phenol was repeated, using *p*-toluenesulfonic acid as catalyst, the washed and dried chloroform solution showed $[\alpha]_D^{20}$ +44° calculated as phenyl tetra-*O*-acetyl-D-allopyranoside. The chloroform was removed *in vacuo*, and the resulting sirup was dissolved in ethanol, diluted with water, and inoculated with the β-anomer. The 1.3 g. of sticky crystals thus obtained consisted principally of the β-anomer as shown by the m.p. 110–120° obtained after one recrystallization from chloroform-pentane. The aqueous alcohol mother liquor deposited an additional 2.2 g. of product (total yield 3.5 g., 64%) consisting principally of the α-anomer. This, after recrystallization once from aqueous ethanol and thrice from chloroform-pentane, gave 160 mg. of the pure phenyl tetra-*O*-acetyl-α-D-allopyranoside as elongated prisms, m.p. 97–98°, and $[\alpha]_D^{20}$ +160° in chloroform (*c*, 1).

Anal. Calcd. for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70; CH_3CO, 40.6. Found: C, 56.76; H, 5.77; CH_3CO, 40.3.

When fused zinc chloride was used as catalyst, the chloroform solution showed $[\alpha]_D^{20}$ +64°, and the first three fractions of crystals (2.8 g.) consisted principally of the α-anomer while the fourth fraction (0.3 g.) consisted principally of the β-anomer; the total yield was 3.1 g. (73%) from 3.9 g. of the β-D-allose pentaacetate.

Phenyl α-D-allopyranoside. A 526-mg. sample of phenyl tetra-*O*-acetyl-α-D-allopyranoside was deacetylated catalytically with methanolic sodium methoxide. The product was a sirup; on solution in absolute ethanol and dilution with pentane a waxy substance was produced. Fine needles were finally obtained by dissolving a small sample in 95% ethanol and allowing the solution to concentrate slowly at room temperature. The main fraction was then crystallized from ethanol-pentane; weight 219 mg. (69%); m.p. 102–106°, unchanged by recrystallization from acetone-pentane. The observed rotation $[\alpha]_D^{20}$ + 179° in water (*c*, 1) was probably about 5% low because the crystalline material appears to be solvated to a variable degree; thus, samples of the air-dried product lost 3.5 and 6.2% when dried at 70° in a high vacuum for 2 hr. and 1 hr., respectively. The samples melted during the drying and were then analyzed.

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.47, 56.36; H, 6.33; 6.30.

Transformation of phenyl β-D-allopyranoside into 1,6-anhydro-β-D-allopyranose by alkali. A 395-mg. sample of phenyl β-D-allopyranoside was refluxed with 40 ml. of 0.6*N* aqueous sodium hydroxide in a silver flask for 8 hr.; the solution had then reached a constant rotation $[\alpha]_D^{20}$ −93° calculated as 1,6-anhydro-β-D-allopyranose, which is known to show $[\alpha]_D^{20}$ −75.8° in water.[4] The solution was deionized, extracted with chloroform to remove phenol, and concentrated to a sirup (150 mg.; theory 250 mg.). The sirup, when dissolved in absolute ethanol and inoculated, deposited 136 mg. (54%) of 1,6-anhydro-β-D-allopyranose, identified by melting point, mixed melting point, and paper chromatography in three different solvents.

Reaction of phenyl α-D-allopyranoside with alkali. When 90 mg. of phenyl α-D-allopyranoside in 30 ml. of 0.8*N* aqueous sodium hydroxide was refluxed the solution developed color slowly, and the rotation dropped from $[\alpha]_D^{20}$ +186° to +151° in 7 hr. At the end of an additional 6 hr. the solution was so dark that the rotation could no longer be read in the polarimeter, and consequently it was decolorized with carbon. The colorless solution was concentrated and its rotation found to be nearly zero; neither phenyl α-D-allopyranoside nor 1,6-anhydro-β-D-allopyranose could be detected by paper chromatography. The decolorizing carbon was extracted with hot acetone and a total of 35 mg. of sirup recovered; from this, 23 mg. of unchanged crystalline phenyl α-D-allopyranoside was obtained, but again no anhydro compound could be detected by paper chromatography.

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Halogenated Progesterones. A Preferential Reaction of Perchloryl Fluoride

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Quite recently various analogs of progesterone having biological activity greatly enhanced over that of the parent hormone have been prepared.[2] Our efforts in this area were initially directed toward the preparation of representative 17α-fluoroprogesterone derivatives. These compounds were potentially of interest, since 21-fluoroprogesterone is reported to be two to four times more active than progesterone.[3]

It was our intention to use the recently discovered[4] reaction of perchloryl fluoride with enol acetates for the preparation of the 17α-fluoro analogs. We initially investigated the reaction of this reagent with 3,20-diacetoxy-3,5,17(20)-pregnatriene (I).[5] The ability of this bisenol acetate to react with cationoid reagents at both C-6 and C-17 was demonstrated by treatment of I with sodium hypochlorite to give the known 6β,17α-dichloroprogesterone (II)[6] in 74% yield. When the bisenol acetate I was treated with perchloryl fluoride in dioxane for three and one-half hours, an amorphous product resulted. The infrared spectrum of this material had bands ascribable to a Δ^4-3-ketone, but it also exhibited strong bands at 5.72 and 8.20 μ, indicative of an enol acetate. Notable by its complete absence was a 20-carbonyl band in the 5.85 μ region. Accordingly, the product was regarded as being essentially 20 - acetoxy - 6 β- fluoro - 4,17(20) - pregnadiene - 3 - one (III).[7] Without purification III was treated successively with *N*-bromosuccinimide and hydrogen chloride in acetic acid to give the

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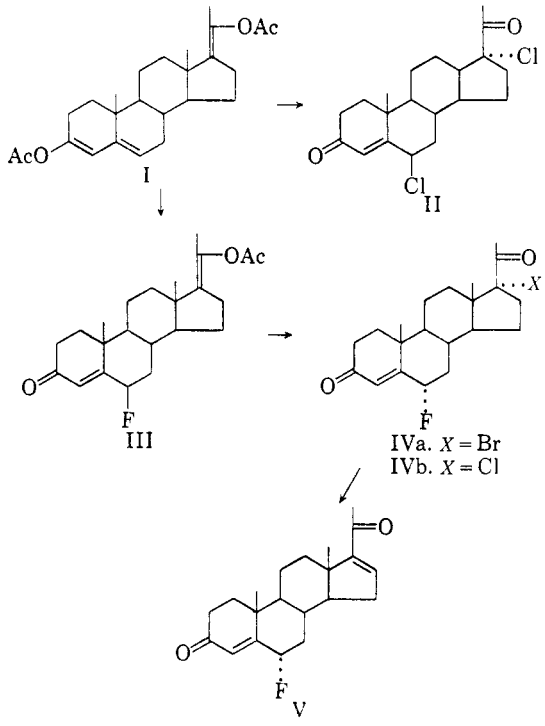

known 17α-bromo-6α-fluoroprogesterone (IVa)[6,8] in 30% yield based on I. In a similar manner, the bisenol acetate I was treated with perchloryl fluoride, alkaline hypochlorite, and hydrogen chloride–acetic acid to give 17α-chloro-6α-fluoroprogesterone (IVb) in 44% over-all yield. It may be noted that the selectivity observed in the reaction of I with perchloryl fluoride is probably greater than 44%, since quantitative yields were assumed for halogenation at C-17 and epimerization at C-6.

The structure assigned to IVb was supported by the marked levorotatory effect of the chloro group on the molecular optical rotation (see Table I),[9] and was confirmed by the isolation of 6α-fluoro-4, 16-pregnadiene-3,20-dione (V)[8a] after treatment of IVb with lithium chloride in dimethylformamide.[10] A similar transformation has been reported for IVa.[8a]

(7) (a) The β-configuration was assigned to the fluoro group in III by analogy to the results previously recorded for the reaction of perchloryl fluoride with the enol acetate of a Δ^4-3-ketone (see ref. 4). (b) After completion of this work E. V. Jensen (Abstr. of Papers presented at the 138th Meeting of the American Chemical Society, New York, N. Y., September 11 to 16, 1960, p. 25M) reported that longer treatment of 17(20)-enol esters does give the corresponding 17α-fluoro-20-ketone.

(8) (a) Ch. R. Engel and R. Deghenghi, *Can. J. Chem.*, **38**, 452 (1960); (b) D. J. Marshall and R. Gaudry, *Can. J. Chem.*, **38**, 1495 (1960).

(9) Engel and his co-workers [*Can. J. Chem.*, **38**, 1199 (1960)] have recorded ΔM_D values of $-355°$ to $-485°$ for the introduction of a 17α-chloro atom into a series of 20,21-ketols.

(10) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

TABLE I

MOLECULAR ROTATIONS AND MOLECULAR ROTATIONAL DIFFERENCES

Compound, Progesterone	M_D[a]	ΔM_D (17α-Chloro–17α-Hydrogen)
6α-Chloro—[b]	+454	
6α,17α-Dichloro—[c]	+111	−343
6β-Chloro—[b]	+258	
6β,17α-Dichloro—	−105	−363
6α-Fluoro—[d]	+660	
17α-Chloro-6α-fluoro—	+187	−473

[a] All rotations measured in chloroform. [b] Cited in A. Bowers, E. Denot, and R. Becerra, *J. Am. Chem. Soc.*, **82**, 4007 (1960). [c] See ref. 6. [d] A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

EXPERIMENTAL[11]

6β,17α-Dichloroprogesterone (II). A 1*N* sodium bicarbonate solution was saturated with chlorine at 0°. A 30-ml. aliquot of this solution was added with magnetic stirring to a solution of 5.000 g. (11.3 mmoles) of 3,20-diacetoxy-3,5,17(20)-pregnatriene (I)[5] in 200 ml. of acetone. Almost immediately an aliquot of the reaction solution failed to color starch-iodide paper. The solution was concentrated and slowly diluted with water to furnish 4.389 g. of solid, m.p. 171–173°. One crystallization from acetone-hexane gave 3.185 g. (74% yield) of material, m.p. 188–191°. The analytical specimen was obtained from a similar experiment as white hexagonal plates, m.p. 194–196°; $[\alpha]_D$ −27.5° (*c* 0.1, chloroform); λ_{max} 240 mμ (ϵ = 14,900); λ_{max} 5.90, 6.00, 6.21 μ. Mills and his co-workers[6] reported m.p. 192–193°; $[\alpha]_D$ −30° (chloroform); λ_{max} 240 mμ (ϵ = 13,200).

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.78; H, 7.36; Cl, 18.50. Found: C, 65.90; H, 7.44; Cl, 18.82.

17α-Bromo-6α-fluoroprogesterone (IVa). A slow stream of perchloryl fluoride was introduced into a magnetically stirred slurry of 2.000 g. (5.03 mmoles) of 3,20-diacetoxy-3,5,17(20)-pregnatriene (I) in 50 ml. of dioxane for 3.5 hr. All solid dissolved after 2 hr. The solution was distributed between methylene chloride and water; the organic solution was washed with saline, dried over magnesium sulfate and taken to dryness. The residual material had λ_{max}^{Nujol} 5.72, 5.95, 6.18, 8.20 μ.

The above material was dissolved in 75 ml. of *t*-butyl alcohol and with magnetic stirring treated with 25 ml. of 10% perchloric acid solution and 0.910 g. (5.10 mmoles) of *N*-bromosuccinimide. Stirring was continued for 2 hr. whereafter a solution of sodium bisulfite was added until the reaction solution failed to color starch-iodide paper. The crude product was isolated with methylene chloride and allowed to stand at room temperature for 2 hr. in 50 ml. of glacial acetic acid previously saturated with hydrogen chloride. The amorphous material, isolated by chloroform extraction, was adsorbed from benzene onto a silica gel column (1.8 × 38 cm.). The column was washed with benzene–ether (99:1), 125-ml. fractions being collected. The material in fractions 15–51, which crystallized after solvent removal, was recrystallized from acetone-hexane to give 0.620 g.

(11) All melting points were determined on a Fisher-Johns block and are uncorrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer. Unless specified otherwise the infrared spectra were determined in chloroform solution on a Baird spectrophotometer (Model AB-2). We are grateful to Dr. L. Throop and his associates for the spectral determinations. Optical rotations were determined at 24° in a 2-dm. semimicro tube. Analyses were furnished by The Schwarzkopf Microanalytical Laboratory, Woodside, L. I.

(30% yield) of white needles, m.p. 177–178° dec. An additional recrystallization from acetone-hexane gave the analytical specimen as white needles, m.p. 179–180° dec.; $[\alpha]_D$ +12° (*c* 0.1, chloroform); λ_{max} 235 mμ (ϵ = 16,100); λ_{max} 5.90, 6.00, 6.18 μ. Engel and Deghenghi[8a] recorded m.p. 169–170° dec.; $[\alpha]_D$ +12.1° (chloroform); λ_{max} 236–237 mμ (ϵ = 15,900). Mills and his associates[6] reported m.p. 180–181°, $[\alpha]_D$ +12° (chloroform) and λ_{max} 236 mμ (ϵ = 15,900).

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.86; Br, 19.43; F, 4.62. Found: C, 61.02; H, 7.17; Br, 19.93; F, 4.77.

17α-Chloro-6α-fluoroprogesterone (IVb). The crude reaction product prepared from 2.000 g. of 3,20-diacetoxy-3,5,17(20)-pregnatriene (I) and perchloryl fluoride as described above was dissolved in acetone. The solution was treated with 5 ml. of a solution prepared by saturation of a 1*N* sodium bicarbonate solution with chlorine. Almost immediately following the addition, an aliquot of the reaction solution failed to give a color with starch-iodide paper. The crude product, isolated with chloroform, was dissolved in 50 ml. of glacial acetic acid that was previously saturated with hydrogen chloride. This solution was kept at room temperature for 16 hr. and then poured into saturated sodium acetate solution. The mixture was extracted with chloroform, and the organic extracts were washed successively with water, sodium bicarbonate solution and water, dried over magnesium sulfate and taken to dryness. The residue was adsorbed from benzene onto a column (1.8 × 36 cm.) that was prepared from silica gel and benzene. The column was washed with benzene-ether (99:1), 125-ml. fractions being collected. Removal of the solvent from fractions 8–24 gave crystalline material which was combined and recrystallized twice from acetone-hexane to give 0.815 g. (44% yield) of white blades, m.p. 192–196°. An additional recrystallization gave the analytical sample as blades, m.p. 195–197°; $[\alpha]_D$ +51° (*c* 0.1, chloroform); λ_{max} 237 mμ (ϵ = 16,700); λ_{max} 5.88, 6.00, 6.18 μ.

Anal. Calcd. for $C_{21}H_{28}ClFO_2$: C, 68.73; H, 7.69; Cl, 9.66; F, 5.18. Found: C, 68.61; H, 7.92; Cl, 9.94; F, 5.44.

6α-Fluoro-4,16-pregnadiene-3,20-dione (V). *Method A.* 17α-Bromo-6α-fluoroprogesterone (IVa) (150 mg.) was treated with 25 mg. of lithium chloride in 25 ml. of dimethylformamide as described previously.[8a] The product was obtained as white needles, m.p. 169–171°; $[\alpha]_D$ +157° (*c* 0.1, chloroform); λ_{max} 237 mμ (ϵ = 29,200); λ_{max}^{Nujol} 5.95, 6.00, 6.16, 6.29 μ. Engel and Deghenghi[8a] reported m.p. 162–163°, $[\alpha]_D$ + 158.4° (chloroform), and λ_{max} 238 mμ (ϵ = 22,000).

Anal. Calcd. for $C_{21}H_{27}FO_2$: C, 76.33; H, 8.24. Found: C, 76.21; H, 8.32.

Method B. 17α-Chloro-6α-fluoroprogesterone (IVb) (150 mg.) when treated in the same manner, gave after recrystallization from ether 57 mg. of white needles, m.p. 169–171°. The identity of this material with that of Method A was shown by mixture melting point and spectral comparisons.

DEPARTMENT OF NATURAL PRODUCTS RESEARCH
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Stereochemistry of a 3-Phenylnorbornane-2-amine[1]

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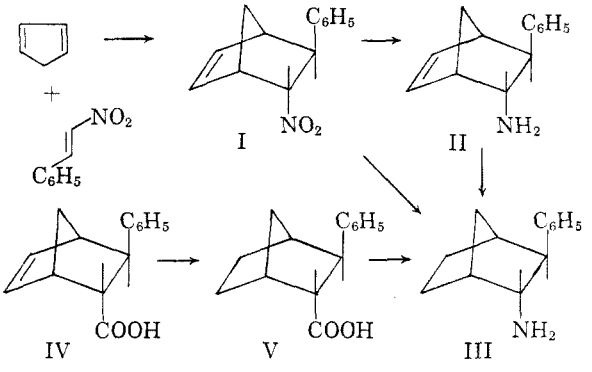
The reaction of cyclopentadiene and β-nitrostyrene leads to a 2-nitro-3-phenyl-5-norbornene. This had been reduced by iron and hydrochloric acid to a 3-phenyl-5-norbornene-2-amine which by hydrogenation over platinum gave a 3-phenylnorbornane-2-amine. This compound was also obtained directly by a Raney nickel catalyzed hydrogenation of the 2-nitro-3-phenyl-5-norbornene.[2] We have now determined the stereochemistry of these products and prepared some of their simple derivatives.

Consideration of the Alder rules[3] suggested that the initial adduct was *endo*-2-nitro-*exo*-3-phenyl-5-bornene, since interaction between the nitro group and the diene was felt to be stronger than similar interaction between the phenyl group and the diene. The success of iron and acetic acid[4] in reducing optically active nitro compounds to the corresponding amines with a high degree of retention of optical activity suggested that the same reagents would also reduce the 5-nitro-6-phenylnorbornene with retention of configuration. We have found that iron and acetic acid, iron and hydrochloric acid, or tin in acetic acid all gave the same 3-phenyl-5-norbornene-2-amine. Furthermore, catalytic reduction of this product gave the same 3-phenylnorbornane-2-amine that could be obtained by direct reduction of the initial adduct with hydrogen and Raney nickel. This implied that the saturated amine was *trans* with the amino group in an *endo* configuration.



In order to establish this, pure *exo*-3-phenylnorbornane-*endo*-2-carboxylic acid was prepared by reduction of *exo*-3-phenyl-5-norbornene-*endo*-2-carboxylic acid which had been purified by carrying it through the iodolactonization procedure.[5] This was converted to authentic *exo*-3-phenylnorbornane-*endo*-2-amine by use of the modified Curtius reaction which we have shown to proceed without

(1) Presented in part at the Third Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, Pa., February 25, 1960. On presenting this work we discovered that several other laboratories had also investigated this problem, *i.e.*, Chester Trivette, Jr., Ph.D. thesis, Duke University, 1958; George Poos, McNeil Laboratories, personal communication.

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