihydroallocortisone acetate[39] (XX) (2.5 g.) in acetic anhydride (25 cc.) and heated under reflux in an atmosphere of nitrogen for 24 hours. Filtration and removal of the solvent *in vacuo* furnished a product which after one crystallization from methanol gave the diacetate XXI (1.7 g.), m.p. 227–231°, raised by several crystallizations from methanol to 234–235°, $[\alpha]D$ +35°; lit.[40] m.p. 228–230°, $[\alpha]D$ +32°.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67; O, 25.09. Found: C, 67.49; H, 7.70; O, 24.66.

The Δ^2-Allopregnene-3,17α,21-triol-11,20-dione Triacetate (XXII). (a) From Dihydroallocortisone.—*p*-Toluenesulfonic acid monohydrate (3.5 g.) was added with stirring to a suspension of dihydroallocortisone (5.0 g.) in acetic anhydride (200 cc.). After one hour all the steroid

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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]

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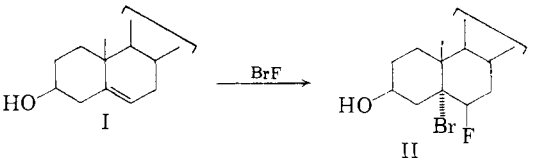
Contrary to expectation, the addition of I–F (N-iodosuccinimide–hydrogen fluoride) to Δ^5-3β-hydroxy steroids afforded the corresponding 6β-iodo-5α-fluoro dihalides. Evidence is presented to support the stereochemical assignments. The mechanism of halogen type addition to Δ^5-double bonds is discussed.

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

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