However, when several residues have added, this configuration becomes unstable and following a transitional period the D residues take up their own stable configuration, the mirror image of the L peptide helix.[9]

(9) This work was supported by the Office of Naval Research (N5ori-07654). The anhydrides were kindly furnished by Dr. E. R. Blout and R. H. Karlson.

DEPARTMENT OF CHEMISTRY
HARVARD UNIVERSITY PAUL DOTY
CAMBRIDGE, MASSACHUSETTS R. D. LUNDBERG*
*Public Health Service Research Fellow (1955–56).

RECEIVED JULY 23, 1956

N-MONOALKYLATION AND ARYL BROMINATION OF CERTAIN AMINES WITH ETHYL BROMIDE IN DIMETHYL SULFOXIDE[1]

Sir:

In a study of alkylation of certain weak aromatic amines by alkyl phosphates and phosphonates,[2] we found that alkyl bromides in trialkyl phosphates gave good yields, for example, of N-monoalkylated 2-aminofluorenone.[3] We have therefore tried a limited number of other solvents, with other reaction conditions unchanged, finding none as good as the phosphates (or phosphonates), until use of dimethyl sulfoxide (generously donated by the Stepan Chemical Co., Chicago) resulted in a novel reaction which we wish to report briefly.

From 2-aminofluorenone and ethyl bromide in dimethyl sulfoxide, kept under reflux at a bath temperature of 150° for 1.5 hours, stirred into cold water and purified, there was obtained a product in crude yields of 50–60%, which we have identified as 2-N-ethylamino-3-bromofluorenone (I), m.p.[4] (of analytical sample) 164.5–165.5°. *Anal.* Calcd. for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; Br, 26.45; N, 4.64. Found: C, 59.65; H, 3.98; Br, 26.63; N, 4.91. About 8–15% of 2-amino-3-bromofluorenone (II) was also isolated, m.p. 215.5–216°. *Anal.* Calcd. for $C_{13}H_8BrNO$; N, 5.11. Found: N, 5.04.

A similar reaction with *p*-nitroaniline gave 2-bromo-4-nitro-N-ethylaniline, m.p. 66.5–68° (reported[5] m.p. 65–66°), and 2-bromo-4-nitroaniline, m.p. 103.5–104.5° (m.p.[6] 104.5°). *Anal.* Calcd. for $C_6H_5BrN_2O_2$: N, 12.91. Found: N, 12.92.

Finding no report of direct bromination of 2-aminofluorenone, we attempted this reaction at 20° in acetic acid, obtaining 80–85% of a crude product (III), m.p. (after two crystallizations from benzene) 215.5–216°; the mixture m.p. with II was not depressed. *Anal.* Calcd. for $C_{13}H_8BrNO$: N, 5.11. Found: N, 5.09. Monoethylation[2] of III gave I (m.p. and mixture m.p.). Diazotization of III and treatment with hypophosphorous acid[7] (1°) for 22 hours gave 3-bromofluorenone (IV), m.p. 165.5–166° (reported m.p. 162°,[8a] 165.5°[8c]). *Anal.* Calcd. for $C_{13}H_7BrO$: C, 60.26; H, 2.72; Br, 30.84. Found: C, 60.34; H, 2.91; Br, 30.90. Reduction of the latter compound with sodium borohydride[9] gave 3-bromofluorenol, m.p. 169.5–170.5° (reported[8b] m.p. 142–145°). *Anal.* Calcd. for $C_{13}H_9BrO$: C, 59.79; H, 3.47; Br, 30.61. Found: C, 60.00; H, 3.71; Br, 30.73. This upon further reduction with phosphorus and iodine[8b] yielded 3-bromofluorene (V), m.p. 89–90° (reported[8b] m.p. 90–91°).

For further confirmation, acetylation of III (*i.e.*, II) followed by reduction with sodium borohydride[9] to the corresponding 9–01 and further reduction with phosphorus and iodine[8b] gave 3-bromo-2-acetamidofluorene, m.p. 208–209° (after melting, this substance solidified with pressure and remelted 210–211°). *Anal.* Calcd. for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; Br, 26.45; N, 4.64. Found: C, 59.70; H, 3.86; Br, 26.50; N, 4.30. Bell and Mulholland[10] report isolation of "3 (or 1)-bromo-2-acetamidofluorene," m.p. 206–207°. In support of evidence in the preceding paragraph our substance cannot be the 1-bromo derivative since diazotization of III would have given 1-bromofluorenone which is reported to melt at 134–134.3°.[11] It is also highly unlikely that the 1-position would be attacked in this reaction to the exclusion of significant amounts of other isomers.

It would appear that dimethyl sulfoxide, offering a favorable environment for alkylation with ethyl bromide, reacts with eliminated hydrogen bromide, giving $(CH_3)_2SBr_2$.[12] The latter then effects ring bromination of the N-alkylated amine (or the free amine remaining) and is finally released as dimethyl sulfide, a supposition which is in agreement with the odor of the filtrate after aqueous treatment of the crude reaction product.

(1) This work was supported in part by a research grant (C-1744) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Mention of the effect of lithium bromide on alkyl phosphate alkylations of 2-aminofluorenone was included in T. L. Fletcher, M. E. Taylor and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955).

(3) Included in a further report which will be presented shortly by this Laboratory.

(4) All melting points are corrected, and were taken on a Fisher–Johns apparatus. We wish to thank Mr. Murray E. Taylor of this Laboratory for nitrogen microanalyses.

(5) M. S. Kharasch and I. M. Jacobson, THIS JOURNAL, **43**, 1894 (1921).

(6) B. H. Nicolet and W. L. Ray, *ibid.*, **49**, 1801 (1927).

(7) N. Kornblum, in "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 277.

(8) (a) H. F. Miller and G. B. Bachman, THIS JOURNAL, **57**, 2443 (1935); (b) H. F. Miller and G. B. Bachman, *ibid.*, **57**, 2447 (1935). The wide m.p. reported for 3-bromofluorenol may have resulted from impurity. Reported Br analysis 30.45 (no C or H). A small amount of IV remaining in the reduction product would change this analysis only slightly. Our melting points for IV and V agree with the literature; (c) P. J. Montagne and J. M. v. Charante, *Rec. trav. chim.*, **32**, 164 (1913).

(9) The reduction of approximately fifteen fluorenone derivatives in high yield has been carried out in this Laboratory and forms part of a paper in preparation.

(10) F. Bell and D. B. Mulholland, *J. Chem. Soc.*, 2020 (1949).

(11) E. H. Huntress, K. Pfister, 3rd, and K. H. T. Pfister, THIS JOURNAL, **64**, 2845 (1942).

(12) See, for example, R. Connor in "Organic Chemistry, An Advanced Treatise," ed. H. Gilman, Vol. 1, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., p. 872.

CHEMISTRY RESEARCH LABORATORY
DEPARTMENT OF SURGERY T. LLOYD FLETCHER
UNIVERSITY OF WASHINGTON HSI-LUNG PAN
SCHOOL OF MEDICINE
SEATTLE 5, WASHINGTON

RECEIVED JULY 16, 1956

21-FLUORO DERIVATIVES OF 9α-FLUORO- AND 1-DEHYDROCORTICOIDS

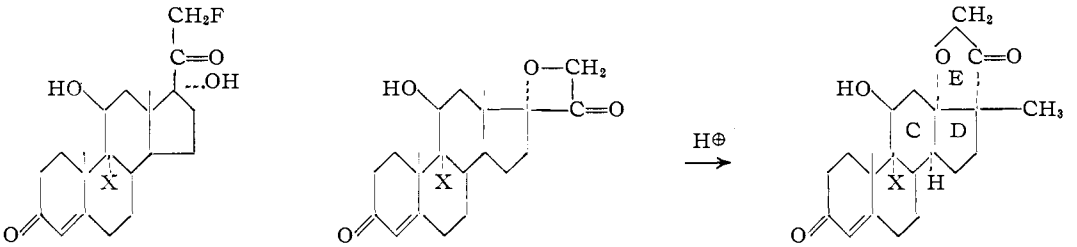
Sir:

The preparation of a series of 21-fluorinated steroids by the action of silver fluoride on 21-iodo-

steroids in acetonitrile has been described recently.[1] Prior to the appearance of that publication, while studying the displacement reactions of steroid 21-mesylates we have found that potassium fluoride in DMF or DMS[2] can effect substitution of the mesyloxy group by fluoride ion.[3]

Treatment of hydrocortisone mesylate, m.p. 186–187° (dec.), $[\alpha]_D^{CHCl_3}$ +150°. *Anal.* Found: C, 60.29; H, 7.32; S, 7.08, with anhydrous potassium fluoride in DMF or DMS at 110° for 18–24 hours furnished 21-fluoro-Δ^4-pregnene-11β,17α-diol-3,20-dione (I), m.p. 242–244°; $[\alpha]_D^{alc}$ +163°; λ_{max}^{alc} 242 mμ (15,000); λ_{max}^{Nujol} 2.87, 3.05, 5.84, 6.05–6.10, 6.20 μ; *Anal.* Found: C, 69.29; H, 8.09; F, 5.46,[4] L.G., 0.5,[5] and 17α,21-oxido-Δ^4-pregnen-11β-ol-3,20-dione (II), m.p. 244–246°; $[\alpha]_D^{CHCl_3}$ +237°; λ_{max}^{alc} 241 mμ (16,300); λ_{max}^{Nujol} 2.96, 5.55, 6.09, 6.19 μ; *Anal.* Found: C, 73.51; H, 8.11. Structure II is based on the infrared band at 5.55 μ[6] and on the following considerations. Recently Allen, *et al.*,[7] described the 3,20-diketal of II and related 17α, 21-oxido-ketals, which on hydrolysis with dilute acid yielded what were believed to be the parent 17α,21-oxides mainly on the basis of infrared bands at 5.70–5.72 μ. Such a structural assignment seemed hardly justified by the evidence given, which favors a five- rather than a four-membered ring ketone. Moreover, the unusual stability of the oxides to acid noted by the authors appeared to militate against the 17α, 21-oxide structure for the hydrolysis products. We have indeed found that II is unstable under the hydrolysis conditions employed by Allen, *et al.*, and that it rearranges to an isomeric substance (III), m.p. 199–201°; $[\alpha]_D^{CHCl_3}$ +44°; λ_{max}^{alc} 240 mμ (16,800); λ_{max}^{Nujol} 2.82, 2.95, 5.72, 6.04, 6.19 μ; *Anal.* Found: C, 72.79; H, 7.97, whose constants are in agreement with those reported by Allen, *et al.*, for the product arising by "hydrolysis" of the 17α,21-oxido-ketal derived from hydrocortisone. Structure III[8] is therefore proposed not only for our rearrangement product but for the "hydrolyzed" ketal of Allen, *et al.*, as well.

Extension of the reaction with potassium fluoride in DMS to the mesylates of 9α-fluorohydrocortisone, m.p. 226–227° (dec.); $[\alpha]_D^{diox}$ +129°; *Anal.* Found: C, 57.92; H, 6.80; S, 7.39, 1-dehydro-9α-fluorohydrocortisone[9] and 1-dehydro-hydrocortisone, m.p. 200° (dec.); $[\alpha]_D^{alc}$ +106°. *Anal.* Found: C, 60.21; H, 6.89 furnished the corresponding chloroform-insoluble 21-fluorides,[10] all of which were highly active in the rat liver glycogen assay,[5] Ia, m.p. 268–270°; $[\alpha]_D^{diox}$ +147°; λ_{max}^{alc} 239 mμ (16,400); *Anal.* Found: C, 65.96; H, 7.43; F, 9.87; L.G., 7.0; Ib, m.p. 266–268° (dec.); $[\alpha]_D^{alc}$ +111°; λ_{max}^{alc} 237 mμ (15,500); *Anal.* Found: C, 66.27; H, 6.87; F, 9.93, L.G., 10–15, and Ic, m.p. 257–262°; $[\alpha]_D^{diox}$ +86°; λ_{max}^{alc} 243 mμ (15,100); *Anal.* Found: C, 69.76; H, 7.42; F, 4.92; L.G., 3.0, as well as the 17α,21-oxides[10] IIa, m.p. 272–274°; $[\alpha]_D^{CHCl_3}$ +186°; λ_{max}^{alc} 237 mμ (18,300); *Anal.* Found: C, 69.77; H, 7.77; F, 5.37; IIb, m.p. 308–310°; $[\alpha]_D^{CHCl_3}$ +183°; λ_{max}^{alc} 237 mμ (17,200); *Anal.* Found: C, 69.85; H, 6.96; F, 5.20 and IIc, m.p. 243–244°; $[\alpha]_D^{CHCl_3}$ +182° λ_{max}^{alc} 243 mμ (15,400); *Anal.* Found: C, 73.58, H, 7.48. IIa was rearranged with acid to IIIa, m.p. 252–254° (dec.); $[\alpha]_D^{CHCl_3}$ +49°; λ_{max}^{alc} 237 mμ (17,700); λ_{max}^{Nujol} 2.98, 5.70, 6.10, 6.18 μ; *Anal.* Found: C, 69.46; H, 7.36; F, 5.12, and IIc to IIIb, m.p. 218–219°; $[\alpha]_D^{CHCl_3}$ +19°; λ_{max}^{alc} 243 mμ (15,900); *Anal.* Found: C, 73.56; H, 7.67.



I, X = H
Ia, X = F
Ib, X = F; Δ^1
Ic, X = H; Δ^1
Id, X = F; F = Cl

II, X = H
IIa, X = F
IIb, X = F; Δ^1
IIc, X = H; Δ^1

III, X = H
IIIa, X = F
IIIb, X = H; Δ^1

The conclusion appears justified that introduction of a fluorine atom into the 21-position enhances the glucocorticoid activity of the corresponding 21-desoxy corticords by approximately 3–5 times.[11] The significance of this finding is stressed by the fact that 9α-fluoro-21-chloro-Δ^4-pregnene-11β,17α,21-triol-3,20-dione (Id), m.p. 267–269°; $[\alpha]_D^{diox}$ +153°; λ_{max}^{alc} 238 mμ (17,700);

(1) P. Tannhauser, R. J. Pratt and E. V. Jensen, THIS JOURNAL, **78**, 2658 (1956).

(2) DMF = Dimethylformamide; DMS = dimethyl sulfoxide.

(3) *Cf.* also W. F. Edgell and L. Parts, THIS JOURNAL, **77**, 4899 (1955); G. C. Finger and C. W. Kruse, Abstr. of Papers, 129th Meeting, Amer. Chem. Soc., Dallas, 1956, 44N; and F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956).

(4) Reported (*cf.* ref. 1): m.p. 240–242°; $[\alpha]_D^{CHCl_3}$ +145°.

(5) We are grateful to Drs. A. Borman and F. M. Singer of our laboratories for the rat liver glycogen values (L.G.; cortisone acetate = 1).

(6) The C=O stretching band in cyclobutanone occurs at 5.63 μ (D. H. Whiffen and H. W. Thompson, *J. Chem. Soc.*, 1005 (1946), in propiolactone at 5.44 μ (P. D. Bartlett and P. N. Rylander, THIS JOURNAL, **73**, 4275 (1951)).

(7) W. S. Allen, S. Bernstein, M. Heller and R. Littell, *ibid*, **77**, 4784 (1955).

(8) Structure III is in harmony with the infrared data and can be rationalized to arise from II by a mechanism involving synchronous migration of a methyl and an alkoxy group to produce a practically strain-free (C/D *cis*, D/E *cis*) from a highly strained system.

(9) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. Singer, THIS JOURNAL, **77**, 4181 (1955).

(10) The infrared spectra of all 21-fluorides and 17α,21-oxides are in harmony with the assigned structures.

(11) For the potencies of 21-desoxy corticords *cf.* ref. 9 and papers quoted therein.

Anal. Found: C, 63.25; H, 7.34; Cl, 8.44, prepared from the corresponding 21-mesylate with lithium chloride in acetic acid was inactive in the liver glycogen assay at 10 times the minimum effective dose of cortisone acetate.

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
NEW BRUNSWICK, N. J.

JOSEF E. HERZ
JOSEF FRIED
PAUL GRABOWICH
EMILY F. SABO

RECEIVED JULY 20, 1956

A CONTRIBUTION TO THE CHEMISTRY OF STEROID 17,21-OXIDES

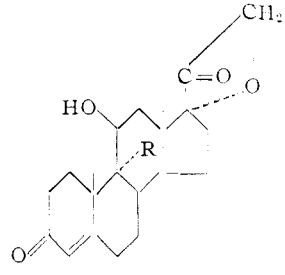
Sir:

Treatment of 11β,17α-dihydroxy-21-iodo-4-pregnene-3,20-dione[1] (I) with silver dihydrogen phosphate afforded, in addition to the steroid 21-phosphate, a water-insoluble by-product, m.p. 237–243° (dec.), $[\alpha]_D^{Chf}$ +246°; λ_{max}^{MeOH} 240.5 mμ (ϵ = 16,300); λ_{max}^{Chf} 2.72 μ, 2.8–2.88 μ (OH), 5.54 μ (20-ketone), 6.0 μ (3-ketone), 6.15 μ (Δ^4-double bond); λ_{max}^{Nj} 2.95 μ, 5.55 μ, 6.0–6.05 μ, sh 6.12 μ; Found: C, 73.49; H, 8.15. The mobility of the compound by paper strip chromatography is nearly identical with that of 11β-hydroxyprogesterone. The product was formulated as 17α,21-epoxy-11β-hydroxy-Δ^4-pregnene-3,20-dione (II). The same structure has been assigned[2] to a different product VII (m.p. 198.5–201°; $[\alpha]_D^{Chf}$ +69°; λ_{max}^{Chf} 5.72 μ, 6.02 μ, 6.16 μ) which Allen, *et al.*, obtained by treating 17,21-epoxy-11β-hydroxy-Δ^4-pregnene-3,20-dione 3,20-bisethylene ketal with aqueous methanolic sulfuric acid. However, the infrared spectrum of VII is inconsistent with structure II, since 3-oxetanones generally absorb at 5.55 μ.[3] The properties of VII are, however, in fair agreement with a substance III (m.p. 201–206°; $[\alpha]_D^{Chf}$ +52°; λ_{max}^{MeOH} 240 mμ (ϵ = 16,400); λ_{max}^{Nj} 2.79 μ, 2.95 μ, 5.72 μ, 6.03 μ, 6.17 μ; Found: C, 73.37; H, 7.96) which resulted from treating II with methanolic sulfuric acid. III was shown to be 13α,21-epoxy-11β-hydroxy-17β-methyl-18-nor-17α-Δ^4-pregnene-3,20-dione by relating the position of the oxide-bridge to the hydroxyl function at C-11. Oxidation of III with chromium trioxide–pyridine[4] gave the 11-ketone IV (m.p. 157–158°; λ_{max}^{MeOH} 236 mμ (ϵ = 15,200); λ_{max}^{Nj} 5.70 μ, 5.83 μ, 5.97 μ, 6.16 μ (no OH); λ_{max}^{Chf} 5.70 μ, 5.82 μ, 5.99 μ, 6.16 μ; Found: C, 73.49; H, 7.56). When the latter was refluxed with pyridine and acetic anhydride, a large increment in the extinction at 238 mμ occurred, demonstrating the formation of a second α,β-unsaturated ketone group. Since the product (V) (m.p. 185–186°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ϵ = 26,200); λ_{max}^{Nj} 5.72 μ and 5.83 μ (21-acetate, 20-ketone), 6.02 μ and 6.18 μ (3-keto-Δ^4 and 11-keto-Δ^{12}-systems), 8.08 μ (acetate); Found: C, 71.69; H, 7.17) in contrast to III, gave a positive tetrazolium test, it is formulated as 21-acetoxy-17β-methyl-18-nor-9ζ,14ζ-17α-$\Delta^{4,12}$-pregnadiene-3,11,20-trione.

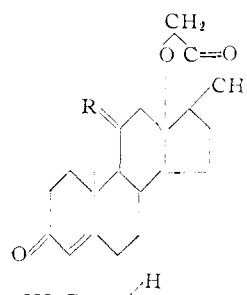
Structure VI, an unlikely alternative for the methanol–sulfuric acid product on mechanistic grounds, is ruled out further by the u.v. spectrum of V, and because the reaction sequel I → V can be paralleled in the 9α-fluorohydrocortisone series.

The conversion of II to III resembles the conversion of 3β-acetoxy-16α,17α-epoxy-Δ^5-pregnene-20-one to 3β-acetoxy-16β-formyloxy-17β-methyl-18-nor-17α-$\Delta^{5,13}$-pregnadiene-20-one with formic acid in the presence of sulfuric acid.[5] The stabilization of the intermediate carbonium ion at C-13 by ring closure rather than by formation of an olefin had, however, not been previously described.

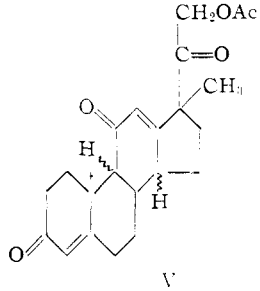
We have also prepared 17α,21-epoxy-9α-fluoro-11β-hydroxy-Δ^4-pregnene-3,20-dione (VIII), m.p. 236° (dec.), $[\alpha]_D^{DMA}$ +192°; λ_{max}^{MeOH} 237 mμ (ϵ = 16,900); λ_{max}^{Nj} 3.0 μ, 5.5 μ, 6.07 μ, sh 6.17 μ; Found: C, 69.18; H, 7.47.[6] It is of considerable interest that whereas compounds II–V are essentially inactive[7] in the systemic granuloma inhibition and liver glycogen tests, VIII exhibited anti-inflammatory activity of the same order of magnitude as hydrocortisone in these tests.[7]



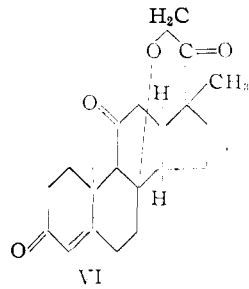
II, R = H
VIII, R = F



III, R = 
IV, R = =O



V



VI

CONTRIBUTION OF THE
MERCK-SHARP & DOHME
RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
RAHWAY, NEW JERSEY

RALPH HIRSCHMANN
GEORGE A. BAILEY
GEORGE J. POOS
ROBERT WALKER
JOHN M. CHEMERDA

RECEIVED JULY 27, 1956

(1) C. T. Bergstrom, U. S. Patent 2,684,968, July 27, 1954.

(2) W. S. Allen, S. Bernstein, M. Heller and R. Littell, THIS JOURNAL, **77**, 4784 (1955). Dr. Bernstein, whom we advised of our results, informed us that he, too, has come to question the correctness of his structural assignment and that he is pursuing the matter himself.

(3) G. B. Hoey, D. O. Dean and C. T. Lester, *ibid.*, **77**, 391 (1955); B. L. Murr, G. B. Hoey and C. T. Lester, *ibid.*, **77**, 4430 (1955).

(4) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(5) K. Heusler and A. Wettstein, *Ber.*, **87**, 1301 (1954).

(6) The 11-keto-analog of II was first isolated by Dr. R. E. Beyler and Miss F. Hoffman in another connection and independently assigned a 17,21-oxide structure.

(7) We are very much indebted to Dr. C. A. Winter and Dr. C. C. Porter for the animal assays.