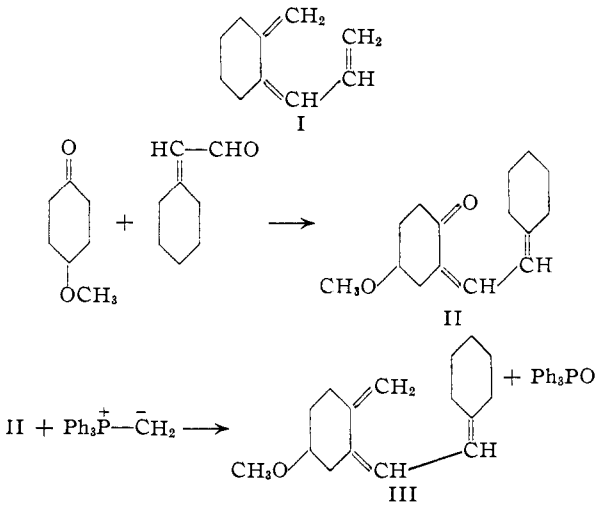

prepared triphenyl phosphine methylene[7] in a pressure bottle using dry ether as solvent and nitrogen at 65° for three hours. From the mixture was obtained, after two chromatographic separations, a highly viscous liquid; yield, 14%. *Anal.* Calcd. for $C_{16}H_{24}O$ (III): C, 82.69; H, 10.41. Found: C, 82.61; H, 10.34; ϵ (265 mμ), 23,200. The infrared absorption spectrum showed bands due to the presence of the $=CH_2$ group at 890, 1594, 1625 and 1646 cm.$^{-1}$. The corresponding bands for vitamin D_3 examined at the same time were at 892, 1600, 1630 and 1650 cm.$^{-1}$.

We wish to acknowledge financial support from the Research Corporation and to thank Dr. S. M. Nagy and his associates of this Institute for the analyses and the infrared spectra.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1- AND 6-DEHYDRO-9α-HALOCORTICOIDS

Sir:

It has been demonstrated in our laboratories that substitution of a chlorine[1,2] or more effectively of a fluorine[2,3] atom in the 9α-position of 11-oxygenated corticoids leads to considerable enhancement in glucocorticoid[1,2,3,4] anti-inflammatory[5] and sodium retaining activity.[6] More recently, others have shown that introduction of a double bond into the 1,2-position of cortisone and hydrocortisone leads to 3–4 fold increases in both glucocorticoid[7] and antirheumatic[8] activity. It was therefore of considerable interest to prepare steroids possessing both a 1,2-double bond and a 9α-halogen atom for biological evaluation. A recent publication[9] describing one such steroid, 1-dehydro-9α-fluorohydrocortisone acetate prompts us to report on our experiences with this and related compounds.

1-Dehydrohydrocortisone acetate[7] was dehydrated with methanesulfonyl chloride and pyridine in dimethylformamide to $\Delta^{1,4,9(11)}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (m.p. 222–223°, $[\alpha]^{23}D$ +52° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ϵ = 16,100)[10]; found: C, 71.81; H, 7.10), which on treatment with N-bromoacetamide and perchloric acid in dioxane furnished 1-dehydro-9α-bromohydrocortisone acetate I (m.p. 180–185° (dec.), $[\alpha]^{23}D$ +123° (dioxane), λ_{max}^{alc} 241 mμ (13,400); found: C, 57.04; H, 6.29; Br, 16.66; L.G.[11] 4, Na[11] 10). Treatment of I with potassium acetate in boiling alcohol furnished 9β,11β-oxido-$\Delta^{1,4}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (m.p. 213–215°, $[\alpha]^{23}D$ +64° ($CHCl_3$), λ_{max}^{alc} 249 mμ (15,800); found: C, 69.06; H, 7.07), which with HBr in chloroform (0°) reverted to I, and with HCl and HF afforded the most potent glucocorticoids presently known, 1-dehydro-9α-chlorohydrocortisone acetate II (m.p. 242–243° (dec.), $[\alpha]^{23}D$ +145° (alc.), λ_{max}^{alc} 238 mμ (15,000); found: C, 63.13; H, 6.62; Cl, 8.38; L.G. 13, Na 20–30) and 1-dehydro-9a-fluorohydrocortisone acetate III (m.p. 243–245°, $[\alpha]^{23}D$ +99° (acetone), λ_{max}^{alc} 238 mμ (14,500); found: C, 65.88; H, 7.20; F, 4.64; L.G. 28, Na 2–3), respectively. Oxidation of II and III with CrO_3 in acetic acid produced 1-dehydro-9α-chlorocortisone acetate (m.p. 262–264° (dec.), $[\alpha]^{23}D$ +244° ($CHCl_3$), λ_{max}^{alc} 236 mμ (15,500); found: C, 63.60; H, 6.38; L.G. 12–15) and 1-dehydro-9α-fluorocortisone acetate (m.p. 274–277°, $[\alpha]^{23}D$ +158° (alc.), λ_{max}^{alc} 235 mμ (15,600); found: C, 65.91; H, 6.40; L.G. 25–30).

Alternatively, we have independently prepared III from 9α-fluorohydrocortisone acetate[3] as described by Hirschmann, *et al.*[9] Catalytic reduction (Pd–$BaSO_4$ in ethyl acetate or alcohol) furnished 9α-fluoro*allo*pregnane-11β,17α,21-triol-3,20-dione 21-acetate[12] (m.p. 234–235°; $[\alpha]^{23}D$ +67° (acetone); found: C, 65.34; H, 7.69; L.G. < 0.1, Na < 0.1), which with two moles of bromine in acetic acid afforded an amorphous mixture of dibromides. The latter upon dehydrobromination with boiling collidine and chromatography on acid-washed alumina yielded successively 2-bromo-9α-fluoro-Δ^1-pregnene-11β,17α-21-triol-3,20-dione 21-

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(10) The infrared spectra of this and other $\Delta^{1,4}$-3-keto steroids possess bands in the ranges characteristic of the acetylated dihydroxyacetone side chain (5.72–5.76 μ and 5.80–5.85 μ) and of the 1,4-diene-3-one system (6.01–6.04 μ, 6.14–6.20 μ and 6.20–6.26 μ).

(11) The rat liver glycogen assay (L. G.) represents an excellent measure of glucocorticoid, and in our experience also of antiinflammatory, activity. The figures given are expressed in terms of cortisone acetate = 1. The sodium retention test (Na) employed here has been described in ref. 6. The standard of comparison is DCA = 1.

(12) The reduction product possesses the *allo*-configuration since on monobromination it yielded mainly the 2-bromo derivative, which on dehydrobromination with collidine afforded 9α-fluoro-Δ^1-*allo*pregnene-11β,17α,21-triol-3,20-dione 21-acetate[9] (m.p. 237–239°, $[\alpha]^{24}D$ +90° ($CHCl_3$), λ_{max}^{alc} 228 mμ (6,100); found: C, 65.56; H, 7.19).

acetate (monoalcoholate: m.p. 184–185° (dec.) after melting and resolidification at 126–139°, $[\alpha]^{23}D$ +79° ($CHCl_3$), λ_{max}^{alc} 250 mμ (8,000), λ_{max}^{Nujol} 2.85 μ, 2.98 μ, 5.80 μ, 5.90 μ, 5.98 μ, 6.24 μ; found: C, 54.48; H, 6.78; Br, 14.50; OC_2H_5, 7.57; L.G. < 0.3), 2-bromo-9α-fluoro-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate[13] (m.p. 174–175° (dec.): $[\alpha]^{23}D$ +136° ($CHCl_3$); λ_{max}^{alc} 242 mμ (12,200). $\lambda_{max}^{CHCl_3}$ 2.85–2.95 μ, 5.78 μ, 5.85 μ, 5.94 μ, 6.15 μ; found: C, 55.70; H, 6.30; Br, 15.16; L.G. 1.0, Na 10), 6-dehydro-9α-fluorohydrocortisone acetate[9,14] (IV) (m.p. 216–217, $[\alpha]^{23}D$ +123° (alc.), +135° ($CHCl_3$), λ_{max}^{alc} 281 mμ (23,000), λ_{max}^{Nujol} 3.00 μ (OH), 5.76 μ, 5.81 μ (acetylated side chain; 6.10 μ. 6.16 μ, 6.22 μ ($\Delta^{4,6}$-3-ketone); found: C, 65.75; H, 7.04; L.G. 5, Na 20–30), the desired III, and an isomer of III (m.p. 271–272°, $[\alpha]^{23}D$ +73° (alc.), λ_{max}^{alc} 237 mμ (15,200), λ_{max}^{Nujol} 3.00 μ, 5.75 μ, 5.92 μ, 6.04 μ, 6.18 μ, 6.24 μ; found: C, 65.96; H, 6.84; L.G. < 1).

Substitution of a hydrogen atom for a hydroxyl group at C-21 results in a greater decrease of salt retaining than of glucocorticoid activity.[15] We have therefore prepared the 21-desoxy derivatives of III and IV as follows. Saponification of III and IV with potassium carbonate in aqueous methanol yielded the respective dehydro-9α-fluorohydrocortisones (Δ^1: m.p. 274–275° (dec.), $[\alpha]^{23}D$ +94° (alc.), λ_{max}^{alc} 238 mμ (15,500); found: C, 66.68; H, 7.16) and (Δ^6: m.p. 257–259°, $[\alpha]^{23}D$ +101° (alc.), λ_{max}^{alc} 281 mμ (25,600); found: C, 66.30; H, 7.00), which were converted into the 21-mesylates in pyridine at 0° (Δ^1: m.p. 220° (dec.), $[\alpha]^{23}D$ +98° (alc.), λ_{max}^{alc} 238 mμ (15,000); found: C, 58.04; H, 6.36; S, 7.52) and (Δ^6: m.p. 237–238° (dec.), $[\alpha]^{23}D$ +94° (alc.), λ_{max}^{alc} 281 mμ (27,500); found: C, 58.19; H, 6.05; S, 7.54). The latter were converted into 9α-fluoro-$\Delta^{1,4}$-pregnadiene-11β,17α-diol-3,20-dione (m.p. 313–314° (dec.), $[\alpha]^{23}D$ +47° (pyridine), λ_{max}^{alc} 238 mμ (15,500); found: C, 69.47; H, 7.66; L.G. 4, Na < 0.1) and 9α-fluoro-$\Delta^{4,6}$-pregnadiene-11β,17α-diol-3,20-dione (m.p. 294–296°, $[\alpha]^{23}D$ +112° (dioxane), λ_{max}^{alc} 281 mμ (26,000); found: C, 69.66; H, 7.48; L.G. 0.3, Na <0.1) either directly with sodium iodide in boiling acetic acid or via the 21-iodo derivatives (sodium iodide in acetone) and reduction of the latter with sodium bisulfite in aqueous dioxane.

Our present data may be summarized by stating that introduction of a double bond in the 1,2-position of a 9α-halocorticoid leads to increases in both glucocorticoid and sodium retaining activity in the rat ranging from about 2.5-fold in the case of the fluoro to 10-fold in the case of the bromo derivatives. Dehydrogenation in the 6,7-position, on the other hand, effects in the two cases examined a two-fold decrease in glucocorticoid and a 20-fold increase in salt-retaining activity.

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(13) This compound was formed in good yield when the reaction temperature was lowered to 100°. It was reduced to 9α-fluorohydrocortisone acetate with zinc and acetic acid.

(14) It is noteworthy that in contrast to the experience with 9-unsubstituted steroids (*cf.* A. L. Wilds and C. Djerassi, THIS JOURNAL, **68**, 2125 (1946)) the yield of IV exceeded that of III. IV is more satisfactorily prepared, however, by treatment of the dibromide with lithium chloride in dimethylformamide (*cf.* Holysz, *ibid.*, **75**, 4432 (1953)).

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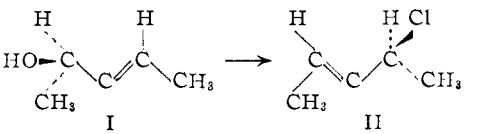
THE REACTION OF THIONYL CHLORIDE WITH ALLYLIC ALCOHOLS[1a]

Sir:

Several mechanisms are available for the reaction of allylic alcohols with thionyl chloride.[1b] Without a solvent, mixtures of isomeric chlorides are always obtained. However, we have found that the SNi′ mechanism[2] may be made very dominant by the use of dilute ether solution, where the liberated hydrogen chloride is rendered quite inactive.[3] Under these conditions, crotyl alcohol yields 99% α-methylallyl chloride and α-methylallyl alcohol yields 100% crotyl chloride.

The ether technique has now been found successful even in some more reactive systems.

With optically active *trans*-α,γ-dimethylallyl alcohol (I) the more likely conformation of the transition state of the SNi′ process would lead to active *trans*-chloride (II) and the configuration of the new asymmetric center would be opposite to that of the original one. The less likely conformation would give optically active *cis*-chloride. We have found that *trans*-alcohol (I) is converted to *trans*-chloride (II) (100% *trans*-isomer) which has the opposite configuration of the alcohols as illustrated below. In fact, the optical purity of the chloride is higher than that which results under conditions favorable for direct displacement of chlorosulfinate ion by providing a soluble hydrochloride.[3]



I II

Another α,γ-dialkylsubstituted allyl system for which the ether technique is successful involves the isomeric 5-methyl-2-cyclohexenols.[4] We find it is also successful even with cinnamyl alcohol in ether solution 0.1*M* in each reagent. Under these conditions, the reaction, slow enough to be followed kinetically, is approximately first order in both alcohol and thionyl chloride. Ultraviolet spectra

(1a) Acknowledgment is made of the partial support of this research by a National Science Foundation grant.

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