mole, m.p. 61–63°)[13] in 100 ml. of ether was added dropwise with stirring to 0.15 mole of phenyllithium in 130 ml. of ether during 0.5 hr., and was stirred for an additional 2.5 hr., then was refluxed for 3 hr. It was treated with 100 ml. of water, neutralized with acetic acid, and extracted with ether (discard ether layer). Most of the water was evaporated under aspirator vacuum with heating and the remainder at 300 μ at 50°. Final drying was over phosphorus pentoxide under vacuum.

The reaction mixture was acetylated with acetic anhydride and sodium acetate at 100°, poured into ice–water, and extracted with chloroform. The chloroform solution was extracted with sodium bicarbonate solution and then with water before being dried with magnesium sulfate and treated with charcoal. Filtration and evaporation left a brown oil which could not be induced to crystallize.

Part of the oil was deacetylated with potassium methoxide in absolute methanol and aliquots chromatographed on paper in two solvent systems (A, triethylamine–*t*-butyl alcohol–water, 2:10:3, and B, pyridine–*n*-butyl alcohol–water, 4:6:3). The R_f values of the principal component of the reaction mixture, of pure VII, and of glucose were 0.77, 0.77, and 0.31 in A and 0.81, 0.83, and 0.44 in B, respectively.

Part of the material which had been acetylated at 100° was subjected to vigorous acetylation conditions (refluxing acetic anhydride in the presence of sodium acetate), producing another noncrystalline reaction mixture. Gas chromatography of this material showed a principal peak at 10.1 min. (6-ft. column, QF-1 on Gas-Chrom P, 20 p.s.i.), identical with that of the pure tetra-*O*-acetate of VII (m.p. 142–143°). Both materials showed subsidiary peaks, presumably the result of impurities in the first instance and of partial pyrolysis on both experiments.

Spectra.—Infrared spectra were taken on several of the compounds, with results given below. Alcohol-free chloroform was taken as solvent and 7% solutions were used unless otherwise noted. A 0.03-mm. cell was used. The spectra for the tetraacetates of VI and II followed each other closely, but significant differences appeared at 8.50, 9.4–9.8, and 10.4–10.9 μ. The tri- and tetraacetates of VI also were close, differing from each other primarily at 2.8, 8.5, 8.7, 9.8, and 10.5–10.9 μ. These assignments are applicable: hydroxyl 2.8, phenyl 3.3 and 6.7, carbonyl (ester) 5.7, C-methyl (of acetyl) 7.3, acetic ester 8.0–8.1, sulfonic ester 8.40 and 8.47, and cyclic ether 9.0–9.1 μ.

VI triacetate, m.p. 162–163°: weak at 2.8, 6.6, 6.8, 10.4, 10.55, and 10.9; medium at 3.3, 7.3, 9.0, 9.36 and 9.53; strong at 5.7 and 8.1 μ.

VI tetraacetate, m.p. 142–143°: weak at 3.3, 6.6, 6.8, 8.5, 8.7, 10.4, and 10.7; medium at 7.3, 9.0, 9.36, 9.53, and 9.8; strong at 5.7 and 8.1 μ.

II tetraacetate, m.p. 155–156°: weak at 3.3, 6.6, 6.8, and 10.9; medium at 7.3, 9.0, and 9.44–9.64; strong at 5.7 and 8.1 μ.

1β-*C*-Phenyl-1,5-D-anhydroxylitol triacetate,[14] m.p. 170°, 16% solution: weak at 3.5, 6.69, 10.7, 11.0, and 11.4; medium at 3.3, 6.87, 7.03, and 10.2; strong at 5.71, 7.30, 8.00–8.12, 9.2, 9.4, and 9.7 μ.

2-*C*-Phenyl-1,5-D-anhydroglucitol 3,4-diacetate 6-*p*-toluenesulfonate, m.p. 164–165° dec.: weak at 2.84, 3.5, 6.25, 6.70, and 11.0; medium at 3.35, 6.94, 8.40, 9.1, 9.4, 9.6, 10.2, and 10.6; strong at 5.71, 7.30, 8.07, and 8.47 μ. The anomalous hydroxyl band at 2.85 μ was weak, but definite.

IV diacetate, m.p. 177–178°: weak at 2.82, 3.35, 6.70, 6.92, 7.07, 8.84, 10.0, 10.4, 10.6, and 11.1; medium at 7.30, 8.34, 9.03, 9.40, and 9.57; strong at 5.70 and 8.07 μ.

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(13) K. Maurer, *Ber.*, **62**, 332 (1929).

(14) C. D. Hurd and W. A. Bonner, *J. Am. Chem. Soc.*, **67**, 1759 (1945)

Catalytic Isomerization of Polyhydric Alcohols.[1]

II. The Isomerization of Isosorbide to Isomannide and Isoidide

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At 220–240° and 150 atm. of hydrogen pressure the reversible interconversion of the 1,4;3,6 dianhydrohexitols of D-glucitol, D-mannitol, and L-iditol reaches a steady state after 2–6 hr. in the presence of nickel–kieselguhr catalyst. At this time the approximate concentrations are 57%, 1,4;3,6-dianhydro-L-iditol; 36%, 1,4;3,6-dianhydro-D-glucitol; and 7%, 1,4;3,6-dianhydro-D-mannitol. These figures are shown to be consistent with probability considerations; *i.e.*, the relative amounts of the dianhydrohexitols are related to the probability of a given hydroxyl group being either *exo* or *endo*. Taking the steady-state mole fraction of 1,4;3,6-dianhydro-L-iditol as 0.57, it is calculated that the probability of a hydroxyl being *exo* is three times the probability of its being *endo*. Calculation of the mole fraction of the other two anhydrohexitols on the basis of these relative probabilities yields values in close agreement with those found experimentally. The isomerization is strongly accelerated by increasing alkalinity of the catalyst–dianhydrohexitol slurry.

Recently[1] we reported on the existence of isomerization equilibrium between the hexitols, D-glucitol, D-mannitol, and L-iditol, established at 170° in the presence of nickel–kieselguhr catalyst and 100 atm. of hydrogen. Our interest in polyhydric alcohols prompted us to reinvestigate the isomerization behavior of the dianhydrohexitols.[2] The analytical problems were simplified by application of gas–liquid chromatography to the analysis of the reaction products.

Fletcher and Goepp[2] had previously shown that 1,4;3,6-dianhydro-L-iditol could be isolated from the reaction products obtained by treating the dianhydride of either D-glucitol or D-mannitol with Raney nickel at 200° and 250 atm. of hydrogen. The present paper extends this work and demonstrates that isomerization equilibrium is established between the three dianhydrohexitols of D-glucitol, D-mannitol, and L-iditol at 220–240°. The isomerization reaction constitutes a good method for the preparation of 1,4;3,6-dianhydro-L-iditol,[3] recoverable yields of 52% being achieved in this work.

Results and Discussion

In the Experimental part of this paper, a description is given of the isolation and identification by gas–liquid chromatography of isomannide and isoidide as the isomerization products of isosorbide. In order to obtain information that would lead to a better understanding of the isomerization reaction, a study was made of the effect of temperature on the isomerization of isosorbide. The results are given in Table I. The data show that

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(1) For the first paper of this series, see L. Wright and L. Hartmann, *J. Org. Chem.*, **26**, 1588 (1961).

(2) H. G. Fletcher, Jr., and R. M. Goepp, Jr., *J. Am. Chem. Soc.*, **68**, 938 (1946).

(3) L. W. Wright and J. D. Brandner, U. S. Patent 3,023,223 (Feb. 27, 1962), assigned to Atlas Chemical Industries, Inc.

TABLE I

ISOSORBIDE ISOMERIZATION[a]

Temp., °C.	Time, hr.	Solvent	G.l.c. analysis, %[b] Isoidide	Isosorbide	Isomannide
200	2.0	H_2O	12.7	83.3	3.8
210	2.0	H_2O	18.8	74.6	5.7
220	1.0	H_2O	49.2	42.7	8.2
220	2.0	H_2O	58.9	35.5	5.7
230	2.0	H_2O	53.6	38.6	7.6
220	2.0	Isopropyl alcohol	55.7	35.1	9.1
220	2.0	none	56.4	34.6	9.0

[a] Isosorbide solution 50% (except in isopropyl alcohol), 1500-p.s.i.g. hydrogen pressure (at room temperature), 2.0% nickel. [b] Isoidide = 1,4;3,6-dianhydro-L-iditol; isosorbide = 1,4;3,6-dianhydro-D-glucitol; and isomannide = 1,4;3,6-dianhydro-D-mannitol.

TABLE II

ISOSORBIDE ISOMERIZATION[a]

Temp., °C.	220	220	230	220	220	230	220	220	220	230	230	230	230	220	230	230
Nickel concn., wt. %	2.0	2.0	2.0	2.0	1.0	2.0	2.0	1.0	1.0	1.0	1.0	2.0	2.0	1.0	1.0	1.0
Reaction time, hr.	2.0	2.0	1.0	1.0	2.0	2.0	1.0	1.0	1.0	1.0	2.0	2.0	1.0	2.0	1.0	2.0
pH	10.0	8.0	8.0	10.0	10.0	10.0	8.0	8.0	10.0	8.0	8.0	8.0	10.0	8.0	10.0	10.0
Product analysis, wt. % dry basis																
Isomannide	9.6	7.0	7.9	7.9	7.4	4.8	5.2	3.6	6.4	8.5	6.8	7.8	6.6	5.8	7.5	6.9
Isosorbide	38.9	58.0	50.3	47.8	52.4	39.1	68.8	82.5	62.7	58.1	58.3	51.7	40.1	73.4	43.2	39.4
Isoidide	51.5	35.0	41.8	44.3	40.2	56.1	26.0	13.9	30.9	33.4	34.9	40.5	53.3	20.8	49.3	53.7

[a] Analysis was by gas–liquid chromatography.

isomerization proceeds slowly, at temperatures of 200–210°, but that the composition is relatively steady after 1 to 2 hr. at 220–230°.

A two-level factorial statistical study was then made of the isomerization reaction to learn more about the factors influencing the rate of reaction. The effects of temperature (220–230°), nickel concentration (1–2%), reaction time (1–2 hr.), and pH of the aqueous slurry (8–10) were investigated. The concentration of isosorbide (70% aqueous solution) and the hydrogen pressure (1300 p.s.i.g. at room temperature) were held constant in this study. The analytical results are given in Table II. In analyzing these data statistically by Yates' method,[4] the yield of isoidide was chosen as the response measured with the following results.

Response = isoidide yield, %
A = temperature effect = +13.7
B = nickel concn. effect = +8.9
C = reaction time effect = +6.1
D = pH effect = +16.7

The small interactions between these effects are negligible compared with the effects themselves. It is clear that operation at the high levels of the factors tested yields significantly more isoidide than operation at the low levels.

The supposition that the higher levels of the statistical experiment correspond to near-equilibrium conditions for production of isoidide was investigated by operation at 240°, all other factors remaining at the high level. A product was obtained containing 57.0% isoidide. Since a product with 56.1% isoidide is obtained at 230° it seems possible that equilibrium is approached at 230° under the conditions used. The extremely large positive pH effect is not surprising in view of the fact that a similar effect, although not so striking, was found in the hexitol isomerization system.[1] The large pH effect was verified by operation at pH 11, 220°, and 1.0% nickel for 1.0 hr. (low levels from the statistical study except for pH). The product contained 51.7% isoidide compared with 30.9% at pH 10 and 13.9% at pH 8. At pH 12 a poorer result was obtained, possibly due to side reactions at this high alkalinity.

To support the view that the isohexide steady-state composition contains approximately 57% isoidide, 36% isosorbide, and 7% isomannide, it was desirable to show that a synthetic mixture of this composition undergoes no significant change when contacted with nickel catalyst and hydrogen at 220°. When this was done with a mixture containing 54.8% isoidide, 38.0% isosorbide, and 7.2% isomannide, the product contained after 2.0 hr. 58.2% isoidide, 35.6% isosorbide, and 6.2% isomannide.

In order to establish that the dianhydrohexitols could be readily interconverted, the isomerizations of isomannide and isoidide were studied at 230° as a function of time. The data are presented in Tables III and IV.

TABLE III

ISOMANNIDE ISOMERIZATON[a]

Time, hr.	Product analysis,[b] wt. % dry basis Isoidide	Isosorbide	Isomannide	Unknown isohexide[c]
0.5	15.0	48.4	36.6	...
1.0	25.6	50.2	24.2	...
1.5	35.7	48.0	16.3	...
2.0	43.2	45.3	10.6	0.9
3.0	52.0	39.2	7.1	1.7
4.0	54.2	36.7	7.2	1.9
5.0	55.5	37.2	6.5	0.8

[a] 230°, 2.0% nickel, 50% isomannide concentration, 1400-p.s.i.g. hydrogen pressure (at room temperature), pH 10.0. [b] By gas-liquid chromatography. [c] Believed to be neomannide (1,5;3,6-dianhydro-D-mannitol).

TABLE IV

ISOIDIDE ISOMERIZATION[a]

Time, hr.	Product analysis,[b] wt. % dry basis Isoidide	Isosorbide	Isomannide	Unknown isohexide[c]
2.0	82.8	16.8	0.8	0.6
4.0	61.5	31.5	4.3	2.7
6.0	50.7	37.3	7.0	5.0

[a] 230°, 2.0% nickel, 70% isoidide concentration, 1400-p.s.i.g. hydrogen pressure (at room temperature), pH 10.0. [b] By gas–liquid chromatography. [c] Believed to be neomannide (1,5:3,6-dianhydro-D-mannitol).

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(4) See "Design and Analysis of Industrial Experiments," Owen L. Davies, Ed., Hafner Publishing Co., New York, N. Y., 1956, p. 263.

It is clear from the data in Table III that isomannide rapidly isomerizes over a 3–4-hr. time period to a mixture of isohexides closely similar to that obtained with isosorbide. Isoidide is somewhat more difficult to isomerize than isosorbide; however, after 6 hr. at 230°, the product contained approximately 51% isoidide, 37% isosorbide, 7% isomannide, and 5% of an unknown compound, possibly neomannide. In both cases, however, the steady-state isohexide composition approximated that obtained from isosorbide.

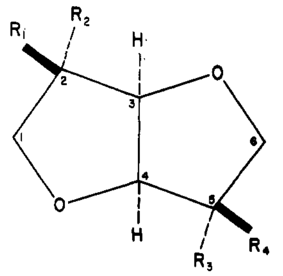
To lend further support to the concept that a steady-state isohexide composition is obtained in 2–6 hr. at 230°, an experiment was carried out with isosorbide at double the catalyst concentration used in the statistical study. After 2.0 hr. at 230°, the mixture analyzed 56.0% isoidide, 36.5% isosorbide, 5.6% isomannide, and 1.9% of the unknown compound. The isolation and identification of the unknown compound is being pursued.

General Discussion

The 1,4;3,6-dianhydrohexitols of sorbitol, mannitol, and iditol, are a useful series of polyols for the study of reaction mechanisms. These compounds contain two fused five-membered rings having a *cis* arrangement of the two rings. The rings are nearly planar and are inclined to one another at an angle of approximately 120°. The hydroxyl substituents on C-2 and C-5 can be either on the outside of the V formed by the rings or on the inside. In the former case the substituents are called *exo*, in the latter case *endo* (*cf.* Fig. 1). The conformation of the ring system is rigid in that it cannot undergo changes of the type occurring in cyclohexane.[5]

It is possible to express the steady-state composition of the isohexide mixture obtained in this study in terms of a probability treatment of the configuration of the hydroxyl groups. Thus, in isoidide the hydroxyls at both C-2 and C-5 are in an *exo* configuration, isomannide has both hydroxyls in an *endo* configuration, and isosorbide has one *endo* hydroxyl (at C-5) and one *exo* hydroxyl (at C-2). If one assigns the probability of a group being *exo* as x, the probability of a group being *endo* is $1 - x$. For isoidide, with two *exo* hydroxyl groups, the mole fraction of isoidide in a random statistical mixture of isohexides would be equal to x^2, the mole fraction of isomannide, with two *endo* hydroxyls, would be equal to $(1 - x)^2$, and the mole fraction of isosorbide, with one *endo* and one *exo* hydroxyl would be equal to $2x(1 - x)$. Taking the value of 0.568 as the mole fraction of isoidide from the approximate steady state composition, one calculates the mole fraction of isosorbide as 0.37 and the mole fraction of isomannide as 0.062, in good agreement with the experimental values of 0.36 and 0.070, respectively. Solution of the above equations for x yields the value 0.75 for the probability of a hydroxyl being *exo*. By difference, the probability of a hydroxyl being *endo* is 0.25. These data correspond to the probability of a hydroxyl being *exo* favored by a factor of 3 over a hydroxyl being *endo*.

One may conclude from these calculations that at temperatures of 220–240° the hydroxyl groups of the steady-state isohexide mixture of isosorbide, isomannide, and isoidide approach a statistical equilibrium based upon the two possible configurations available for the hydroxyl groups.



ISOMANNIDE	R_1 = OH	R_2 = H	R_3 = H	R_4 = OH
ISOSORBIDE	H	OH	H	OH
ISOIDIDE	H	OH	OH	H

Fig. 1.—Isohexide structural formula.

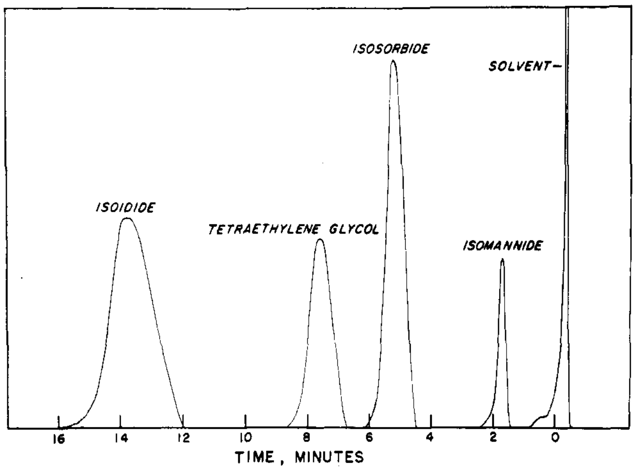


Fig. 2.—Chromatogram (g.l.c.) of isohexide mixture.

By way of speculation, the isomerization reaction may well occur through a ketone intermediate and a rapidly established hydrogenation–dehydrogenation equilibrium between the alcohol and ketone groups as suggested by Fletcher and Goepp.[2] The fact that the reaction is accelerated by alkali suggests that a keto–enol equilibrium may be involved[6] although hydride abstraction is also a possible alternative route.

Experimental

Materials.—Isosorbide (1,4;3,6-dianhydro-D-glucitol)[7] and isomannide (1,4;3,6-dianhydro-D-mannitol)[8] were prepared by the procedures of Hockett, *et al.* Isoidide (1,4;3,6-dianhydro-L-iditol)[2] was prepared by the procedure of Fletcher and Goepp.[2]

The nickel–kieselguhr catalyst used in this work was prepared as previously described.[1]

Electrolytic hydrogen obtained from the Air Reduction Corporation was used without further purification.

Procedure.—Recrystallized isosorbide[7] (100 g., 0.68 mole) was dissolved in 100 ml. of distilled water and the solution was slurried under a nitrogen atmosphere with a sufficient quantity of nickel–kieselguhr catalyst to obtain a nickel content of 2.0%. The slurry (pH 8.5) was charged to a 1-l. stainless steel, stirred autoclave,[1] purged with nitrogen, and 1500 p.s.i.g. of hydrogen (3.3 moles) was admitted to the autoclave at room temperature. The autoclave was then heated with agitation to 230° over a 45-min. period and held there for 2.0 hr. The autoclave was then cooled to room temperature and vented. No consumption of

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[5] J. A. Mills, "Advances in Carbohydrate Chemistry," Vol. 10, Academic Press, New York, N. Y., 1955, p. 46.

[6] R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

[7] R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, and R. M. Goepp, Jr., *J. Am. Chem. Soc.*, **68**, 927 (1946).

[8] R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, *ibid.*, **68**, 930 (1946).

hydrogen occurred during the experiment. After filtration of the reaction products to remove catalyst, the solvent was stripped at 20 mm. and 50°, yielding 98.5 g. of sirup. A sample of the sirup was analyzed by gas–liquid chromatography using a Podbielniak Chromacon isothermal unit equipped with thermal conductivity cells for detection. The three dianhydrohexitols were separated at 200° on a 2 ft. × 0.25 in. i.d. copper tubing column packed with 20% Carbowax 20M[9] on Chromosorb W.[10] Calibration with known samples of the three dianhydrohexitols established the identity of the three peaks found on the chromatogram. The composition of the mixture was estimated by measuring the areas under each peak by the peak height times width at half-height method. The absolute amounts were determined by the method of internal standardization using tetraethylene glycol as an internal standard (*cf.* Fig. 2). Analyses by the two methods were in close agreement.

The dianhydrohexitol mixture was separated on a macroscale by fractionation of a 100-g. distillation charge through a 12-in. glass column (23-mm. i.d.) packed with porous stainless steel packing. Three cuts were taken. Cut 1, 7.5% of the charge, b.p. 123–130° (2 mm.), was mainly isomannide contaminated with traces of isosorbide. Cut 2, 40.5% of the charge, b.p. 148–151° (2 mm.), was mainly isosorbide. Cut 3, 52.0% of the charge, b.p. 159–162° (2 mm.), was relatively pure isoidide. G.l.c. analysis of cut 3 indicated a purity of 99.9%. Recrystallization of a small sample of cut 3 from methyl ethyl ketone yielded isoidide, melting point and mixture melting point with an authentic sample of isoidide 63–64°.

Acknowledgment.—The authors wish to express their appreciation to Dr. A. D. Cooper for advice on the development of analytical procedures and to Dr. C. F Smullin, Dr. J. W. LeMaistre, and Mr. R. L. Birkmeier for helpful discussions during the course of this work.

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[9] A product of the Union Carbide Chemicals Co., a division of Union Carbide Corp.

[10] A product of the Johns-Manville Corp.

Reaction of Perchloryl Fluoride with Derivatives of Methyl 3,11-Diketo-4,17(20)-*cis*-pregnadien-21-oate. Synthesis of 4-Fluoro- and 6-Fluorohydrocortisone Acetate

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Treatment of the 3-enol ether, 3-enol acetate, and the 3-enamine of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate with perchloryl fluoride to form 4-fluoro and 6-fluoro steroids is described. These intermediates were converted to the corresponding cortical hormones.

Our continuing interest in the synthesis of 6-fluoro-[1] and 6,16-difluoro corticoids[2] made a simple method for the introduction of fluorine into a 3-keto-Δ^4 steroid highly desirable. Particularly sought was a method to utilize the intermediates available from the unique synthesis of hydrocortisone described from these laboratories.[3]

Reaction of perchloryl fluoride with enol ethers and enol acetates of 3-keto-Δ^4 steroids to yield 6-fluoro steroids[4,5] offered a means of attaining this goal. The 3-enol ether of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate[3] (**1**) was treated with an excess of perchloryl fluoride in pyridine or aqueous tetrahydrofuran solution. When the reaction was carried out in pyridine solution up to 52% yield of fluorinated product was obtained from which by chromatography the pure 6α-fluoro and 6β-fluoro steroids **2** and **3** were isolated, the former predominating. A higher yield (86%) of a mixture of **2** and **3** was obtained when the fluorination was performed in aqueous tetrahydrofuran. From the reaction mixture in this solvent another fluorinated steroid was isolated in modest yield. This compound was assigned structure **4**, namely methyl 4α-fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate, on the following evidence. Elemental analysis indicated a monofluoro steroid. An ultraviolet absorption maximum assigned to the unsaturated ester function was found at 222 mμ, while infrared absorption bands were noted in the carbonyl region at 1739, 1710 and 1705 cm.$^{-1}$. The latter two bands were assigned to the unsaturated ester and 11-keto groupings, respectively. The band at 1739 cm.$^{-1}$ was assigned to the α-halo-3-keto function. The hypsochromic shift in the infrared spectrum to 1739 cm.$^{-1}$ from that of an unsubstituted 3-keto steroid is consistent with the presence of a 4α-fluoro substituent.[6] The ultraviolet and infrared absorption data for these compounds are summarized in Table I. When treated with hydrogen chloride in chloroform, **4** was isomerized to a monofluoro steroid possessing an ultraviolet absorption maximum at 237 mμ and infrared absorption in the carbonyl region at 1720, 1708, and 1690 cm.$^{-1}$. The spectral data indicate the presence of a newly formed unsaturated system. Structure **5** was assigned to this compound. The isolation of **4** is also consistent with the proposed mechanism of perchloryl fluoride reactions involving the electrophilic attack of the reagent at a center of high electron density.[5,6a]

Methyl 4α-fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate (**4**) was converted to 4-fluorohydrocortisone acetate (**8**) *via* the 3-enamine by methods previously disclosed from this laboratory[3] (reaction sequence, **4** → **6** → **7** → **8**.) Owing to the difficulty of obtaining pure **4** on a large scale, partially purified material was usually used in the reduction sequence. Therefore a method to evaluate the purity of **6** and to purify this material prior to the introduction of the

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[1] J. A. Hogg, *et al.*, *Chem. Ind.* (London), 1002 (1958).

[2] B. J. Magerlein, F. H. Lincoln, R. D. Birkenmeyer, and F. Kagan, *ibid.*, 2050 (1961).

[3] J. A. Hogg, *et al.*, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

[4] S. Nakanishi, K. Morita, and E. V. Jensen, *ibid.*, **81**, 5259 (1959).

[5] B. M. Bloom, V. V. Bogert, and R. Pinson, Jr., *Chem. Ind.* (London), 1317 (1959).

[6] (a) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958); (b) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960); (c) see also R. Joly and J. Warnant, *Bull. soc. chim. France*, **28**, 569 (1961), who described the synthesis 4-fluoro steroids from steroidal 3-enamines subsequent to the completion of this work.