bond, of which it is a part, is stretched, so that the right side of eq. (3) may be equated to zero, at least to good approximation for our purposes. Or, alternatively, we may simply say that the field, E, may be assumed constant for small stretchings of a bond, the change in the longitudinal polarizability being the more important quantity. With this assumption, together with equation (9) of the preceding paper,<sup>3</sup> eq. (2) reduces to

$$\epsilon = \frac{\mu}{b_1} \cdot \frac{\mathrm{d}b_1}{\mathrm{d}R} \tag{5}$$

For H-X molecules, Denbigh<sup>4</sup> found  $b_t/b_1 = 0.75$ . Assuming this relation to be satisfied as the bond is stretched, we find, using  $\alpha = (1/3) (b_1 + 2b_t)$ , that  $db_1/dR = 1.20 \ d\alpha/dR$ . Hence we are now prepared to calculate values of  $\epsilon$  for diatomic molecules for which  $\mu$ ,  $b_1$ , and  $d\alpha/dR$  are known experimentally, namely, HCl and HBr. These data, together with calculated and observed values of  $\epsilon$ , are summarized in Table I.

## TABLE I

CALCULATED AND OBSERVED VALUES CF & FOR HCl AND HBr

| Molecule | $\mu$ , <sup>1</sup> $D$ | b1,4 Å₽ | $d\alpha/dR$ , s Å | e(calcd.),e | e(obs.) <sup>2</sup> , e |
|----------|--------------------------|---------|--------------------|-------------|--------------------------|
| HC1      | 1.03                     | 3.13    | 1.23               | 0.102       | 0.086                    |
| HBr      | 0.79                     | 4.23    | 1.07               | 0.050       | 0.075                    |

Since both the observed  $\epsilon$  values and the  $d\alpha/dR$  values are somewhat uncertain, the agreement between calculated and observed  $\epsilon$  values seems satisfactory, and apparently adds justification to the use of the model we have proposed for the origin of electric dipole moments.

| DEPARTMENT OF CHEMISTRY | RICHARD P. SMITH <sup>6</sup> |
|-------------------------|-------------------------------|
| UNIVERSITY OF UTAH      | HENRY EYRING                  |
| Salt Lake City, Utah    |                               |
| RECEIVED SEPTEMBER      | 24, 1951                      |

(4) K. G. Denbigh, Trans. Faraday Soc., 36, 936 (1940).

(5) R. P. Bell, *ibid.*, **38**, 422 (1942).

(6) Department of Chemistry, Harvard University, Cambridge, Mass.

## STEROIDAL SAPOGENINS. XV. EXPERIMENTS IN THE HECOGENIN SERIES (PART 3).<sup>1</sup> CONVERSION TO CORTISONE

Sir:

In two recent communications<sup>2,3</sup> there was recorded the partial synthesis of cortisone from ring C unsubstituted plant steroids such as diosgenin, ergosterol and stigmasterol. Another potentially very attractive starting material for the preparation of cortisone is the class of C-12 oxygenated steroidal sapogenins, as exemplified by hecogenin (I) (22-isoallospirostan- $3\beta$ -ol-12-one), which occurs in a wide variety of Agave's indigenous to the southwestern part of the United States,<sup>4</sup> Mexico,<sup>4</sup> and East Africa.<sup>5</sup> We should now like to record the successful conversion of hecogenin to cortisone.

(1) Part 2, C. Djerassi, H. Martinez and G. Rosenkranz, J. Org. Chem., 16, 1278 (1951).

(2) J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, THIS JOURNAL, 73, 4052 (1951).

- (3) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, 73, 4055 (1951).
- (4) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, and C. H. Ruof, *ibid.*, **69**, 2167 (1947).

(5) R. K. Callow, J. W. Cornforth and P. C. Spensley, Chemistry and Industry, 699 (1951).



Of the two most useful methods<sup>6,7</sup> employed in the bile acid series for shifting a keto group from position 12 to C-11, that of Kendall and co-workers<sup>6</sup> is inapplicable to hecogenin (I) and related sapogenins, because they do not possess the required steric configuration at C-3 ( $\alpha$ ) and C-5 ( $\beta$ ); Gallagher's<sup>7</sup> procedure in its initial stages (bromination at C-11, followed by alkaline hydrolysis and isomerization to the 11-one-128-ol) as applied<sup>8</sup> to hecogenin (I) leads in good yield to 22-isoallospirostan- $3\beta$ ,  $12\beta$ -diol-11-one (II), but the subsequent reaction of a 3-monoacylated-12-ol with phosphorus tribromide proceeds exceedingly poorly in the sapogenin series because of interaction with the spiroketal side chain. It has now been observed that bismuth oxide, a specific oxidizing agent for acyloins,<sup>9</sup> does not attack tigogenin (22-isoallospirostan- $3\beta$ ol), but reacts smoothly with a ketol such as methyl  $3\alpha$ , 12 $\beta$ -dihydroxy-11-ketocholanate (Marker-Lawson acid)<sup>10</sup> to afford after acetylation the known<sup>11</sup> enol acetate of methyl  $3\alpha$ -acetoxy-11,12-diketo-cholanate (m.p. 130–132°,  $[\alpha]^{20}D$  +117°,  $\lambda_{\max}^{EtOH}$ 244 mµ, log e 3.97; found: C, 69.31; H, 8.70). On applying the bismuth oxide oxidation (18 hrs. refluxing in acetic acid solution) to 22-isoallospirostan- $3\beta$ ,  $12\beta$ -diol-11-one (II), <sup>8</sup> there was obtained in over 70% yield 22-isoallospirostan-3 $\beta$ ol-11,12-dione as a mixture of keto (III) and enol forms (m.p. 196–197°, dark green color with ferric chloride,  $[\alpha]^{20}$ D –21° (all rotations in chloroform),  $\lambda_{max}^{EtOH}$  282 mµ, log  $\epsilon$  3.28; found: C, 73.45; H, 9.40), further characterized by the exceedingly soluble enol acetate,  $\Delta^9$ -22-isoallospirosten-3 $\beta$ ,11-diol-12-one 3,11-diacetate (IVb) (m.p. 188–192°,  $[\alpha]^{20}$ D +14°,  $\lambda_{\text{max.}}^{\text{EtoH}}$  244 m $\mu$ , log  $\epsilon$  4.05; found: C, 70.90; H, 8.31). Huang-Minlon reduction<sup>12</sup> of III yielded 22-isoallospirostan- $3\beta$ -ol-11-one (V), contaminated by some of the 11-hydroxy derivative and purifica-

(6) B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, J. Biol. Chem., 173, 271 (1948), and earlier papers.

(8) C. Djerassi, H. Martinez and G. Rosenkranz, J. Org. Chem., 16, 303 (1951).

- (9) W. Rigby, J. Chem. Soc., 793 (1951).
- (10) Cf. T. F. Gallagher, J. Biol. Chem., 162, 539 (1946).
- (11) O. Wintersteiner and M. Moore, *ibid.*, 162, 725 (1946).
- (12) Huang-Minlon, THIS JOURNAL: 68; 2487 (1946).

<sup>(7)</sup> E. Borgstrom and T. F. Gallagher, ibid., 177, 951 (1949).

tion was accomplished most conveniently by oxidizing the crude product with chromium trioxide to 22-isoallospirostan-3,11-dione (m.p.  $236-237^{\circ}$ .  $[\alpha]^{20}D - 1\overline{7}^{\circ}$ ; found: C, 75.16; H, 9.22), followed by Raney nickel hydrogenation (room temperature) to 22-isoallospirostan-3 $\beta$ -ol-11-one (V)<sup>13</sup> (m.p. 223–226°,  $[\alpha]^{20}D - 29^\circ$ ; found: C, 75.28; H, 9.93. The acetate<sup>14</sup> showed m.p. 222–224°,  $[\alpha]^{20}D - 31^\circ$ ; found: C, 73.92; H, 9.60). Alternately, the mixture of III and IVa was converted with ethanedithiol in the presence of zinc chloride to 22-isoallospirostan- $3\beta$ -ol-11,12-dione 12-cycloethylenemercaptol (m.p. 289-291°; found: Š, 11.98), which upon Raney nickel desulfurization led directly to the 11ketone V. This substance (V) has already been transformed<sup>14</sup> into allopregnan-3*β*-ol-11,20-dione and thence<sup>3</sup> to cortisone.

(13) The 3,11-dione as well as V proved to be identical with specimens prepared from diosgenin by the performic acid method (cf. G-Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, 73, 3546 (1951)).

(14) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler, ibid., 73, 2396 (1951), reported m.p. 224-229°, [a]<sup>21</sup>D - 39.4° for a sample prepared from diosgenin.

| RESEARCH LABORATORIES | CARL DJERASSI     |
|-----------------------|-------------------|
| SYNTEX, S. A.         | HOWARD J. RINGOLD |
| LAGUNA MAYRAN 413     | G. ROSENKRANZ     |
| MEXICO CITY 17, D. F. |                   |
|                       |                   |

RECEIVED OCTOBER 1, 1951

## THE TEMPERATURE OF THE HYDROGEN-FLUORINE FLAME

Sir:

The reaction  $H_2(g) + F_2(g) \rightarrow 2HF(g)$  is highly exothermic and in addition gives rise to a reaction product possessed of exceptional thermal stability. These factors combine to produce a very high flame temperature which heretofore has not been measured.

Theoretical calculations based on the method described in Wenner<sup>1</sup> have produced the following flame temperature-composition relationships:

| Feed com  | position     | Theoretical flame<br>temperature at 1 atm |
|-----------|--------------|---|
| Mole % F2 | % H:         | total pressure, °K.                       |
| 10.0      | <b>90</b> .0 | 1920                                      |
| 33.3      | 66.7         | 3550                                      |
| 50.0      | 50.0         | 4300                                      |
| 66.7      | 33.3         | 3800                                      |

In these calculations the latest thermodynamic data were employed.2,8,4,5

The construction and operation of the hydrogenfluorine torch has already been described by Priest and Grosse.<sup>6</sup> This torch produces a diffusion-type flame due to the present inability to premix hydrogen and fluorine.

The flame temperature was measured by means of the line-reversal technique.<sup>7</sup> The tungsten ribbon-

(1) R. R. Wenner, "Thermochemical Calculations," McGraw-Hill (a) R. Men York, N. Y., 1941.
(2) G. M. Murphy and J. E. Vance, J. Chem. Phys., 7, 806 (1939).

(3) M. G. Evans, E. Warhurst, and E. Whittle, J. Chem. Soc., 1524 (1950).

(4) W. M. Latimer, MDDC-1462, United States Atomic Energy Commission, Declassified Document, November 13, 1947.

(5) A.P.I. Research Project 44, National Bureau of Standards

(6) H. F. Priest and A. V. Grosse, Ind. Eng. Chem., 39, 431 (1947).

(7) See B. Lewis and G. v. Elbe's chapter in "Temperature, Its Measurement and Control in Science and Industry," Reinhold Publ. Corp., New York, N. Y., 1940; and C. W. Jones, B. Lewis, J. B. Friauf. and C. St. J. Perrott, THIS JOURNAL, 53, 869 (1931).

filament lamp, ordinarily used as the comparison radiator for measurements of this type, could not be employed due to the fact that the flame temperature is above the melting point of tungsten  $(3640^{\circ} \text{ K.})$ ; the same is true of the ordinary carbon arc (sublimation point of carbon 3810°K. at atm. pressure). Since no simple man-made radiator seemed to be available which had the desired characteristics the optical train was modified to use the sun as the comparison source. A two-mirror heliostat was used in keeping the sun's image focused on the spectroscope slit. A neutral, variable absorbing agent of good optical quality was used in adjusting the brightness of the sun so that line-reversal could be readily obtained and easily reproduced. An optical pyrometer reading of the sun through the same filter then gave the flame temperature. The maximum flame temperature was measured at 4300°K. using stoichiometric quantities of hydrogen and fluorine. The agreement between this value and the theoretical temperature is admittedly fortuitous, the accuracy of our measurements being approximately  $\pm 150^{\circ}$ .

In this particular line-reversal application it is not possible to employ the sodium lines for reversal due to the occurrence of sodium in the solar spec-Lithium was used in the present work trum. since, for all practical purposes, it does not appear in the solar spectrum.

Complete details of our theoretical calculation and experimental work will be published elsewhere.

| -                          | -                 |
|----------------------------|-------------------|
| THE RESEARCH INSTITUTE OF  | R. H. WILSON, JR. |
| TEMPLE UNIVERSITY          | J. B. CONWAY      |
| Philadélphia, Pennsylvania | A. ENGELBRECHT    |
|                            | A. V. GROSSE      |

**RECEIVED OCTOBER 1, 1951** 

## THE SYNTHESIS OF THE BLOOD SERUM VASOCON-STRICTOR PRINCIPLE SEROTONIN CREATININE SULFATE

Sir:

The existence of a potent vasoconstrictor agent in the sera of mammals was reported as early as 1868 by Ludwig and Schmidt<sup>1</sup> and since that time has been the subject of over eighty publications.<sup>2</sup> Experiments with sera obtained under various conditions and allowed to stand for variable periods before use have produced a maze of conflicting biological data. This problem has been clarified only recently by Rapport<sup>3,4</sup> who isolated from beef serum a very active vasoconstrictor substance in crystalline form. Rapport was able to show that the crystalline material was a complex, or mixed salt, composed of equimolecular proportions of sulfuric acid, creatinine and an indole base.<sup>5</sup> On the basis of chemical tests as well as analytical and spectral data Rapport has proposed that the indole base is 5-hydroxy-3-beta-aminoethylindole (I) (5-hydroxytryp-

(2) For literature reviews see (a) T. C. Janeway, H. B. Richardson, and E. A. Park, Arch. Int. Med., 21, 565 (1918); (b) G. Reid and M. Bick, Austral. J. Exp. Biol. Med. Sci., 20, 33 (1942).

(3) M. M. Rapport, A. A. Green and I. H. Page, Science, 108, 329 (1948).

(4) M. M. Rapport, A. A. Green and I. H. Page, J. Biol. Chem., 176, 1243 (1948).

(5) M. M. Rapport, ibid. 180, 961 (1949).

<sup>(1)</sup> C. Ludwig and A. Schmidt, Arb. physiol. Anstall Leipsig, 1 (1868).