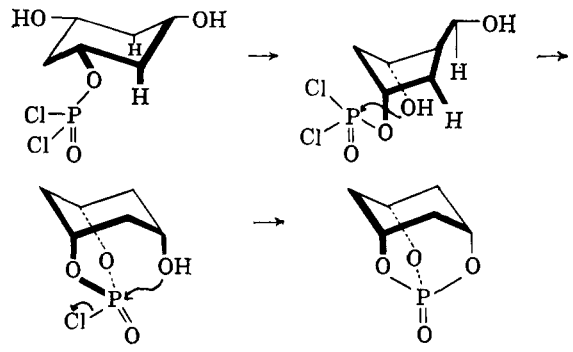
CHART II



2,8,9-trioxaadamentane 1-oxide[5] seems to suggest that a back-side attack[9] of OH on the P–Cl bond is more likely in the last step as shown in Chart II.[10]

Experimental[11]

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Oxide (V).—Ten grams of VII was dissolved in 20 ml. of carbon tetrachloride and 20 ml. of hexane. The solution was treated with ozone at room temperature. A crystalline solid formed instantly by feeding gas above the magnetically stirred liquid. This gave 7.0 g. of solid precipitate, m.p. 200–207°, and 4.0 g. solid, m.p. 180–200°, from the residue of the solution, quantitative yield. This higher melting product was recrystallized twice from boiling water and then crystallized from acetone to give a solid, m.p. 207–208°, lit. m.p. 207°[2] and 202°.[3]

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Selenide (VII).—Ten grams of IV was mixed with selenium (3.0 g.) and benzene (50 g.) It was stirred and refluxed for 1 hr., but no evidence of reaction was observed. After 0.01 g. of sodium selenide was added to the refluxing mixture, the selenium dispersion suddenly coagulated and the solution became transparent and colorless. This mixture was stirred and refluxed for an additional 2 hr., and then kept at 25° overnight. Crystals had formed. These were redissolved by heating and the unused selenium was removed by filtration. The filtrate was concentrated to obtain crystals melting at 172–194°. These were recrystallized twice from 2-methoxyethanol to give 3.6 g. of product, m.p. 207–210°, yield 27.8%.

Anal. Calcd. for $C_6H_{11}O_3PSe$: C, 29.90; H, 4.60; P, 12.85. Found: C, 30.56; H, 4.76; P, 12.75.

4-Phenyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Oxide (VIII).—The following procedure is used for all the next five reactions, the only change being the polyols and the phosphorus halides used. To a two-necked, 50-ml., round-bottom flask equipped with drying tube and dropping funnel, with magnetic stirring and external cooling, there were added 5.0 ml. of pyridine and 1.0 g. of α,α,α-toluenetrimethanol. After the mixture was homogeneous, a solution of 1.0 g. of phosphorus oxychloride in 20.0 ml. of dry ether was added dropwise at room temperature. Stirring was continued for 0.5 hr. and the mixture was kept at room temperature overnight to ensure completion of the reaction, whereupon solvent was removed from the mixture on steam bath *in vacuo*. Chloroform (20 ml.) and water (20 ml.) were added. The chloroform solution of the product was separated and again evaporated to dryness. The residue was dissolved in acetone to give a turbid solution which was then filtered through a short silica gel packed column. The residue of the filtrate was crystallized three times from methanol–acetone to give 0.25 g. of product, m.p. 247–248°, 20.2% yield.

Anal. Calcd. for $C_{10}H_{11}O_4P$: C, 53.10; H, 4.90; P, 13.70. Found: C, 53.04; H, 5.00; P, 13.82.

4-Phenyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (IX).—The same procedure except for the use of phosphorus thiotrichloride was used. The product weighed 0.30 g., m.p. 207–209°, yield 22.5%.

Anal. Calcd. for $C_{10}H_{11}O_3PS$: C, 49.58; H, 4.58; P, 12.79; S, 13.24. Found: C, 49.21; H, 4.80; P, 12.70; S, 13.03.

4-(Pentachlorophenoxymethyl)-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (XI).—The procedure was the same as that above but with (pentachlorophenoxy)methanetrimethanol and phosphorus thiotrichloride as reagents, 0.30 g., m.p. 218–222°, yield 27.1%.

Anal. Calcd. for $C_{11}H_8Cl_5O_4PS$: C, 29.72; H, 1.81; P, 6.97. Found: C, 29.83; H, 1.52; P, 6.47.

4-(Pentachlorophenoxymethyl)-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Oxide (X).—The reagents used were (pentachlorophenoxy)methanetrimethanol and phosphorus oxychloride, giving 0.6 g., m.p. 241.5–242°, yield 52.2%.

Anal. Calcd. for $C_{11}H_8Cl_5O_5P$: C, 30.84; H, 1.88; Cl, 41.38; P, 7.23. Found: C, 30.66; H, 1.97; Cl, 41.30; P, 7.18.

4-(Pentabromophenoxymethyl)-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (XII).—The reagents used were (pentabromophenoxy)methanetrimethanol and phosphorus oxychloride, giving 0.6 g., m.p. 234–239°, 54.6%.

Anal. Calcd. for $C_{11}H_8Br_4O_4PS$: C, 19.81; H, 1.21; P, 4.46. Found: C, 20.07; H, 1.75; P, 4.59.

(9) Some tetrasubstituted phosphorus compounds are known to afford products with inverted configurations on phosphorus atom: L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and R. Beck, *Tetrahedron Letters*, **No. 5**, 191 (1961); L. Horner and H. Winkler, *ibid.*, **No. 3**, 179 (1964); **No. 9**, 455 (1964).

(10) This is based on the assumption that the solvated oxygen atom is bulkier than the chlorine atoms, and the oxygen atom demands to stay at the least sterically hindered configuration.

(11) Melting points are not corrected. Analyses were by Dr. Galbraith, Knoxville, Tenn.

Structures of the Isomeric 20-Hydroxy-4,16-Pregnadien-3-ones

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Received June 25, 1964

In a recent communication, the photolysis of a steroidal nitrite derived from a 20-hydroxy-4,16-pregnadien-3-one was described.[2a] The starting alcohol was obtained, together with its C-20 isomer, from the reduction of the 3-methyl enol ether[2b] of 4,16-pregnadiene-3,20-dione with lithium aluminum hydride, followed by removal of the enol ether protecting group. The material in question was eluted as the more polar of the two alcohols from a Florisil column, and the 20α-stereochemistry was assigned since it could also be obtained by microbiological oxidation from the known 5,16-pregnadiene-3β,20α-diol.[3] It was subsequently discovered that the optical rotatory dispersion curve of the derived nitrite resembled that of the 20β-analog in the corresponding 16-saturated series in possessing a negative Cotton effect.[4] Conversely, the nitrite derived from the less polar alcohol demonstrated a positive Cotton effect, as does the 20α-analog in the 16-saturated series. It was felt at the time, however, that any doubt cast on the stereochemical assignment by O.R.D. measurements should not be given too much weight since each situation had to be considered strictly *sui generis* because of the conformational lability of the nitrite

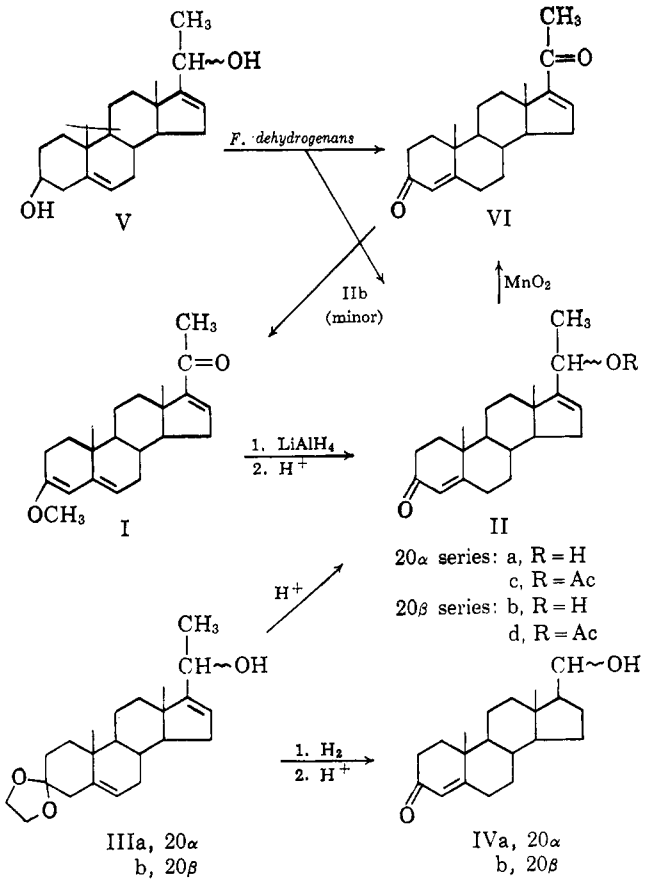
(1) G. D. Searle and Co.

(2) (a) A. L. Nussbaum, R. Wayne, E. Yuan, O. Zagneetko, and E. P. Oliveto, *J. Am. Chem. Soc.*, **84**, 1070 (1962); (b) A. L. Nussbaum, E. Yuan, D. Dinçer, and E. P. Oliveto, *J. Org. Chem.*, **26**, 3925 (1961).

(3) (a) A. Ercoli and P. de Ruggieri, *Farmaco* (Pavia), *Ed. Sci.*, **7**, 11, 129, 287 (1952); *Chem. Abstr.*, **46**, 10186 (1952); **47**, 2129, 3325 (1953). (b) E. L. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 2912 (1955).

(4) C. Djerassi, I. T. Harrison, O. Zagneetko, and A. L. Nussbaum, *J. Org. Chem.*, **27**, 1173 (1962). See also C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **85**, 2835 (1963).

CHART I



chromophore, and that the chemical correlation established conclusively the stereochemical assignment.

The question was reopened, however, by the recent discovery[5] that the presumed 5,16-pregnadiene-3β,20α-diol[3] is in fact a molecular complex of the epimeric 20α- and 20β-diols, which could be resolved only with great difficulty. This conclusion followed from measurements of the nuclear magnetic resonance spectra, a technique not available to the original investigators. The assignment by correlation thus fell by the wayside, and the present paper describes *in extenso* the experiments leading to unequivocal stereochemistry.

Chart I summarizes the chemical transformations carried out. Reduction of 3-methoxy-3,5,16-pregnatrien-20-one (I) with lithium aluminum hydride, followed by acid hydrolysis, gave rise to the two allylic alcohols IIa and IIb mentioned above. Both could be reconverted to 16-dehydroprogesterone (VI) with manganese dioxide. Acetylation gave the isomeric 20-acetates IIc and IId, respectively. Some properties of these substances are summarized in Table I: it may be observed that IIa and IIc fit in well with the 20α-series previously compiled,[5] whereas IIb and IId fall into the corresponding 20β-pattern. Chemical correlation follows from the conversion of the ketals[5] IIIa and IIIb to IIa and IIb, respectively; the former have now been themselves converted to the C-16 saturated isomers IVa and IVb of known stereochemistry at C-20.[6]

Accordingly, the starting alcohol used for the nitrite photolysis studies of ref. 1 has actually the 20β-stereochemistry. Hence, the product of the photolysis, and its conversion products in turn, may also be 20β. This point will be discussed further in the detailed paper of the photolysis in question.

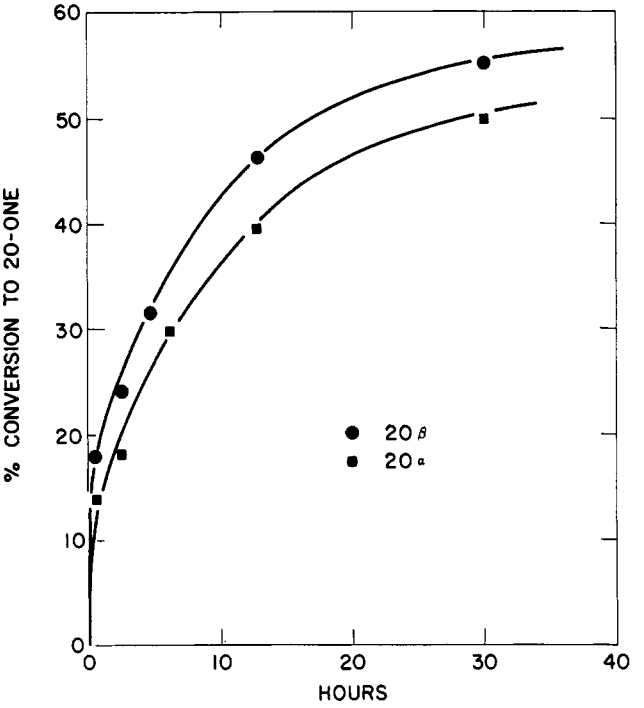


Fig. 1.—Microbiological oxidation of 20-hydroxy-4,16-pregnadien-3-ones.

The microbiological oxidation of complex V failed to demonstrate the stereoselectivity exhibited in the C-16-saturated series[7]; in fact, the rate of oxidation was unexpectedly high, resulting in the isolation of a high proportion of 16-dehydroprogesterone (VI), the overoxidized product. The loss of stereoselectivity is demonstrated by the experiment summarized in Fig. 1: both isolated isomers are oxidized at C-20 at about the same rate. The isolation of one of the two intermediate allylic alcohols from the original microbiological conversion is thus seen to be fortuitous.

There is an interesting reversal of the chromatographic polarity of allylic alcohols IIa and IIb as compared to the C-16-saturated analog IVa and IVb: whereas in the latter instance the R_f of β is greater than α, the opposite is true for the former. This reversal is observed in chromatography on paper as well as column and thin layer chromatography. It is tempting to speculate that this polarity reversal is somehow connected with the change in susceptibility to microbiological oxidation.

In summary, it is concluded that the stereochemistry of the C-20 isomers of 20-hydroxy-4,16-pregnadien-3-one can be safely assigned as described, and that the optical rotatory dispersion curves of the corresponding nitrites, the nuclear magnetic resonance spectra, and the values of ΔM_D (OAc–OH)[5] (see Table I) conform entirely with the pattern set by the isomers in the series saturated at C-16.

(5) W. R. Benn, *J. Org. Chem.*, **28**, 3557 (1963).

(6) (a) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949); (b) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951).

(7) A. L. Nussbaum, E. Yuan, E. P. Oliveto, C. Federbush, and W. Charney, *Chem. Ind.* (London), 836 (1960).

TABLE I

MOLECULAR ROTATION DIFFERENCES AND P.M.R. FREQUENCIES[a]

	5,16-Pregnadiene-3β,20-diols	20-Hydroxy-5,16-pregnadien-3-one 3-ethylene ketals	20-Hydroxy-5,16-pregnadien-3-ones
ΔMD (OH–OAc)			
20α	−63	−90	−78
20β	+128	+145	+226
18-CH_3, c.p.s.			
20α	55 (54.5)	54 (54.5)	57 (55.5)
20β	52 (51)	52 (51.5)	54 (52.5)
21-CH_3, c.p.s.			
20α	75.5, 83 (78, 84.5)	75.5, 82 (78, 84.5)	76.5, 83 (76.5, 83)
20β	78, 84 (70, 86)	78, 84.2 (79.8, 86.5)	78.5, 84.5 (79.5, 86)

[a] Values in parentheses refer to corresponding acetates.

Experimental[8]

20α-Hydroxy-4,16-pregnadien-3-one (IIa). From Enol Ether I.—4,16-Pregnadiene-3,20-dione (16-dehydroprogesterone, VI, 30 g.) was converted to the corresponding methyl enol ether I,[2b] and the latter was dissolved without prior crystallization[9] in 3 l. of dry ether and added to an ice-cold solution of lithium aluminum hydride (40 g.) in tetrahydrofuran (400 ml.). The solution was heated at reflux for 4 hr. and cooled in ice, excess reagent was destroyed with ethyl acetate, and the complex was decomposed with saturated sodium sulfate solution. The decanted solution was concentrated to dryness and taken up in methanol (750 ml.), and 18 ml. of 2 *N* hydrochloric acid was added. After standing overnight, the solution was poured into excess water and brought to neutrality with sodium bicarbonate. The product was extracted into methylene chloride, and the extract was dried over sodium sulfate and concentrated to dryness. The total residue was dissolved in a minimum of benzene and chromatographed over 900 g. of Florisil.[8b] Eluates of 200 ml. were taken. The column was developed with benzene and benzene–ether mixtures. Crystalline material started to appear with 3% ether: each fraction was monitored by thin layer chromatography (70% ether–30% benzene, silica gel). The *less polar* ketol (shown to be α) was eluted preferentially (though not completely free from isomeric contamination); polarity of the solvent was increased slowly with 5 to 10% ether, the more polar ketol (also somewhat contaminated) appeared in the eluate (see below). The two ketols travel 4.9/10 and 4.2/10 cm., respectively, on the plate. The less polar ketol, **20α-hydroxy-4,16-pregnadien-3-one**, 5.96 g., m.p. 165–168°, was crystallized from isopropyl ether. The material gave a positive tetranitromethane reaction for isolated double bonds. An analytical sample had m.p. 167–168°; R_f 0.14 (ligroin–propylene glycol); $[\alpha]^{23}D$ +105°; λ_{max} 240 mμ (ε 16,400); λ_{max}^{Nujol} 2.82, 5.99, 6.13, and 7.61 μ; Δν 57 (18-H), 76.5, and 83 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.11; H, 9.68.

From Ketal IIIa.—A slurry of 100 mg. of 20α-hydroxy-5,16-pregnadien-3-one ethylene ketal[5] (IIIa) in 2.5 ml. of methanol containing 0.06 ml. of 1 *N* HCl was stirred at room temperature for 19 hr. The reaction became homogeneous after about 2 hr.; the course of the reaction was then followed by withdrawing samples periodically for analysis by thin layer chromatography (t.l.c.). After 19 hr. the reaction mixture was observed to consist primarily of the desired 3-ketone IIa accompanied by a small amount of starting material, together with a less polar by-product. This latter material was judged to result from methanolysis of the allylic alcoholic system.[10] The reaction mixture was diluted with water and extracted with methylene chloride. The organic extract was dried over sodium sulfate and evaporated to a crystalline mass. Recrystallization from methylcyclohexane afforded two polymorphic forms. The first crop crystallized as needles having m.p. 140–145 and m.p. 163–167°. A second crop crystallized as hard spheres having m.p. 162–168°. Both forms were shown by t.l.c. as well as by infrared spectra in chloroform to be identical with the 20α-ketol prepared as described earlier.

20α-Acetoxy-4,16-pregnadien-3-one (IIc).—20α-Hydroxy-4,16-pregnadien-3-one (IIa, 500 mg.) was dissolved in 2 ml. of dry pyridine and cooled in ice. Acetic anhydride (2 ml.) was slowly added and the solution was allowed to sit in the ice bath for 0.5 hr. The reaction was then allowed to proceed at room temperature for another 18 hr. and poured into ice slush. Filtration and crystallization from acetone–hexane gave 491 mg., m.p. 100–104°. An analytical sample had m.p. 110–111°; $[\alpha]^{24}D$ +70.2; Δν 55.5 (18-H), 76.5, and 83 (21-H) c.p.s.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.18; H, 9.44.

20β-Hydroxy-4,16-pregnadien-3-one (IIb). From Enol Ether I.—The more polar chromatographic fractions described above were pooled and crystallized from isopropyl ether; thus, 6.90 g. of ketol IIb of m.p. 179–182° was obtained. The material gave a positive tetranitromethane reaction. An analytical sample had m.p. 187–188° (transition at 175°); R_f 0.14 (ligroin–propylene glycol); λ_{max} 241 mμ (ε 15,400); λ^{Nujol} 2.92, 6.02, 6.22, and 12.18 μ; $[\alpha]^{24}D$ +110.2; Δν 54 (18-H), 78.5, and 84.5 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.43; H, 9.87.

By Microbiological Oxidation of the Epimeric Mixture of 5,16-Pregnadiene-3β,20-diols (V).—The reduction product V, now recognized to be an epimeric complex,[5] had constants in agreement with published[3] values: m.p. 179–181°, $[\alpha]^{22}D$ −79°. The infrared spectrum matched that of a genuine sample kindly provided by Mr. E. Shapiro of Schering Corp.

Diol V, 887 mg., was subjected to the action of *Flavobacterium dehydrogenans* as previously described.[11] After 30 hr., the enzymatic reaction was interrupted and the substrate was extracted with chloroform. The extract was washed, dried, and concentrated to an oily residue. The latter was dissolved in benzene and chromatographed over 25 g. of Florisil. From the benzene eluates, 237 mg. of 16-dehydroprogesterone VI, the overoxidized product, was obtained. Further elution with ether–benzene gave 57 mg., m.p. 184–187°, identical by infrared spectrum and R_f with the 20β-hydroxy-5,16-pregnadien-3-one (IIb) described above.

From Ketal IIIb.—The ketal cleavage was carried out in a manner identical with that described earlier for the 20α-isomer (IIIa). The product crystallized from methylcyclohexane–ethyl acetate mixtures as blades having m.p. 185–190°, $[\alpha]D$ +108°. Identity of this material with the 20β-ketol prepared by the other two methods was demonstrated by mixture

(8) (a) Melting points were taken on a micro hot stage. Rotations were measured in chloroform at about 1% concentration, and ultraviolet spectra in methanol. N.m.r. spectra were determined in deuteriochloroform, using a Varian Associates A-60 spectrometer operating at 60 Mc/sec. Resonance frequencies are expressed in cycles per second relative to an internal tetramethylsilane standard. (b) Florisil is the trade-name for a chromatographic grade of magnesium silicate, sold by the Floridin Co.

(9) The material was at least 95% pure, as judged from paper chromatographic control.

(10) In one attempt to cleave the ketal completely, the acid concentration was doubled and the temperature was maintained at 35° for 21 hr. The gummy product had strong absorption in the methoxyl region of the n.m.r. spectrum at 195 c.p.s. and analysis by t.l.c. showed the presence of this less polar by-product together with ketol IIa in equal amounts. For a discussion of acid lability of Δ16-20-hydroxypregnanes, see W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964).

(11) See A. L. Nussbaum, F. E. Carlon, D. Gould, E. P. Oliveto, E. B. Hershberg, M. L. Gilmore, and W. Charney, *J. Am. Chem. Soc.*, **81**, 5230 (1959) for details. We wish to thank Miss C. Federbush of Dr. Charney's staff for carrying out this conversion.

melting point determination, analysis by t.l.c., as well as comparison of infrared spectra.

20β-Acetoxy-4,16-pregnadien-3-one (IId).—20β-Hydroxy-4,16-pregnadien-3-one (150 mg.) was dissolved in 1 ml. of dry pyridine and cooled in ice. Acetic anhydride (1 ml.) was added, and the solution was allowed to stand at room temperature for 18 hr. It was then poured into 30 ml. of ice slush and stirred for 10 min., and the resulting white precipitate was filtered and air-dried. Crystallization from acetone–isopropyl ether gave a first crop of 82 mg., m.p. 155–156°. An analytical sample had m.p. 156–157°; $[\alpha]^{24}D$ +160°; $\Delta\nu$ 52.5 (18-H), 79.5, and 86 (21-H) c.p.s.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.16; H, 9.48.

Oxidation of IIa and IIb with Manganese Dioxide.—In each case, 50 mg. of the respective 20-ol was dissolved in 10 mg. of chloroform. Manganese dioxide, 1 g., was added and the suspension was stirred for 24 hr. Filtration and concentration gave a crystalline residue matching the R_f of 16-dehydroprogesterone (0.6 in the ligroin–propylene glycol system). Crystallization from isopropyl ether in each case gave this compound (V), as verified by the usual criteria.

Reduction of 20α-Hydroxy-5,16-pregnadien-3-one Ethylene Ketal (IIIa).—A solution of ketal IIIa in ethanol was shaken in the presence of palladium on charcoal. Approximately 1 molar equiv. of hydrogen was taken up in 20 min. Spectral analysis of the crude crystalline product indicated a mixture of the expected 16,17-dihydro-20α-hydroxy ketal and about 15% of a material judged to be a saturated 20-carbonyl compound resulting from isomerization of the allylic alcohol. Thus, the n.m.r. spectrum showed major peaks at 41 (18-H), 70.5, and 76.5 (21-H) c.p.s. as expected of the desired product and much weaker signals at 38.5 (18-H) and 127 (21-H) c.p.s., together with a weak band at 5.85 μ in the infrared, pointing to the presence of a minor amount of a saturated ketone.

The ketal group was removed by warming the compound in 80% acetic acid for 30 min., diluting with water, and collecting the precipitate by filtration. A brief sublimation at 85° (0.01 mm.) effectively removed the more volatile 20-carbonyl impurity and the residue was then crystallized from ethyl acetate–petroleum ether. The product had m.p. 147° and 159–162° and did not depress the melting point of an authentic sample of 20α-hydroxy-4-pregnen-3-one, lit.[6b] m.p. 161–162°. The infrared spectra of the samples were identical.

Reduction of 20β-Hydroxy-5,16-pregnadien-3-one Ethylene Ketal (IIIb).—The reduction of the 20β-isomer was carried out in the same manner as described for the 20α-compound. The crude solid had m.p. 182–186° and appeared to be free of any saturated carbonyl by-product. The n.m.r. spectrum had peaks consistent with a saturated 20β-hydroxypregnane derivative[5]: 47 (18-H), 65, and 71 (21-H) c.p.s. Cleavage of the ketal function by warming in dilute acetic acid followed by recrystallization of the product from acetone–petroleum ether gave pure 20β-hydroxy-4-pregnen-3-one, m.p. 175.5–178°, mixture melting point with an authentic sample showed no depression, lit.[6b] m.p. 174–175°.

Preparation and Reactions of Fluoro Ketone Cyanohydrins

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Received March 31, 1964

Fluorinated aldehydes and ketones are strong Lewis acids, forming stable hydrates, hemiketals and acetals, and amine addition products. Strong nucleophiles such as alkoxide ion react with fluorinated carbonyl compounds giving both addition and cleavage of the carbon–carbon bond.[2]

(1) Allied Chemical Corp.

(2) C. Woolf, Abstracts of Papers presented at 132nd National Meeting of the American Chemical Society, New York, N. Y., Sept., 1957, p. 23-M.

We have found that perfluoroacetone and several chlorofluoroacetones react smoothly with both potassium and sodium cyanide in tetrahydrofuran (THF) or ether–THF to give the THF-soluble salts of the acetone cyanohydrins. Acidification of the salts gives the cyanohydrins. This method is a new and simple laboratory procedure for the preparation of these compounds. Neither 1,2-dichlorotetrafluorocyclopentenone-3 nor trichloroacetaldehyde gave the corresponding cyanohydrin salts when treated with sodium cyanide in THF; the cyclopentenone gave a glassy trimeric product and trichloroacetaldehyde gave only tar.[3]

Yields of cyanohydrin salts decreased with increasing numbers of chlorine atoms in the ketone. Cyanide ion was consumed in other ways which must reflect both the greater ease of cleavage of the carbon–carbon bond and the ease of displacement of chlorine by cyanide ion.

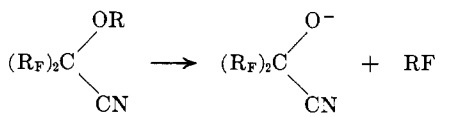
Several esters of dichlorotetrafluoroacetone cyanohydrin were prepared by adding the appropriate acyl, sulfur or phosphorus chloride, or anhydride to the cyanohydrin or the cyanohydrin sodium salt in THF. Table I summarizes these results.

Dichlorotetrafluoroactone cyanohydrin was degraded by a variety of reagents that normally effect replacement of hydroxyl groups. Treatment of the cyanohydrin with either sulfur tetrafluoride[4] or diethylaminotrifluorochloroethane[5] gave only tar.

None of the desired chloronitrile was found in reactions of the cyanohydrin or its sodium salt with the sulfur or phosphorus chlorides. Long heating of the dichlorotetrafluoroacetone cyanohydrin tetrachloro phosphate ester at 250° gave a complex mixture of high-boiling products and starting material.

Probably these reactions failed because of the repression by neighboring fluorine of carbonium ion character in the transition states for reaction. For this same reason, fluoro alcohols fail to give the corresponding chlorides with these same reagents. However, Knunyants has reported the conversion of α,α-bis(trifluoromethyl)-*p*-hydroxybenzyl alcohol to the corresponding chloride using thionyl chloride.[6] In this case, repression of carbonium ion character in the transition state by the trifluoromethyl groups is off-set by the enhanced stability of the benzyl carbonium ion.

Several of the esters were treated with potassium or sodium fluoride in a variety of solvents. The reactions were rapid even at room temperature and in each case the only product isolated corresponded to displacement of 1,3-dichlorotetrafluorocyanoisopropoxy anion by fluoride ion. Thus, *p*-nitrobenzenesulfonyl fluoride and



p-nitrobenzoyl fluoride were isolated from reactions of potassium fluoride with the corresponding esters. No product was isolated from reaction of the bisulfite ester; double displacement by fluoride ion here would have

(3) Aqueous cyanide ion readily reacts with α-haloaldehydes giving acids; see F. D. Chattaway and H. Irving, *J. Chem. Soc.*, 1038 (1929).

(4) Sulfur Tetrafluoride, Technical Information Bulletin, Organic Chemicals Department, E. I. du Pont de Nemours and Co., 1959.

(5) N. Yavorenko and M. Raksha, *J. Gen. Chem. USSR*, **29**, 2125 (1959).

(6) I. L. Knunyants, Tsin-Yun Chen, N. P. Gambaryan, and E. M. Rokhlin, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **5**, 114 (1960); *Chem. Abstr.*, **54**, 20962*i* (1960).