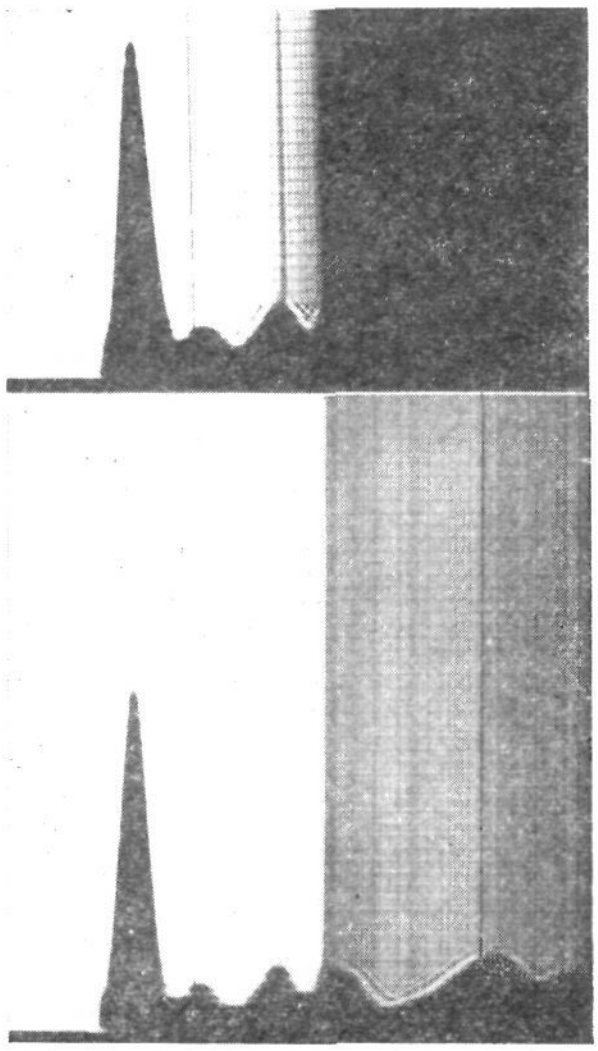

Fig. 1.

is relatively low. For this reason, special infrared sources have been employed,[1] and special adapters have been designed,[2] to permit the interchangeable use of overvoltage tungsten filaments illuminating a slit in the correct focal plane for the schlieren optical system. In an extended study of the sera of a leukemia patient,[3] the critical demand for the analysis of a serum sample which was irreplaceable, but had been hemolyzed when drawn led us to the accidental discovery of a very simple technique for photography, in the absence of a specially designed source of red light. We found that with a Wratten No. 105 (hemoglobin analysis) filter to reduce contrast, Eastman Spectroscopic Type 103F plates are sufficiently sensitive to the mercury red lines to permit satisfactory schlieren scanning photographs[4] in the normal exposure range. Moreover, the lens system used[5] is sufficiently achromatic that satisfactory longitudinal focusing is obtained without shifting the source slit. In the accompanying figure, the upper schlieren scanning photograph of a badly hemolyzed sample was made, after 7200 seconds electrophoresis at 6.29 volts/cm. in 0.1 molar sodium diethylbarbiturate buffer at *p*H 8.60, by use of a Wratten No. 77A (monochromat green) filter and a Kodaline CTC photographic plate. At the position conjugate to the incidence of hemoglobin in the cell, the pattern of the rising boundaries vanishes. The lower schlieren scanning diagram of the same boundaries was obtained with the 105 filter and 103F plate and permits the observation of the globulin and δ-boundaries in the cell. However, since hemoglobin refracts as well as absorbs light its quantitative effect upon the globulin components with which it is associated must not be overlooked in analyzing the pattern. The same light source, filter and photographic plate combination has been used to obtain continuous scanning records[6] of the chromatographic resolution of artificial mixtures of proteins containing hemoglobin as a component,[7,8] and also to obtain cylindrical lens schlieren diagrams in the ultracentrifuge[9] with purified human carbon monoxide hemoglobin solutions up to 2% concentration.

(1) H. P. Treffers and D. H. Moore, *Science*, **93**, 240 (1941).

(2) L. G. Longsworth, *Ind. Eng. Chem., Anal. Ed.*, **18**, 219 (1946).

(3) F. J. Gutter, J. Krevans, G. A. Moulton and G. Kegeles, *J. Nat. Cancer Inst.*, in press.

(4) L. G. Longsworth, THIS JOURNAL, **61**, 529 (1939).

(5) Klett Mfg. Co., New York, N. Y.

(6) G. Kegeles and H. A. Sober, Abstracts of 119th National Meeting, American Chemical Society, April, 1951.

(7) H. A. Sober, G. Kegeles and F. J. Gutter, Abstracts of 117th National Meeting, American Chemical Society, April, 1950.

(8) H. A. Sober and G. Kegeles, *Fed. Proc.*, **10**, 299 (1951).

(9) G. Kegeles and F. J. Gutter, THIS JOURNAL, in press.

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RECEIVED MAY 9, 1951

STEROIDS. XXII. THE SYNTHESIS OF 19-NOR-PROGESTERONE

Sir:

In 1944, Ehrenstein[1] reported the twelve-step degradation of strophanthidine in 0.07% yield to a resin, $[\alpha]_D$ +89°, believed to be 19-norprogesterone (IIIb). The material represented a mixture of stereoisomers, most likely possessing the "unnatural" configuration[2] at C-14(β) and C-17(α) and was reported[3] to exhibit the same biological activity as progesterone. Subsequent work[4] has shown that the "unnatural" configuration at C-14 and C-17 *per se* does not confer progestational activity and it remained, therefore, to be seen whether the lack of an angular methyl group at C-10 in IIIb was responsible for this pronounced biological effect, so surprising in view of the extreme specificity of this type of hormonal activity.[2a]

A modified[5] Birch reduction[6] on 3-methoxy-17-acetyl-1,3,5-estratriene (I)[7] produced $\Delta^{2,5(10)}$-19-nor-3-methoxy-20-hydroxypregnadiene (II), (m.p. 135–138°, $[\alpha]^{20}_D$ +88° (all rotations in chloroform), no selective absorption in the ultraviolet, free hydroxyl band in infrared. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19; methoxy, 9.80. Found: C, 79.33; H, 10.47; methoxyl, 9.15), which without isolation upon boiling with alcoholic hydrochloric acid yielded Δ^4-19-norpregnen-20-ol-3-one (IIIa),

(1) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944).

(2) (a) M. Ehrenstein, *Chem. Rev.*, **42**, 457 (1948); (b) *J. Org. Chem.* **16**, 355 (1951).

(3) W. M. Allen and M. Ehrenstein, *Science*, **100**, 251 (1944).

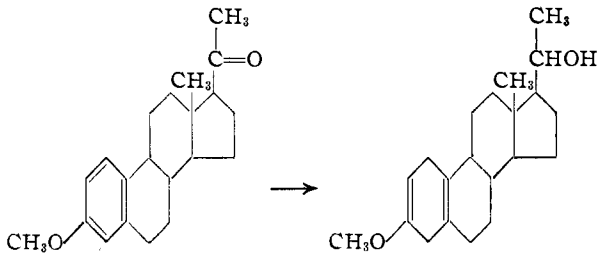
(4) Pl. A. Plattner, H. Heusser and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(5) A. L. Wilds and N. Nelson, to be published. We are greatly indebted to Prof. A. L. Wilds, University of Wisconsin, for advance information on this modified procedure.

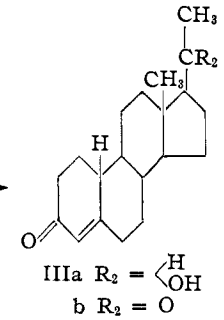
(6) A. J. Birch, *Quart. Rev.*, **4**, 69 (1950); *J. Chem. Soc.*, 2531 (1949).

(7) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, THIS JOURNAL, **73**, 1523 (1951).

probably representing a mixture of 20-epimers; m.p. 174–177°, $[\alpha]^{20}D$ +42°, λ_{max}^{alc} 240 mμ (4.35), infrared bands (CS_2) at 3617 cm.$^{-1}$ (hydroxyl) and 1678 cm.$^{-1}$ (Δ^4-3-ketone). Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.45; H, 10.24. Chromium trioxide oxidation of IIIa in acetic acid solution afforded in 55% over-all yield (based on I) pure 19-norprogesterone (IIIb), m.p. 144–145°, $[\alpha]^{20}D$ +147°, λ_{max}^{alc} 240 mμ (4.36), infrared bands (CS_2) at 1706 cm.$^{-1}$ (20-ketone) and 1674 cm.$^{-1}$ (Δ^4-3-ketone). Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.07; H, 9.28. The reddish-orange 3,20-bis-2,4-dinitrophenylhydrazone possessed m.p. 278–279°, $\lambda_{max}^{CHCl_3}$ 380 mμ (4.78).[8] Calcd. for $C_{32}H_{36}O_8N_8$: C, 58.17; H, 5.49; N, 16.95. Found: C, 58.28; H, 5.37; N, 16.57.



I II



IIIa $R_2 = \langle^{H}_{OH}$
b $R_2 = O$

19-Norprogesterone (IIIb) exhibits approximately the same activity as natural progesterone in rabbits. Since the mode of synthesis automatically establishes the "natural" configuration for all asymmetric centers with the possible exception of C-10,[9] the replacement of the angular methyl group at C-10 by hydrogen in progesterone does not reduce biological activity.[10] This observation is of considerable importance since if it should also apply to the cortical hormones, notably cortisone, it would considerably simplify the total synthesis of anti-arthritic substances. In fact, the present preparation of 19-norprogesterone (IIIb) constitutes the first total synthesis of a potent progestational hormone, since the starting methyl ether I[7] has been obtained[11] from estrone which has already been synthesized totally.[12]

Further work on 19-norsteroids, particularly of the cortical hormone series, is in progress.

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RECEIVED MAY 21, 1951

(8) Progesterone bis-dinitrophenylhydrazone shows $\lambda_{max}^{CHCl_3}$ 383 mμ (4.72) (C. Djerassi, *Anal. Chem.*, **20**, 880 (1948)).

(9) The hydrogen atom at C-10 most likely assumed the more stable "natural" β-configuration during the acid hydrolysis of II.

(10) The reason for the high biological activity of Ehrenstein's (ref. 1) mixture of 19-norprogesterones is still obscure since the presently described isomer IIIb could have been at best only a minor constituent of that mixture.

(11) L. Velluz and G. Muller, *Bull. Soc. Chim. France*, 166 (1950).

(12) G. Anner and K. Miescher, *Helv. Chim. Acta*, **31**, 2173 (1948); W. S. Johnson, D. K. Banerjee, W. P. Schneider and C. D. Gutsche, THIS JOURNAL, **72**, 1426 (1950).

CRYSTALLINE ALLETHRIN ISOMER

Sir:

The insecticide known as allethrin, now being produced commercially, is obtained by acylation of *dl*-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one[1] (*dl*-allethrolone) with a mixture of *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acid chlorides.

Allethrin may be considered a mixture of four racemic forms (or eight individual optical and geometric isomers). Two racemic forms are esters of the *cis* acid and two of the *trans* acid.

When a sample of molecularly distilled allethrin was cooled to a low temperature, it crystallized in part, as likewise did samples of commercial allethrin kept at about 4°. Cold filtration and recrystallization from isooctane or pentane gave colorless crystals, m.p. 50.5–51°.

Anal.[2] Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.41; H, 8.67.

Upon saponification of the crystalline product, *dl-trans*-chrysanthemum monocarboxylic acid was obtained, which, after recrystallization from pentane or nitromethane, melted at 55–56° and gave no depression in a mixture melting-point determination with the authentic acid.[3]

dl-Allethrolone when acylated with *dl-cis*-chrysanthemum monocarboxylic acid chloride furnished an ester mixture, b.p. 146–149° (0.4 mm.), $n^{25}D$ 1.5070,[4] which, on being cooled and seeded with the above-mentioned crystalline compound, could not be induced to crystallize. Acylation of *dl*-allethrolone with *dl-trans*-chrysanthemum monocarboxylic acid chloride furnished an ester mixture, b.p. 147–150° (0.4 mm.), $n^{25}D$ 1.5047,[4] which crystallized in part on being cooled and seeded. When 8.4 g. of this ester mixture was dissolved in 12.6 ml. of isooctane, cooled, and filtered on a cold-jacketed filter kept at about −30°, about half was obtained as the crystalline form. Removal of solvent from the filtrate *in vacuo* left 4.4 g. of oil, $n^{25}D$ 1.5050. The crystalline portion, when recrystallized from isooctane, melted at 50.5–51° and did not depress the melting point of the crystalline compound obtained from allethrin. The crystalline isomer will be called the α-*dl-trans* isomer, and the other isomer found concentrated in the filtrate, the β-*dl-trans* isomer of allethrin. Based on the yield, the concentrate of β-*dl-trans* isomer contained about 5% of dissolved α-*dl-trans* isomer.

The crystalline α-*dl-trans* isomer must consist of one of the racemic ester pairs, *d-trans* acid with *d*-allethrolone plus *l-trans* acid with *l*-allethrolone,

(1) M. S. Schechter, N. Green, and F. B. LaForge, THIS JOURNAL, **71**, 1517 (1949); **71**, 3165 (1949); *Agr. Chemicals*, **4** (6), 57 (1949).

(2) J. S. Ard, Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture.

(3) I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 283 (1945).

(4) Compare, L. Crombie, A. J. B. Edgar, S. H. Harper, M. W. Lowe, and D. Thompson, *J. Chem. Soc.*, 3553 (1950).