this base has been shown to be identical to the bufotenine picrate obtained from *piptadenia peregrina*.[3]

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CYCLOPENTADIENYL COMPOUNDS OF Sc, Y, La, Ce AND SOME LANTHANIDE ELEMENTS

Sir:

The cyclopentadienyl ring is unusual in the number of metals with which it forms organometallic compounds. This property arises from the fact that the ring may be attached to a metal in three ways: (a) by the two electron covalent bond, which may be referred to as the "sandwich bond," to many transitional metals,[1a,b]; (b) by a covalent bond between a metal and a single carbon atom of the ring. The silicon cyclopentadienyl compounds[2] may be of this type, (c) by ionic bonds.

The ability of electropositive elements to form ionic cyclopentadienyl compounds is of a more general nature than has been realized previously, although compounds such as cyclopentadienylsodium have long been known.[3] The elements scandium, yttrium, lanthanum and the lanthanide elements provide an ideal test case, since no organometallic compounds of these elements have been confirmed.

The anhydrous metal chlorides were stirred with cyclopentadienyl sodium in tetrahydrofuran solution. The solvent was removed and the residues heated at 200–250° in vacuum. Tricyclopentadienyl metal compounds of the formula $(C_5H_5)_3M$, where M may be Sc, Y, La, Ce, Pr, Nd, Sm and Gd, were obtained as sublimates in yields of the order of 65%. Typical analyses are: *Sc*—Found: C, 73.7; H, 6.0; Sc, 18.3; required: C, 74.0; H, 6.2; Sc, 18.5; *Ce*—Found: C, 51.6; H, 4.1; Ce, 42.8; required: C, 53.7; H, 4.5; Ce, 41.8; *Nd*—C, 51.8; H, 4.6; Nd, 41.2; required: C, 53.1; H, 4.5; Nd, 42.5. *Sm*—Found: C, 51.3; H, 4.2; Sm, 43.3; required, C, 52.2; H, 4.3; Sm, 43.5.

The compounds are all crystalline solids, thermally stable to at least 400°, which sublime above 220° at 10^{-4} mm.: *Sc*, straw color, m.p. 240°; *Y*, pale yellow m.p. 295°; *La*, colorless, m.p. 395°; *Ce*, orange, m.p. 435°; *Pr*, pale green, m.p. 420°; *Nd*, pale blue, m.p. 380°; *Sm*, orange, m.p. 365°; *Gd*, pale yellow, m.p. 350°. The compounds decompose with water giving cyclopentadiene and the hydroxide. They are insoluble in hydrocarbon solvents but dissolve readily in tetrahydrofuran and glycol dimethyl ether. They react only slowly with air. Tricyclopentadienylcerium is an exception, in that it is blackened instantaneously by even traces of oxygen; it is also unusual in giving a blue green vapor. The ionic nature of the compounds is indicated by their instantaneous and quantitative reaction with ferrous chloride in tetrahydrofuran solution to give ferrocene. The absorption spectra in tetrahydrofuran show complex and very sharp bands reminiscent of those of the lanthanide ions in aqueous solutions; this resemblance is shown also in their magnetic properties.

The remaining lanthanide elements will probably form similar compounds. In the "actinide" series where similar behavior is to be expected we have prepared a brown dicyclopentadienyl chloro compound of uranium.

In the transitional series we have shown that dicyclopentadienyl manganese[4] is ionic. It has a magnetic moment corresponding to five unpaired electrons when magnetically dilute, and forms conducting solutions in liquid ammonia. The formation of the ionic dicyclopentadienylmanganese, rather than a covalent bis-cyclopentadienylmanganese, must be attributed not to a high electropositive nature of the metal, but to the exceptional stability of the manganous ion, which has the 3d shell half filled. It may be noted, however, that since the negative charge will be distributed over the anion, the most likely packing in the crystal will have the cation between the planes of the rings in a "sandwich" configuration similar to that of ferrocene.[1a]

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(1) (a) J. D. Dunitz and L. E. Orgel, *Nature*, **171**, 121 (1953); (b) W. Moffitt, THIS JOURNAL, **76**, 3386 (1954).

(2) K. C. Frisch, *ibid.*, **75**, 6050 (1953).

(3) J. Thiele, *Ber.*, **34**, 68 (1901).

(4) G. Wilkinson and F. A. Cotton, *Chemistry and Industry (London)*, **11**, 307 (1954).

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STEROIDS. LXIII.[1] SYNTHESIS OF Δ^4-19-NOR-PREGNENE-11β,17α,21-TRIOL-3,20 DIONE (19-NORHYDROCORTISONE) AND RELATED 19-NOR-ADRENAL HORMONES

Sir:

The observation that removal of the C-19 angular methyl group in the case of progesterone,[2a] desoxycorticosterone[2b] and 17α-ethynyltestosterone[2c] resulted in a marked increase in hormonal activity has encouraged us to undertake the more complicated task of preparing similar derivatives of 11-oxygenated hormones. We should now like to announce the successful synthesis by a combined chemical-biochemical procedure of the 19-nor analog (III) of the most important adrenal hormone Δ^4-pregnene-11β,17α,21-triol-3,20-dione (hydrocortisone or Compound F) and of some related substances.

Alkaline hydrogen peroxide oxidation of 3-hydroxy-17-acetyl-1,3,5,16-estratetraene[3] gave the corresponding 16α,17α-epoxide [m.p. 234–236°, $[\alpha]^{20}\text{D}$ +124° (all rotations in $CHCl_3$); found: C, 76.72; H, 7.88] which upon conversion to the 3-methyl ether (m.p. 141–144°) followed by hydrogen bromide opening, catalytic debromination to 3-methoxy-17α-hydroxy-17-acetyl-1,3,5-estratriene

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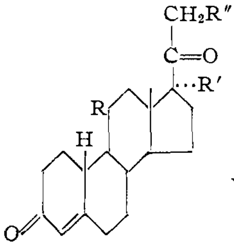
(1) Paper LXII, F. Sondheimer, M. Velasco and G. Rosenkranz, THIS JOURNAL, in press.

(2) (a) C. Djerassi, L. Miramontes and G. Rosenkranz, *ibid.*, **75**, 440 (1953); (b) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953); (c) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

(3) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, *ibid.*, **73**, 1523 (1951).



I, R = R'' = H, R' = OH
II, R = H, R' = R'' = OH
III, R = OH(β), R' = R'' = OH
IV, R = O, R' = R'' = OH
V, R = R' = R'' = H
VI, R = R' = H, R'' = OH
VII, R = OH(β), R' = H, R'' = OH

(m.p. 150–152°, $[\alpha]^{20}D$ +45°; found: C, 77.02; H, 8.30) and then ketalization with ethylene glycol furnished the corresponding 20-cycloethylene ketal (m.p. 124–126°, $[\alpha]^{20}D$ +43°, no C=O band in infrared; found: C, 74.20; H, 8.61). Birch reduction and subsequent acid hydrolysis yielded 19-nor-17α-hydroxyprogesterone (I) (m.p. 204–206°, $[\alpha]^{20}D$ +41°, $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4.23; found: C, 75.58; H, 8.98). Microbiological oxidation[4] at C-21 led to Δ^4-19-norpregnene-17α,21-diol-3,20-dione (II) with m.p. 178–180°, which showed the red color with concd. sulfuric acid and with triphenyltetrazolium chloride typical of the parent hormone (Reichstein's Substance S). It was characterized as the 21-monoacetate, m.p. 241–243°, $[\alpha]^{20}D$ +90°, $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4.22; found: C, 70.63; H, 8.35. Incubation of either I or II with adrenal homogenates[5] gave crystalline Δ^4-19-norpregnene-11β,17α,21-triol-3,20-dione (III) (19-norhydrocortisone), m.p. 255–257°, $[\alpha]^{20}D$ +112° (MeOH), $\lambda_{max.}^{EtOH}$ 241 mμ, log ε 4.23, $\lambda_{max.}^{H_2SO_4}$ 240, 282, 385 and 470 mμ,[6] $\nu_{max.}^{nujol}$ 3500, 3380 and 3230 cm.$^{-1}$ (multiple OH absorption), 1707 cm.$^{-1}$ (20-ketone) and 1670 cm.$^{-1}$ (Δ^4-3-ketone);[7] red color with triphenyltetrazolium chloride; found: C, 68.84; H, 8.22; movement ratio[8] ($CHCl_3$–$HCONH_2$) 0.40. Chromium trioxide oxidation of 19-norhydrocortisone (III) on a micro scale led to 19-norcortisone (IV), m.p. 230–232°, $\lambda_{max.}^{EtOH}$ 238 mμ, log ε 4.21, $\lambda_{max.}^{H_2SO_4}$ 280, 340, 415 and 490 mμ,[6] red color with triphenyltetrazolium chloride, movement ratio[8] ($CHCl_3$–$HCONH_2$) 0.73. The formation by 19-norhydrocortisone of a diacetate[8] and oxidation to a ketone proves that the new hydroxyl group cannot be tertiary, while the ultraviolet absorption spectrum of 19-norcortisone eliminates position 6.

Unequivocal proof for the C-11 location of the hydroxy group in III was provided by sodium bismuthate oxidation to Δ^4-19-norandrostene-3,17-dione-11β-ol (m.p. 193–197°, $\nu_{max.}^{CHCl_3}$ 1739 and 1670 cm.$^{-1}$; found: C, 75.22; H, 8.12); dehydration (*p*-toluenesulfonic acid-benzene) gave an oil which on the basis of its spectral behavior ($\nu_{max.}^{CHCl_3}$ 1740 and 1665 cm.$^{-1}$, $\lambda_{max.}^{EtOH}$ 302 mμ, log ε 4.0) must have been predominantly $\Delta^{4,9(10)}$-19-norandrostadiene-3,17-dione.[9] The formation of this substance is explainable only from an 11-hydroxy-19-nor-steroid. The 11β-configuration is based rather securely on molecular rotation differences[10] and on the argument that in contrast to microbiological oxidation (11α-hydroxylation predominating), adrenal incubation in all recorded cases results in 11β-hydroxylation. Similar incubation of 19-norprogesterone (V)[2a] or 19-nordesoxycorticosterone (VI)[2b] has yielded 19-norcorticosterone (VII), m.p. 195–197°, $[\alpha]^{20}D$ +155° (EtOH), $\lambda_{max.}^{EtOH}$ 241 mμ, log ε 4.21, $\lambda_{max.}^{H_2SO_4}$ 285, 390 and 475 mμ;[6] found: C, 72.06; H, 8.45; movement ratio[8] (C_6H_6–$HCONH_2$) 0.35.

The above-described experiments thus complete the synthesis of the remaining 19-nor analogs of the important steroid hormones. The results of various biological experiments will be published by other investigators.

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RECEIVED NOVEMBER 8, 1954

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[4] *Cf.* A. Wettstein, C. Meystre and E. Vischer, *Helv. Chim. Acta*, **37**, 1548 (1954).

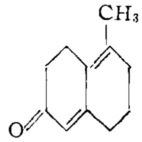
[5] A. Zaffaroni, U. S. Patent 2,671,752.

[6] *Cf.* A. Zaffaroni, *Recent Progress in Hormone Research*, **8**, 51 (1953).

[7] By courtesy of Dr. R. N. Jones, National Research Council, Ottawa.

[8] This is expressed as the ratio of the movement of the 19-nor-steroid compared with the parent hormone on paper in the indicated solvent system. In agreement with theory, it was found that the nor-steroids are less mobile in paper chromatograms and that this becomes particularly pronounced with 11β-hydroxy nor-steroids (*cf.* movement ratios of 0.80 and 0.72 for 19-nor-desoxycorticosterone and 19-nor-"S," respectively) since the latter function now is not subject to hindrance by the angular methyl group. Thus in contrast to hydrocortisone, 19-norhydrocortisone forms a *diacetate* with acetic anhydride–pyridine (2 hr., 25°) as was established on a micro scale by the characteristic mobility ratios on paper (*cf.* A. Zaffaroni and R. B. Burton, *J. Biol. Chem.*, **193**, 749 (1951)).

[9] S. Julia, *Bull. Soc. Chim. France*, 780 (1954), reports $\lambda_{max.}^{EtOH}$ 320 mμ, log ε 4.15 for



[10] The $[M]_D$ shift in passing from III to hydrocortisone is +196 and from III to 11-epihydrocortisone is +34. Since the $[M]_D$ contribution of the C-19 methyl group in steroidal hormones lies in the range +150 to +200 (A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953); A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, in press), the 11β-hydroxy configuration for III is clearly indicated.