ADRENAL HORMONES AND RELATED COMPOUNDS. IV. 6-METHYL STEROIDS[1]

Sir:

The chemical modification of hydrocortisone by the introduction of the 9α-fluoro,[2] 12α-fluoro[3] or 2-methyl[1,4] groups has resulted in analogs which are more active as mineralocorticoid, glucocorticoid and anti-phlogistic substances than the parent steroid.

Consequently, the demonstration of the absence of mineralocorticoid activity in the presence of high glucocorticoid activity for 6-methylhydrocortisone, the synthesis of which is presently described, was unpredictable and is of considerable interest. Extension of the study to the 1-dehydro series[5,6] has resulted in the most pronounced selective enhancement of cortical activities reported to date.[7]

11α-Acetoxyprogesterone[8] was converted to the 3,20-bis ethylene ketal (I), m.p. 186–190°, $[\alpha]_{\mathrm{D}}$ −40° (chl.). *Anal.* Found: C, 70.41; H, 8.40, with ethylene glycol, the expected shift of the double bond[9] to the 5,6-position taking place. Epoxidation of I with peracetic or perbenzoic acid gave a mixture of the 5,6-oxides; α-oxide (II), m.p. 254–256°, $[\alpha]_{\mathrm{D}}$ −59° (chl.). *Anal.* Found: C, 67.82; H, 8.47, β-oxide (IIa), m.p. 215–218°, $[\alpha]_{\mathrm{D}}$ −19° (chl.). Found: C, 68.40; H, 8.66. Treatment of the α-oxide with methylmagnesium bromide in ether–tetrahydrofuran, followed by removal of the ketal groups with dilute sulfuric acid in acetone, gave 5α,11α-dihydroxy-6β-methylpregnane-3,20-dione (III), m.p. 234–235°, $[\alpha]_{\mathrm{D}}$ +48° (chl.). *Anal.* Found: C, 73.09; H, 9.51. Chromic acid or sodium dichromate in acetic acid oxidized III to 5α-hydroxy-6β-methylpregnane-3,11,20-trione (IV), m.p. 244–248°; $[\alpha]_{\mathrm{D}}$ +82° (chl.). *Anal.* Found: C, 73.27; H, 8.78, which on dehydration with 0.005 *N* sodium hydroxide in aqueous methanol at room temperature for 17 hours or with hydrochloric acid in alcohol free chloroform yielded 6α-methyl-11-ketoprogesterone (V), m.p. 160–165°, $[\alpha]_{\mathrm{D}}$ +241° (chl). *Anal.* Found: C, 77.02; H, 8.65. When the oxidation and alkali dehydration reactions were done in the reverse order III gave 6β-methyl-11-ketoprogesterone (Va), m.p. 172–175°; $[\alpha]_{\mathrm{D}}$ +203° (chl.); Found: C, 77.15; H, 8.83. Va was converted to V on treatment with dilute sodium hydroxide. Without isolation of intermediates reaction of either V or Va with two moles of ethyl oxalate and sodium methoxide in *t*-butyl alcohol followed by neutralization with acetic acid and bromination with three moles of bromine in the presence of sodium acetate, and finally rearrangement with sodium methoxide and debromination with zinc dust gave methyl 3,11-diketo-6α-methyl-4,17(20)-pregnadien-21-oate (VI), m.p. 227–229°, $[\alpha]_{\mathrm{D}}$ +131° (chl.), $\lambda_{\max.}^{95\%\text{ alc.}}$ 234 mμ, a_M = 23,100. *Anal.* Found: C, 74.65; H, 8.12. Treatment of VI with pyrrolidine and *p*-toluenesulfonic acid according to procedures described by Heyl and Herr,[10] resulted in the formation of the corresponding 3-enamine (VII), m.p. 136–148° (dec.), $\lambda_{\max.}^{5\%\text{ HCl-MeOH}}$ 272 mμ, a_M = 21,450; 224 mμ, a_M = 16,650; 360 mμ, a_M = 1,200. *Anal.* Found: C, 76.42; H, 9.02; N, 3.37. Compound VII was reduced with lithium aluminum hydride in ether and the crude product was treated with alkali in methanol–water to remove the enamine blocking group and give 6α-methyl-11β,21-dihydroxy-4,17(20)-pregnadien-3-one (VIII), m.p. 178–179.5°; $[\alpha]_{\mathrm{D}}$+127° (chl.), $\lambda_{\max.}^{95\%\text{ alc.}}$ 242 mμ, a_M = 15,000. *Anal.* Found: C, 76.98; H, 9.69, which on acetylation yielded the 21-acetate (IX), m.p. 136–139°, $[\alpha]_{\mathrm{D}}$ +128° (chl.), $\lambda_{\max.}^{95\%\text{ alc.}}$ 243 mμ, a_M = 15,025. *Anal.* Found: C, 74.69; H, 8.94. Oxidative hydroxylation of IX in *t*-butyl alcohol–pyridine with phenyl iodosoacetate in the presence of catalytic amounts of osmium tetroxide gave 6α-methyl-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (6α-methylhydrocortisone acetate) (X), m.p. 213–214°; $[\alpha]_{\mathrm{D}}$ +115° (acetone), $\lambda_{\max.}^{95\%\text{ alc.}}$ 243 mμ, a_M = 14,525. *Anal.* Found: C, 68.60; H, 8.41. Saponification of X gave 6α-methylhydrocortisone (Xa), m.p. 203–208°, $[\alpha]_{\mathrm{D}}$ + 114° (acetone), $\lambda_{\max.}^{95\%\text{ alc.}}$ 243 mμ, a_M = 15,600. *Anal.* Found: C, 70.32; H, 8.50. Dehydrogenation of VIII microbiologically with *Septomyxa affinis* (Sherb.) Wr. A.T.C.C. 6737 gave 6α-methyl-11β,21-dihydroxy-1,4,17(20)-pregnatrien-3-one (XI) as an oil, which on acetylation yielded 6α-methyl-11β-hydroxy-21-acetoxy-1,4,17(20)-pregnatriene-3-one (XII), m.p. 132–134°; $[\alpha]_{\mathrm{D}}$ +109° (chl.), $\lambda_{\max.}^{95\%\text{ alc.}}$ 243 mμ, a_M = 15,000. *Anal.* Found: C, 75.17; H, 8.05. Oxidative hydroxylation of XII gave 6α-methyl-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione (Δ^1-6α-methylhydrocortisone acetate) (XIII), m.p. 205–208°; $[\alpha]_{\mathrm{D}}$ +101° (dioxane); $\lambda_{\max.}^{95\%\text{ alc.}}$ 243 mμ, a_M = 14,825. *Anal.* Found: C, 69.11; H, 7.67, which on saponification gave Δ^1-6α-methylhydrocortisone (XIIIa), m.p. 228–237°; $[\delta]_{\mathrm{D}}$ +83° (dioxane), $\lambda_{\max.}^{95\%\text{ alc.}}$ 243 mμ, a_M = 14,875. *Anal.* Found: C, 70.53; H, 7.94. Oxidation of Xa and XIIIa with N-bromoacetamide and pyridine gave the corresponding cortisone analogs, 6α-methyl-17α,21-dihydroxy-4-pregnene-3,11,20-trione, m.p. 212.5–215°, and 6α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione, m.p. 230–232°. Preparation of Xa and XIIIa from 5α,6α-oxido-11β,17α,21-trihydroxypregnane-3,20-dione 3,20-bis-(ethylene ketal)[11] by a similar series of reactions furnished structural confirmation.

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(1) Previous paper in this series: J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955).

(2) J. Fried and E. F. Sabo, *ibid.*, **76**, 1455 (1954).

(3) J. Fried, J. E. Herz and A. Borman, presented before the Division of Medicinal Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 8 to 13, 1956.

(4) 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).

(5) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(6) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, THIS JOURNAL, **77**, 4438 (1955).

(7) S. C. Lyster, L. E. Barnes, G. H. Lund, M. Menzinger and W. W. Byrnes, *Proc. Soc. Exp. Biol. Med.*, in press.

(8) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, THIS JOURNAL, **74**, 5933 (1952).

(9) E. Fernholz and H. E. Stavely, Abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, New Jersey, September 8–12, 1941, p. M39; E. Fernholz, U. S. Patents 2,356,154 (August 22, 1944) and 2,378,918 (June 26, 1945).

(10) F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(11) R. Littell and S. Bernstein, *ibid.*, **78**, 984 (1956).

The configuration of the methyl group in the 6-methyl-Δ^4-3-keto compounds has been assigned from consideration of molecular rotations and by assumption from the accepted greater stability of the equatorial (6α-methyl) substituent over the axial (6β-methyl) substituent.

These compounds were evaluated in the Department of Endocrinology of the Upjohn Research Division. By subcutaneous administration in the rat Xa was found to be four times as active as hydrocortisone in the glycogen deposition (glucocorticoid) assay, while, by the oral route, XIIIa was sixteen times as active as hydrocortisone. Neither of the compounds showed salt retaining (mineralocorticoid) activity. Similar activities were observed for the corresponding analogs of cortisone.

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RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

G. B. SPERO
J. L. THOMPSON
B. J. MAGERLEIN
A. R. HANZE
H. C. MURRAY
O. K. SEBEK
J. A. HOGG

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BOOK REVIEWS

Gmelins Handbuch der Anorganischen Chemie. BY E. H. ERICH PIETSCH, Editor. Verlag Chemie, G. m. b. H., Weinheim/Bergstr., Western Germany. (American Representative, The Gmelin Institute of Inorganic Chemistry, Dimitri R. Stein, 1074 Washington Avenue, Pelham Manor, N. Y.).
Calcium: System-Nummer 28. Part B, Section 1, 1956. viii + 264 pp. 17.5 × 25.5 cm. Price, $34.99.
Kupfer: System-Nummer 60. Part A, Section 1, 1955. xvi + 710 pp. 17.5 × 25.5 cm. Price, $92.13.
Kupfer: System-Nummer 60. Part A, Section 2, 1955. xxxii + pp. 711–1465. 17.5 × 25.5 cm. Price, $101.98.

Gmelins Handbook of Inorganic Chemistry continues to live up to its well-deserved reputation as the "Bible" of the inorganic chemist with the publication of its three most recent additions to the series. It will be recalled that the current eighth edition is scheduled for completion in 1960. Supplements will be issued for volumes published prior to 1949. If any fault is to be found regarding the Handbook, it can only be that the literature coverage is not entirely up to date. The present volumes are based on a complete survey through 1949, although selected topics in the copper volumes include references through 1954. In recent years the Gmelin volumes have made a much greater use of charts, graphs, diagrams and sketches. It is gratifying to note that this policy has been continued. The volume on calcium contains 28 figures, while a total of 425 are included in the two volumes on copper.

The calcium volume is the second to appear on the element. Part one (1950) covered the historical aspects, while the present volume is concerned with the technology of calcium and its compounds. The first 20 pages review ore dressing methods for calcium fluoride, sulfate, carbonate, and phosphate. The remainder of the volume summarizes the preparation of metallic calcium and some 50 calcium compounds. Many aspects of technological importance are considered, including preparative methods, uses, analyses, transportation, storage, dangers and recommended safety precautions.

The two volumes on copper comprise the first of three parts scheduled for the element and its compounds; Part B will review copper compounds, while Part C will deal with copper alloys. Section 1 of Part A includes an historical survey (34 pp.), occurrence (143 pp.), ore dressing (21 pp.), metal preparation (484 pp.), powder metallurgy (8 pp.) and technical preparation of copper oxides, oxychlorides and sulfate (20 pp.). The extensive chapter on metal production methods is divided as follows: pyrometallurgy, wet processes, electrolytic methods, production from complex ores, from metallurgical product residues, and copper recovery processes. World production and consumption statistics are quoted for the period 1938–53.

Section 2 of Part A is devoted entirely to the preparation and properties of elemental copper. The order of presentation follows the standard Gmelin system. Preparation and purification of copper, including special forms of the element, are reviewed first (18 pp.). Next is an extensive chapter (411 pp.) on physical properties: the nucleus, the atom and the molecule, crystallographic, mechanical, thermal, optical, magnetic and electrical properties. One confusing point here is the placement of the material on crystallographic properties, working and recrystallization of copper. This appears in its proper location in the table of contents, but the text has been bound at the end of the volume. Electrochemical and chemical properties are covered in 231 pages, followed by a brief summary of physiological effects of the element. The final 93 pages are devoted to methods of detection and determination of copper.

CHEMISTRY DIVISION
ARGONNE NATIONAL LABORATORY
P. O. BOX 299
LEMONT, ILLINOIS

HENRY HOEKSTRA

Gmelins Handbuch der Anorganischen Chemie. System-Number 44. Thorium und Isotope. By E. H. ERICH PIETSCH, Editor. Verlag Chemie, G. m. b. H., Weinheim/Bergstrasse, Western Germany. (American Representative, the Gmelin Institute of Inorganic Chemistry, Dimitri R. Stein, 1074 Washington Avenue, Pelham Manor, N. Y.). 1955. xv + 406 pp. 18 × 25 cm. Price, $55.22.

In the almost 30 years since the 7th edition of this reference work on the scientific literature of thorium appeared, considerable change has occurred in the scientific and technological importance of the element. The appearance of the new 8th edition of Gmelin System No. 44 has therefore been awaited with anticipation. The present volume of 406 text pages contains some 82 pages which discuss the history and occurrence of the element, general preparation of compounds and processing of ores, large-scale preparative procedures, and industrial uses. A summary of preparation, physical properties (including nuclear behavior) and mechanical properties of elemental thorium occupy about 95 pages, electrochemical and chemical properties of the metal another 15 pages, and general discussion of thorium chemistry, about a dozen pages. The detailed discussion of the literature of specific compounds, which is characteristic of the Gmelin volumes, commences on page 200, and includes some 50 pages on the naturally occurring radioactive isotopes of thorium, their nuclear properties and nuclear reactions in which they have been used.

The usefulness of an annotated bibliography, which is the essential nature of the Gmelin volumes, is closely linked