showed almost no activity as the amide donor. Under the conditions of the experiment shown in Table II, glutamine supply limits DPN synthesis. Thus, in a separate experiment under similar conditions, with NA held constant at 10 μmoles per vessel, DPN synthesis in the presence of 0, 4, 10 and 20 μmoles of glutamine was 0.052, 0.104, 0.172 and 0.274 μmole, respectively. Further investigations are in progress seeking to elucidate the mechanism of pyridine nucleotide synthesis from nicotinic acid and its amide.

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THE ISOTROPIC LENGTH OF POLYMER NETWORKS

Sir:

A general theory of the elastic properties of polymer networks was developed in a recent paper[1] and this theory was applied to the cross-linking of highly oriented chains. Whereas for a network formed in the usual way by cross-linking chain molecules in random arrangement the isotropic length L_i of the network (*i.e.*, its length under no stress) must obviously be independent of the degree of cross-linking, it was shown that for a network formed by the random cross-linking of highly oriented chains L_i should increase directly as the square root of the fraction ρ of the units cross-linked. Although it has been reported that the cross linking of stretched rubber results in an increase in its isotropic (zero stress) length,[2,3] adequate data are not available to test the aforementioned deduction. We wish to report the results of studies of the isotropic length of natural rubber networks formed from chains in a highly oriented state. These results give strong support to the theoretical conclusions.

The highly oriented state of the rubber, prior to cross-linking is obtained by modification of the "racking process" originally described by Feuchter.[4] The wide angle X-ray pattern[5] indicates that the specimen is in a highly oriented state and the ratio of the extended length to retracted length is about eleven. The samples were cross-linked by subjecting them to γ-ray irradiation from a Co^{60} source. The efficiency of cross-linking in the highly oriented racked rubber was found to be twice that for unoriented rubber.

In Fig. 1 the ratio of L_1 to the initial length L_0 is plotted against $\rho^{1/2}$. A fiftyfold range in cross-linking is encompassed by these experiments and the isotropic length increases by a factor of two and a half. At the higher degrees of cross-linking the data are well represented by a straight line which extrapolates to the origin. However, as the cross-linking density decreases deviations from linearity occur and L_i/L_0 appears to approach unity. According to equation (38) of ref. 1, L_i/L_0 should vary directly as $\rho^{1/2}$ for chains with *perfect* axial orientation, and for an infinitesimal amount of cross-linking L_i should shrink to zero. This behavior is indicated by the linear portion of the curve and its extrapolation to the origin. Since the chains prior to network formation are neither completely nor perfectly oriented, deviations from linearity would be expected at low cross-linking densities where L_i should tend to remain constant as observed. The slope of the linear portion of the curve is fifteen while theoretically it is estimated to be about ten. It appears that "racked rubber" can serve as a good model for the physical behavior of the fibrous proteins.

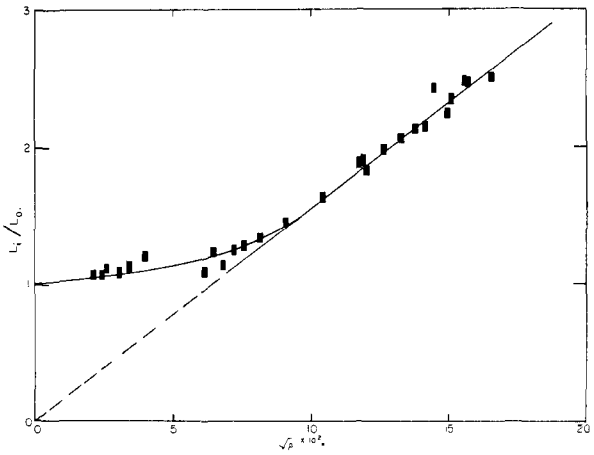

Fig. 1.—Plot of ratio of isotropic length after cross-linking L_i to initial length L_0 against the square root of the fraction of the units crosslinked $\rho^{1/2}$.

Further details of the experimental methods, a more thorough discussion of these results as well as a comparison of the isotropic melting temperature and swelling behavior of different type networks will appear in a forthcoming paper.[6]

(1) P. J. Flory, THIS JOURNAL, **78**, 5222 (1956).

(2) R. D. Andrews, E. E. Hanson and A. V. Tobolsky, *J. Appl. Phys.*, **17**, 352 (1946).

(3) J. P. Berry, J. Scanlan and W. F. Watson, *Trans. Faraday Soc.* **52**, 1137 (1956).

(4) H. Feuchter, *Kautschuk*, Dec., p. 6 (1925); pp. 8, 28 (1928).

(5) C. C. Davis and J. T. Blake, "The Chemistry and Technology of Rubber," Reinhold Publishing Corporation, New York, N. Y., 1937, p. 78.

(6) D. E. Roberts and L. Mandelkern, in preparation.

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ADRENAL HORMONES AND RELATED COMPOUNDS. V. FLUORINATED 6-METHYL STEROIDS

Sir:

We recently have reported[1] the preparation of a number of 6-methylated analogs of adrenal hormones which show unusual potentiation of glucocorticoid activity with no sodium-retaining properties. The group of 9α-fluoro- and 21-fluoro-6-methyl steroids reported herein represents a continuation of this work. Compound III described below is by far the most potent glucocorticoid reported to date.

(1) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956).

The 6α-methyl-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione[1] was dehydrated by thionyl chloride in pyridine to 6α-methyl-17α-hydroxy-21-acetoxy-1,4,9(11)-pregnatriene-3,20-dione (I), m.p. 192–194°; $[\alpha]_D$ + 18° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, a_M = 15,450. *Anal.* Found: C, 72.03; H, 7.57. This was converted by known methods[2] to a crude 9,11-bromohydrin and then to the 6α-methyl-9β,11β-oxido-17α-hydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione (II), m.p. 260–265°; $[\alpha]_D$ + 60° (pyridine); $\lambda_{max}^{95\% \text{ alc.}}$ 249 mμ, a_M = 16,150. *Anal.* Found: C, 69.48; H, 7.21. Reaction of II with hydrofluoric acid gave 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione (III), m.p. 237–239°; $[\alpha]_D$ + 87° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, a_M = 15,250. *Anal.* Found: C, 65.94; H, 6.95; F, 4.72. Hydrolysis of III with potassium bicarbonate in methanol produced 6α-methyl-9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (IV), m.p. 243–250 (dec.); $[\alpha]_D$ + 93° (dioxane); $\lambda_{max}^{95\% \text{ alc.}}$ 238 mμ, a_M = 15,150. *Anal.* Found: C, 67.48; H, 7.61; F, 5.02. Conversion of IV to the corresponding 21-fluoro analog[3] gave 6α-methyl-9α,21-difluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (V), m.p. 262–274 (dec.); $[\alpha]_D$ + 71° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, a_M = 15,000. *Anal.* Found: C, 66.87; H, 7.69; F, 9.80.

In a like manner 6α-methyl-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione[1] was converted to a similar series of compounds: 6α-methyl-17α-hydroxy-21-acetoxy-4,9-(11)-pregnadiene-3,20-dione (VI), m.p. 175–176°; $[\alpha]_D$ + 91° (Chf.); $\lambda_{max}^{95\% \text{ alc.}}$ 239.5 mμ, a_M = 16,400. *Anal.* Found: C, 71.75; H, 7.71; 6α-methyl-9α-bromo-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (VII), m.p. 153–155° (dec.); $[\alpha]_D$ + 148° (Chf.); $\lambda_{max}^{95\% \text{ alc.}}$ 239.5 mμ, a_M = 14.225. *Anal.* Found: Br, 16.0; 6α-methyl-9β,11β-oxido-17α-hydroxy-21-acetoxy-4-pregnene-3,20-dione (VIII), m.p. 180–182°; $[\alpha]_D$ + 65° (Chf.); $\lambda_{max}^{95\% \text{ alc.}}$ 242 mμ, a_M = 14, 625. *Anal.* Found: C, 69.41; H, 7.93; 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (IX), m.p. 219–220°; $[\alpha]_D$ + 113° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, a_M = 15,775. *Anal.* Found: C, 65.69; H, 7.49; F, 4.29; 6α-methyl-9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (X), m.p. 228–230°; $[\alpha]_D$ + 112° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, a_M = 16,400. *Anal.* Found: C, 67.20; H, 8.01; F, 5.47; and 6α-methyl-9α,21-difluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (XI), m.p. 210–212°; $[\alpha]_D$ + 89° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, a_M = 14,225. *Anal.* Found: C, 66.35; H, 8.07; F, 9.24.

In addition, using the method of reference 3, 6α-methyl-11β,17α,21-trihydroxy-4-pregnene-3,20-dione[1] was converted to 6α-methyl-11β,17α-dihydroxy-21-fluoro-4-pregnene-3,20-dione (XII), m.p. 220–223°. *Anal.* Found: C, 70.14; H, 7.95; F, 6.76. Likewise, 6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione[1] gave 6α-methyl-11β,17α-dihydroxy-21-fluoro-1,4-pregnadiene-3,20-dione (XIII), m.p. 216–222°. *Anal.* Found: F, 3.63.

Compounds III, IV, V, IX, X, XI, XII and XIII all show considerably greater glucocorticoid and anti-inflammatory activity[4] than does hydrocortisone in animal assays. Compound III, 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione, was more active in the anti-inflammatory assay than any of the previously reported analogs of hydrocortisone of which we are aware. Its enhancement of the glucocorticoid activity was particularly noteworthy, being 120 times as active as hydrocortisone when administered parenterally, and 190 times hydrocortisone by oral administration. None of the above compounds exhibited appreciable sodium retaining properties.[5]

(2) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(3) By a modification of the method of P. Tannhauser, R. J. Pratt and E. V. Jensen, *ibid.*, **78**, 2658 (1956).

(4) Assays were performed by members of the Department of Endocrinology of The Upjohn Company and will be reported in detail elsewhere. The glucocorticoid assays were by the method of R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955); the anti-inflammatory assays by a modified granuloma pouch technique (A. Robert and J. E. Nezamis, *Acta Endocrinologica*, in press).

(5) This may be contrasted with the activity of 2-methyl-9α-fluorohydrocortisone reported by W. W. Byrnes, L. E. Barnes, B. J. Bowman, W. E. Dulin, E. H. Morley and R. O. Stafford, *Proc. Soc. Exp. Biol. Med.*, **91**, 67 (1956), where the mineralocorticoid properties were shown to be enhanced to a much greater extent than the glucocorticoid.

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A NEW ANALGETIC

Sir:

To date the preparation of effective synthetic analgetics has been confined to a great extent to pyrazolone derivatives, *e.g.*, aminopyrin (1-phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone)[1] and phenylbutazone (1,2-diphenyl-4-butyl-3,5-pyrazolidinedione),[2] and to morphine-like analogs, such as meperidine (ethyl 1-methyl-4-phenylisonipecotate)[3] and levorphan (3-hydroxy-N-methylmorphinan).[4] Each of these and related type compounds have suffered from certain disadvantages, such as addiction and dependence (morphine and analogs), as well as toxic effects on the hematopoetic system (pyrazolone derivatives). More recently it has been reported[5] that replacement of the 1-methyl group of meperidine with the phenyl ethyl or para-amino phenyl ethyl moiety leads to a less toxic morphine-like compound.

At this time we wish to present a preliminary report on the preparation of a compound which we have found to possess good analgetic activity in experimental animals. The constitutional aspects of this new preparation are far removed from the usual features attending previously outlined anal-

(1) A. Stolz, U. S. Patent 579,412 (1897).

(2) J. R. Geigy, A.-G., Swiss Patent 269,980 (1950).

(3) O. Eisleb, U. S. Patent 2,167,351 (1939).

(4) O. Schnider and A. Grussner, *Helv. Chim. Acta*, **32**, 821 (1949).

(5) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956); J. Weijlard, *et al.*, THIS JOURNAL, **78**, 2342 (1956).