XMP to GMP reactions occurred with no extensive dilution of specific activity.

The mechanisms of the amination reactions are being investigated. Carter and Cohen[5] have reported the formation of adenylosuccinic acid from AMP and fumaric acid. It seems likely that this compound is an intermediate in AMP formation from IMP, and that the corresponding guanylo-glutaric acid is an intermediate in GMP formation from XMP.

(5) C. E. Carter and L. H. Cohen, THIS JOURNAL, **77**, 499 (1955).

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RAUWOLFIA ALKALOIDS. XXII. FURTHER OBSERVATIONS OF THE STEREOCHEMISTRY OF RESERPINE

Sir:

Four lines of evidence have been offered recently in support of Ia as representing the stereochemistry of reserpine[1,2]: (1) the C-3 epimerization of reserpine, (2) molecular rotational differences indicating β-orientation of the C-3 hydrogen, 16-carbomethoxyl and 18-acyloxy groups, (3) the inability of 3-isoreserpic acid to lactonize and (4) data strengthening the presently accepted structures of allo- and 3-epialloyohimbane. We now wish to describe new findings demonstrating conclusively the validity of Ia.

When 3-iso-reserpinol (II)[3] was treated with *p*-toluenesulfonyl chloride in pyridine at room temperature overnight, a substance crystallized directly from the reaction mixture in high yield. An inspection of its properties made it evident that the substance must be a quaternary salt. It has a high melting point (320–330° (dec.)) and is virtually insoluble in chloroform. Analysis indicated it to be a mixed tosylate–chloride salt. *Anal.* Calcd. for $C_{22}H_{29}N_2O_2^+ \cdot 0.6\ SO_3C_7H_7^- \cdot 0.4Cl^-$: C, 66.86; H, 7.09; N, 5.96; S, 4.09; Cl, 3.02. Found: C, 66.64; H, 7.10; N, 6.02; S, 3.89; Cl, 2.87. Addition of an excess of sodium iodide to a hot aqueous solution gave an immediate precipitate of the crystalline iodide salt (m.p. 360–365° (dec.)). *Anal.* Calcd. for $C_{22}H_{29}N_2O_2^+ \cdot I^-$: C, 54.98; H, 6.10. Found: C, 55.33; H, 6.17. A free base extractable in chloroform could not be liberated from the salt with dilute ammonia. The infrared spectrum of the mixed tosylate–chloride salt showed the bands characteristic of the *p*-tosylate ion[4] and the presence of chloride ion was revealed by an instantaneous precipitate with silver nitrate. Formulation of this quaternary salt as III requires a *cis* relationship of the hydrogens at C-15 and C-16 restricting the stereochemistry of reserpine to Ia. Similarly, reserpinol (Ib)[5] gave a quaternary tosylate best characterized as its iodide salt (m.p. 315–316° (dec.)).

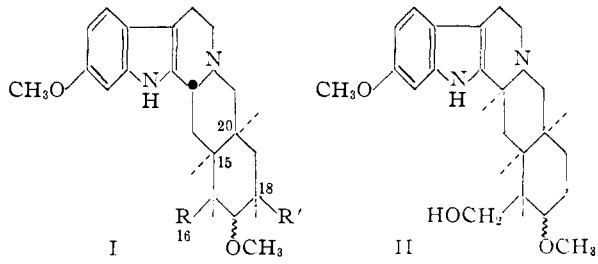
(1) C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *Experientia*, in press.

(2) E. Wenkert and L. H. Liu, *ibid.*, in press.

(3) H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André and P. R. Ulshafer, THIS JOURNAL, in press.

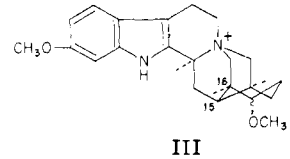
(4) P. A. Diassi, F. H. Weisenborn, C. M. Dylion and O. Wintersteiner, *ibid.*, **77**, 2028 (1955).

(5) C. F. Huebner, H. B. MacPhillamy, A. F. St. André and E. Schlittler, *ibid.*, **77**, 472 (1955).



I II

a: R = —COOCH$_3$, R′ = —OCOC$_6$H$_2$(OCH$_3$)$_3$
b: R = —CH$_2$OH, R′ = H.



III

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STUDIES IN THE SYNTHESIS OF THE ANTIRACHITIC VITAMINS. III. THE SYNTHESIS OF 1-CYCLOHEXYLIDENE-2-[5′-METHOXY-2′-METHYLENECYCLOHEXYLIDENE-1′]-ETHANE

Sir:

Several years ago we reported[1] the synthesis of a simple model (I) of vitamin D. However, subsequent work in this Laboratory[2] showed that the method used was impractical for the synthesis of vitamin D_2 or D_3. In view of work undertaken in other laboratories[3] we wish to report at this time the synthesis of 1-cyclohexylidene-2-[5′-methoxy-2′-methylenecyclohexylidene-1′]-ethane (III) using a method which can easily be adapted for the synthesis of all vitamin Ds.

Cyclohexylidene acetaldehyde (6.8 g.)[4,5] prepared by the chromic acid oxidation[6] of 1-ethenylcyclohexanol-1 was allowed to condense with 14 g. of 4-methoxycyclohexanone with stirring under nitrogen in 900 cc. of methanol containing 4 g. of sodium hydroxide and 10 cc. of water. After twelve hours the mixture was acidified and from it was obtained 6.1 g. (58.6%) of the ketone (II), recrystallized from ligroin, m.p. 79.5–80.5°. *Anal.* Calcd. for (II): C, 76.92; H, 9.46; mol. wt., 234. Found: C, 76.77; H, 9.45; mol. wt. (in exaltone), 224; ε (309 mμ), 29,100. The infrared spectrum shows strong bands for the dienone. 2,4-Dinitrophenylhydrazone, m.p. 178–179°. *Anal.* Calcd. for $C_{21}H_{26}N_4O_5$: C, 60.86; H, 6.33; N, 13.52. Found: C, 61.05; H, 6.68; N, 13.66.

The ketone (II) was allowed to react with freshly

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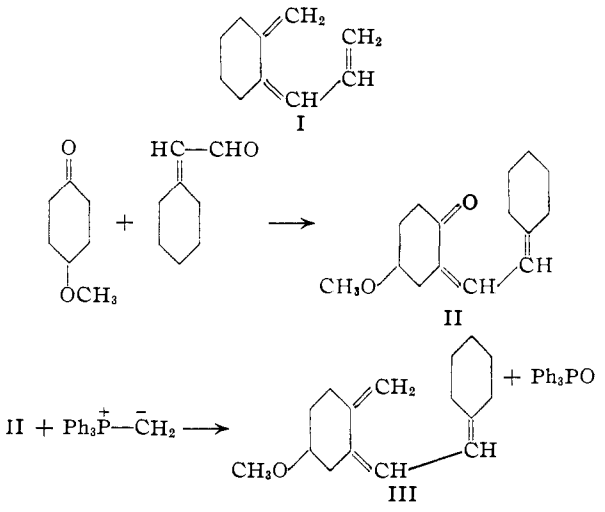
(2) Unpublished results.

(3) I. T. Harrison, B. Lythgoe and S. Trippett, *Chem. and Ind.*, April, 507 (1955).

(4) J. B. Aldersley, G. N. Burkhardt, A. E. Gillam and N. C. Hindley, *J. Chem. Soc.*, 10 (**1940**).

(5) V. K. Paranjpe, N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **28**, 38 (1949–50).

(6) R. Kuhn and C. Grundmann, *Ber.*, **70**, 1897 (1937).



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.

(7) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).

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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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(2) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *ibid.*, **77**, 1068 (1955).

(3) J. Fried and E. F. Sabo, *ibid.*, **76**, 1455 (1954).

(4) A. Borman and F. M. Singer, *Fed. Proc.*, **13**, 185 (1954).

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(6) A. Borman, F. M. Singer and P. Numerof, *Proc. Soc. Exp. Biol. Med.*, **86**, 570 (1954).

(7) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P.L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(8) J. J. Bunim, M. M. Pechet and A. J. Bollet, *J. Am. Med. Assoc.*, **157**, 311 (1955).

(9) R. F. Hirschman, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, THIS JOURNAL, **77**, 3166 (1955).

(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°, $[\alpha]^{23}D$ +90° ($CHCl_3$), λ_{max}^{alc} 228 mμ (6, 100); found: C, 65.56; H, 7.19).