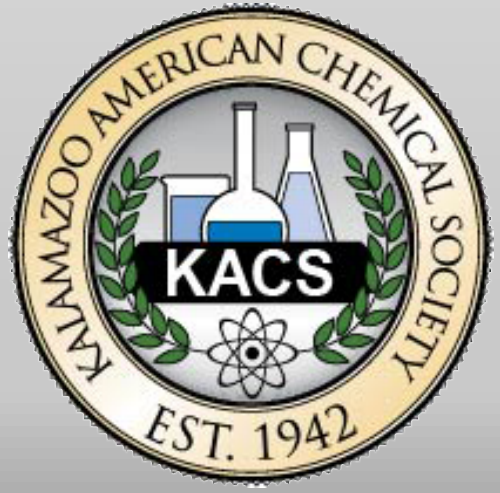
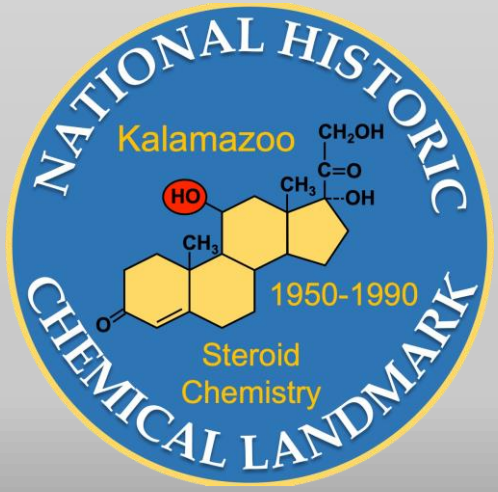
National Historic Chemical Landmark Dedication Event, May 16-17, 2019

Kalamazoo Steroid Chemistry





Thank You Sponsors

Figure 2 George C. Cartland and Marvin H. Kuizenga.

INTERIM CORTISONE PLANT
BUILDING 44

JAN 14, 1952


UPJOHN

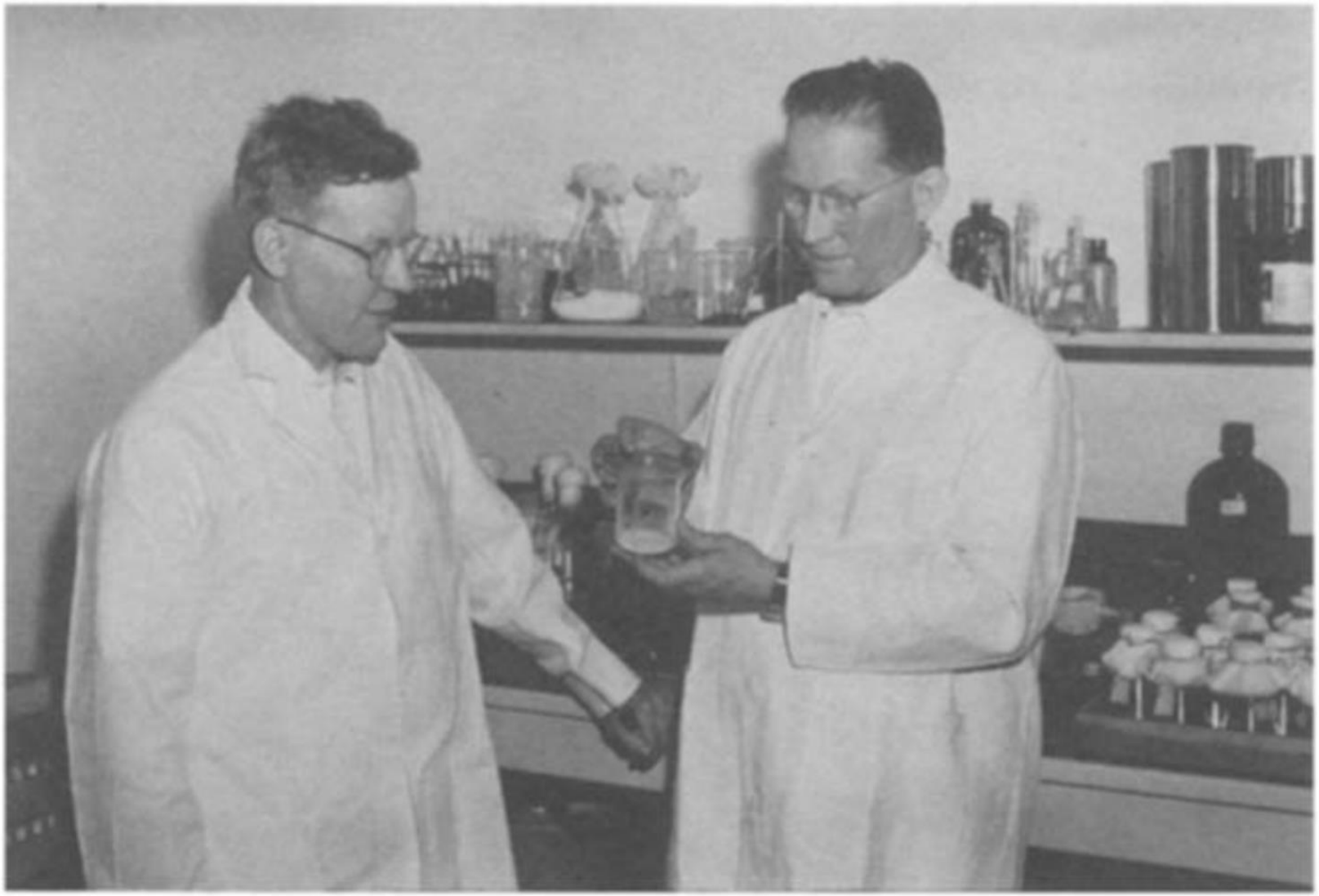


Figure 9 Herbert C. Murray and Durey H. Peterson.

Patented Feb. 23, 1954

2,670,358

UNITED STATES PATENT OFFICE

2,670,358

14 ALPHA-HYDROXYPROGESTERONE

Herbert C. Murray, Hickory Corners, and Durey H. Peterson, Kalamazoo, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

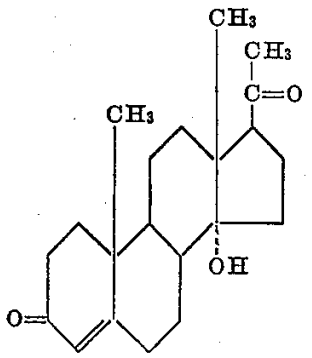
No Drawing. Application August 28, 1952, Serial No. 306,924

1 Claim. (Cl. 260—397.45)

1

This invention relates to steroids and more particularly to 14α-hydroxyprogesterone.

The novel compound of the present invention, 14α-hydroxyprogesterone represented by the formula:



2

sesses lyophobic and an increased proportion of lyophilic groups causing the compound to be a valuable interfacial tension modifying agent useful as an emulsifying agent, emulsion breaker, suspending agent, and emulsion stabilizing agent. The compound may be used to prepare absorption bases having improved water absorption and emollient characteristics of utility in pharmacy and cosmetology alone, or as a carrier for known medicaments. A suitable absorption base preparation may be made by melting together a mixture of 85 percent white petroleum, stearyl alcohol, and five percent oxygenated steroid, 14α-hydroxyprogesterone, and cooling the mixture while stirring until it congeals. The resulting absorption base may be readily triturated with

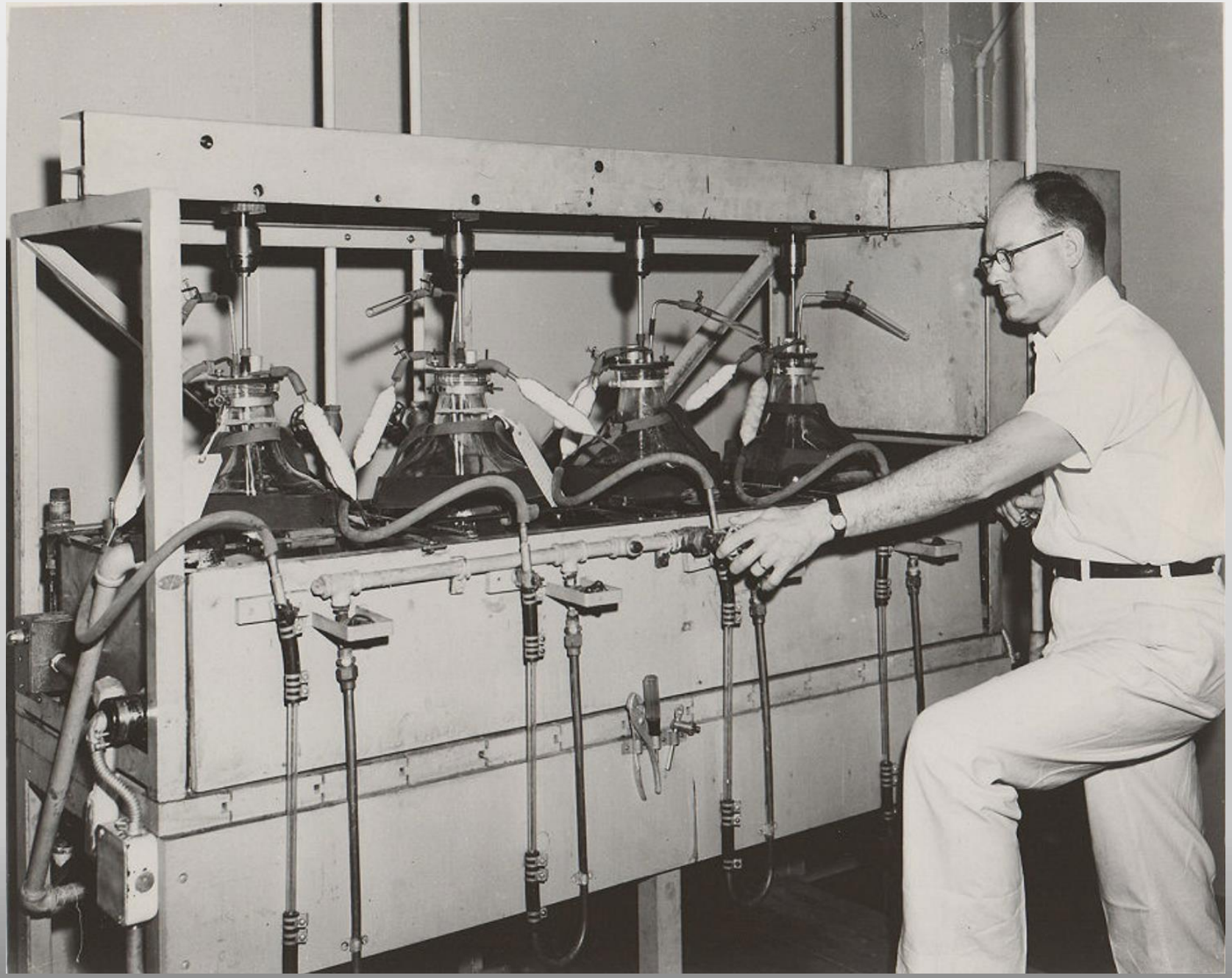
Thank You Sponsors

described. The fermented steroid results from the fermentation of steroid by organic tissues, enzymes, or microorganisms, illustratively Euthallophyta inclusive of Schizomycetes, Eumycetes, Lichenes and Algae. Following the fermentation of steroid using, for example, tissue perfusion or brew as in Haines, "Studies on the Biosynthesis of Adrenal Cortex Hormones," from Recent Progress in Hormone Research, vol. VII, Academic Press Inc., N. Y., 1952; Streptomyces as in Colingsworth, Brunner and Haines, J. Am. Chem. Soc., 74, 2381 (1952); Mucorales as in the Murray and Peterson Patent 2,602,769, issued July 8, 1952; Phycomyces, Eremothecium or Ustilago as in Perlman, Science, 115, 529 (1952); Yeast (reduction), Mamdi and Vercellone, Ber., 70B, 470 (1934); Corynebacterium, Mamoli, Ber., 71, 2701 (1938); Azotobacter, Horvath and Kramli, Nature, 160, 639 (1947); Proactinomyces, Horvath and Kramli, Nature, 163, 219 (1949) instead of the cumbersome method heretofore used, namely the extraction of fermented steroid from the aqueous medium by means of

temperature of 28 degrees centrigrade using a rate of aeration and agitation such that the oxygen uptake was 6.3 to 7 millimoles per hour per liter of Na_2SO_3 according to the method of Cooper, Fernstrom and Miller, Ind. Eng. Chem., 36, 504 (1944). To this medium containing a 24-hour growth of *Rhizopus nigricans* was added two grams of 11-desoxy-17-hydroxycorticosterone dissolved in a minimum of acetone. After an additional 24-hour period of incubation the beer was filtered. Three separate fifty-milliliter portions of the beer filtrate were each treated respectively with one-gram, five-gram or ten-gram portions of Nuchar activated carbon for five minutes and then the mixture was filtered.

The separated carbon residues were slurried with methanol into chromatograph columns and eluted with solvents as given in Table I. The eluate fractions were concentrated and the components were separated and analyzed by paper chromatography.

EXAMPLE 2



United States Patent Office

2,697,715

Patented Dec. 21, 1954

2,697,715

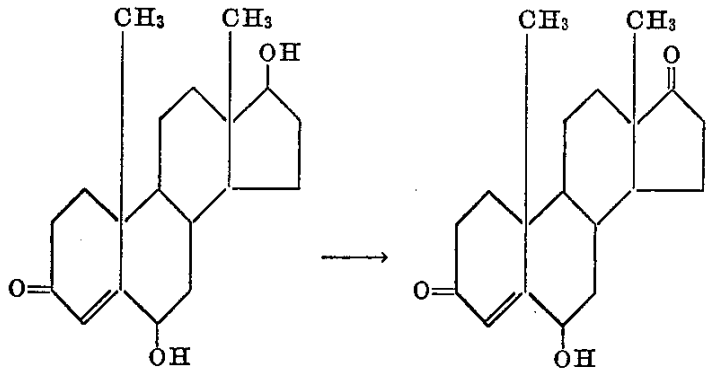
PROCESS FOR SELECTIVE OXIDATION OF 17β-HYDROXY GROUP OF 6β-HYDROXYTESTOSTERONE

Samuel H. Eppstein, Galesburg, and Hazel Marian Leigh, Kalamazoo, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

No Drawing. Application July 16, 1953, Serial No. 368,493

3 Claims. (Cl. 260—397.4)

The present invention relates to steroid compounds and is more particularly concerned with a novel process for the selective oxidation of the 17β-hydroxy group in 6β-hydroxytestosterone to a 17-keto group without oxidation of the 6β-hydroxy group and the 4-double bond, a process which may be represented by the formulae:



benzene as the solvent and the chromic acid being produced by the reaction of an alkali dichromate and acetic acid, or by small amounts of water and chromic anhydride. Whether the reaction is carried out in a homogeneous phase or in a heterogeneous phase, the temperature of the reaction mixture is kept below fifteen degrees centigrade, but above the freezing point of the mixture, preferably between about zero and about ten degrees centigrade. While highest yields are usually obtained when an amount of oxidant between about 1.0 and about 1.1 times the theoretical amount required to convert the 17β-hydroxy group to a 17-keto group is used, between about 0.8 and about 2.0 times the theoretical amount results in good yields. Larger amounts of oxidant can be used satisfactorily at low temperatures using a short reaction period. The reaction time depends in part on the temperature and may vary from about one-half hour to about ten hours, or even longer. At zero degrees centigrade, the reaction time is usually between about one and four hours. At the termination of the reaction, any unused amount of chromic acid may be destroyed by adding methyl or ethyl alcohol to the solution. The 6β-hydroxy-4-androstene-3,17-dione obtained is isolated from the reaction mixture by conventional procedure, e. g., by addition of water to the reaction mixture, then extraction with an organic solvent, for example, ether, ethyl acetate, chloroform, methylene dichloride, etc., and subsequent removal of the extraction solvent. The isolated product can be purified by recrystallization, chromatography, etc., if desired.

The following examples are illustrative of the processes and products of the present invention, but are not to be construed as limiting.

PREPARATION 1—6β-HYDROXYTESTOSTERONE

United States Patent Office

2,769,823

Patented Nov. 6, 1956

2,769,823

PREPARATION OF 17α-HYDROXY-20-KETO-PREGNENES

William P. Schneider, Kalamazoo, and Arthur R. Hanze, Kalamazoo Township, Kalamazoo County, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

No Drawing. Application April 23, 1954, Serial No. 425,315

20 Claims. (Cl. 260—397.45)

amount of osmium tetroxide, followed by hydrolysis with aqueous sodium sulfite, to produce a 17,20-dihydroxy-pregnane steroid. U. S. Patent 2,493,780 also discloses that hydrogen peroxide can be used with a catalytic amount of osmium tetroxide. Similar hydroxylation reactions involving a double bonded compound, hydrogen peroxide and a catalytic amount of a metal oxide, may be found in U. S. Patents 2,373,942; 2,402,566; 2,414,385; and 2,437,648.

The oxygenation of unsaturated steroids of the pregnane series with osmium tetroxide and certain oxidizing agents is also known in the art. Prins and Reichstein, Helv. Chim. Acta, 25, 300 (1942) report that oxidation

United States Patent Office

2,735,854

Patented Feb. 21, 1956

2,735,854

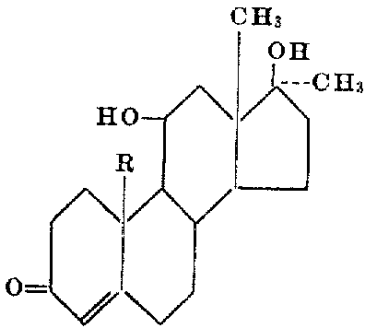
STEROID COMPOUNDS

Milton E. Herr, Kalamazoo Township, Kalamazoo County, Mich., assignor to The Upjohn Company, a corporation of Michigan

No Drawing. Application March 11, 1955, Serial No. 493,807

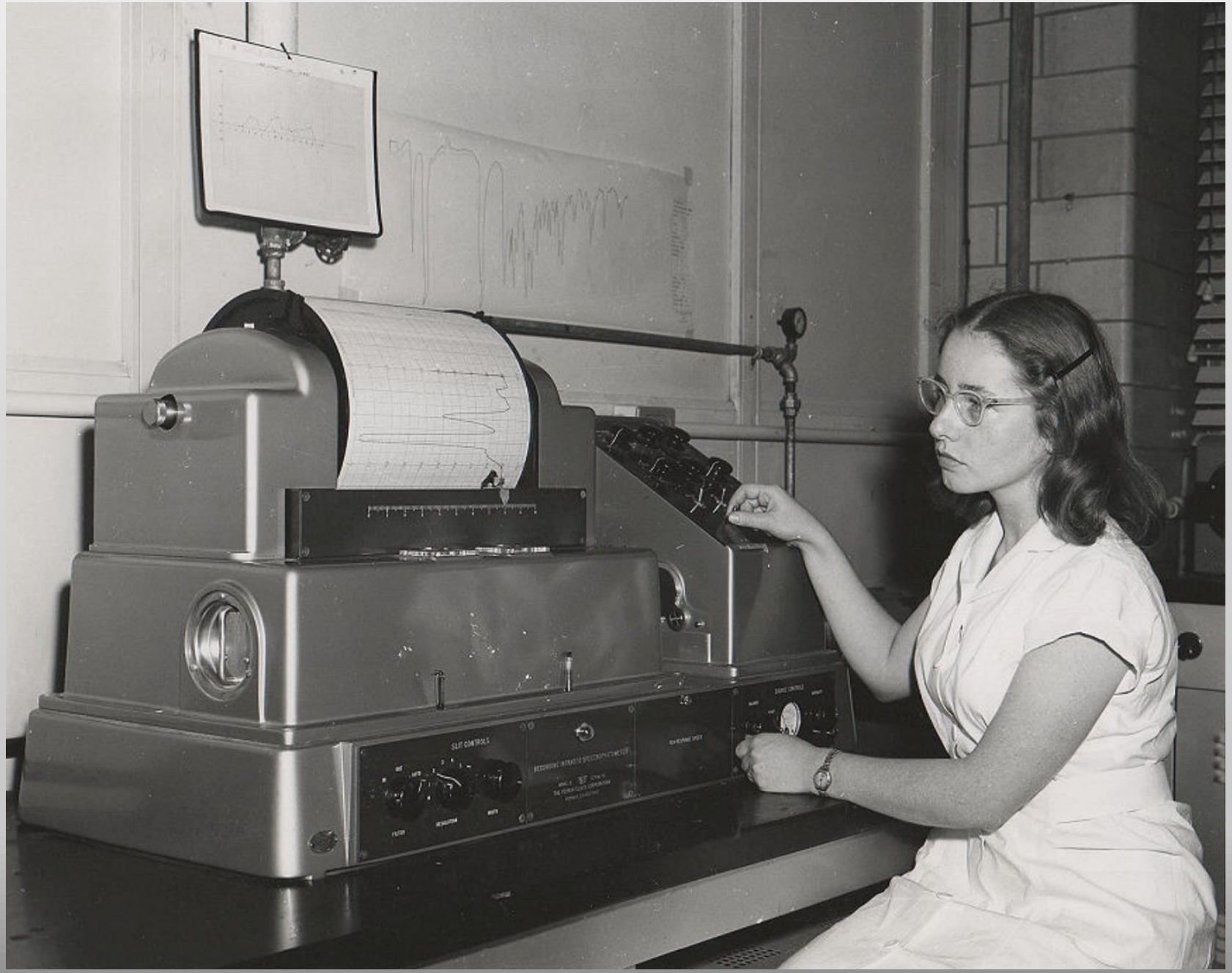
3 Claims. (Cl. 260—397.45)

This invention pertains to steroid compounds related to testosterone and is more particularly concerned with novel 11β-hydroxy-17α-methyltestosterones of the formula



In the table, "Potency Ratio of Test Compound to 17α-Methyltestosterone" was determined by administering the test compounds orally in equal daily doses of 0.2 milligram in 0.2 milliliter of cottonseed oil to 26 to 27-day-old castrate, male rats for 9 days; and, at autopsy on the day following the last oral dose, determining the body weight, seminal vesicle weight, and levator ani muscle weight; the weight of the seminal vesicle per 100 grams of body weight being used as an index of androgenic activity, and the weight of the levator ani muscle per 100 grams of body weight being used as an index of anabolic activity. From the table, it can be seen that 11β-hydroxy-17α-methyltestosterone has distinctive superiority in the high ratio of oral anabolic activity to androgenic activity as well as in requiring a smaller dosage to obtain equal anabolic effects.

The 11β-hydroxy-17α-methyltestosterones of the present invention can be readily prepared from the corresponding 11-keto-17α-methyltestosterones (U. S. 2,678,933) by first protecting the 3-keto group with a protecting group, e. g., an enamine group, or a ketal group, then reducing the 11-keto group to an 11β-hydroxy group, e. g., with $LiAlH_4$, and finally hydrolyzing the protecting group at the 3-position to regenerate the 3-keto group. The 11β-hydroxy-17α-methyltestosterones of the present invention can also be prepared from the corresponding 11β-hydroxy-4-androstene-3,17-diones by first protecting the 3-keto group with a protecting group, e. g., an enamine group, or a ketal group, then converting the 17-keto group to a 17β-hydroxy-17α-methyl grouping by


SLIT CONTROLS

Thank You Sponsors

United States Patent Office

2,752,369

Patented June 26, 1956

2,752,369

OXIDATION OF STEROID-ENAMINES

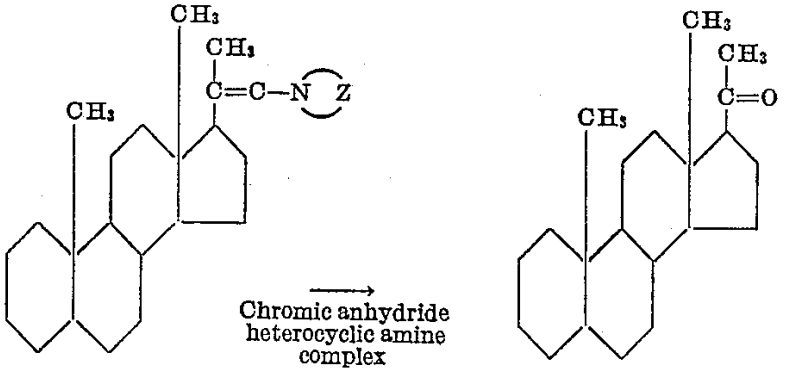
Roman P. Holysz and John C. Babcock, Kalamazoo Township, Kalamazoo County, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

No Drawing. Application February 25, 1954, Serial No. 412,637

15 Claims. (Cl. 260—397.3)

The present invention relates to a process of production of 20-ketopregnane compound and is particularly concerned with the oxidation of 22-tertiaryamino-$\Delta^{20(22)}$-steroids by chromic anhydride-heterocyclic amine complexes.

The process of the instant invention is illustratively presented by the formulae:



anhydride-pyridine complex would split a 20,22-double bond of a 22-tertiaryamino-$\Delta^{20(22)}$-steroid with high yields.

It is an object of the present invention to provide a novel method of oxidizing a 22-tertiaryamino-$\Delta^{20(22)}$-steroid to obtain a 20-ketosteroid. Another object of this invention is to provide a method for producing progesterone. A further object of the present invention is to provide an oxidation method in a basic medium with the avoidance of changes of acid sensitive groups. Other objects of the present invention will be apparent to those skilled in the art to which this invention pertains. The process is useful in the production of physiologically and therapeutically active 20-ketosteroids or 20-ketosteroids which serve as intermediates for physiologically active steroids by the oxidation of 22-tertiaryamino-$\Delta^{20(22)}$-steroids. For example, oxidation of 22 - N - piperidyl-4,20(22) - bisnorcholadien - 3 - one yields progesterone; oxidation of 22 - N - piperidyl - 4,20(22) - bisnorcholadiene - 3,11 - dione yields 11 - ketoprogesterone (effective in the treatment of ketosis of cattle); from the oxidation of 11β - acetoxy - 22 - N - piperidyl - 5,20(22) - bisnorcholadien - 3 - one 3 - ethylene ketal followed by acid hydrolysis 11β - acyloxyprogesterone is obtained which by vigorous alkali hydrolysis in ethylene glycol yields 11β - hydroxyprogesterone possessing an ACTH suppressing function; oxidation of 3α,12α - dihydroxy - 22 - N-morpholinyl - 20(22) - bisnorcholene yields pregnane-3,12,20 - trione (Selye, Encyclopedia of Endocrinology, vol. IV, A. W. T. Franks Publishing Company; Montreal, 1943, p. 603), oxidation of 3α,12α - diacetoxy - 22 - N-morpholinyl - 22 - bisnorcholene gives 3α,12α - diacetoxy-pregnan-20-one which can be converted by enol acetylation, epoxidation, hydrolysis, and acetylation to the known

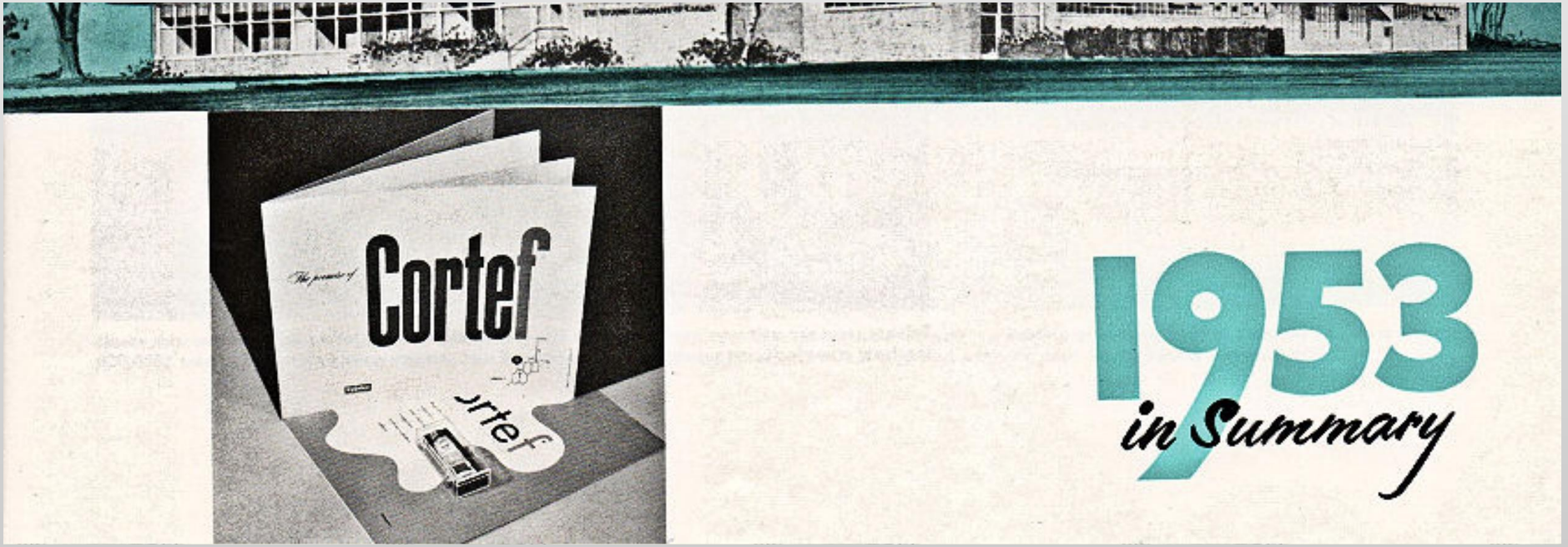
ployed, has the meaning customarily attributed thereto in organic chemistry, viz., adjacent, neighboring, or consecutively positioned.

Many transformations of cyclopentanopolyhydrophenanthrene compounds require the protection of nuclear double bonds. The addition of chlorine or bromine to the nuclear double bond, prior to the transformation, is a standard method for accomplishing such protection. After the desired transformation or reaction has been completed, it becomes necessary to introduce a carbon-carbon double bond into the steroid nucleus to complete the synthesis, and this is accomplished by removal of the halogens which have been introduced previously for protective purposes. Such reaction has been accomplished in the art by use of zinc in acetic acid or alcohol, by the use of chromous chloride (United States Patent 2,374,683), and by the use of alcoholic sodium iodide [J. Biol. Chem. 110, (1935); United States Patents 2,203,611 and 2,319,808].

The use of sodium iodide has been found effective, according to the references mentioned

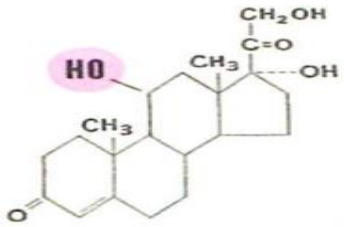
the dehalogenation of vicinally nuclearly-dihalogenated steroids which involves the employment of a quaternary ammonium iodide as the dehalogenating agent. Other objects of the invention will be apparent hereinafter.

It has now been found that quaternary ammonium iodides are superior steroid debrominating or dechlorinating agents as compared with the previously-employed alkali metal iodides. Yields of pure unsaturated product are considerably higher than attained by employment of the previously-used dehalogenating agents, in some instances being practically quantitative. The crude product, obtained by the method of the present invention, is generally sufficiently pure to be used without additional purification in subsequent chemical reactions. While debromination and dechlorination with the agents of this invention can, if desired, be carried out at elevated temperatures, such as the boiling point of the reaction solvents, these agents are sufficiently powerful so that the dehalogenation can be carried out at room temperature in a reasonable



1953 in Summary

from: The Upjohn News, April 1954



The story about our Cortef *products*

Systemic *administered internally: circulates throughout body*

Oral administration

Tablets

Injection

Intramuscular *(under clinical investigation)*

Intravenous *(under clinical investigation)*

Topical: *applied externally*

Skin

Ophthalmic: *applied to the eye*

Eye

Rex Mann and Eldon Nielson, Department of Endocrinology Research, Gordon French, Antibiotics Production, and Joe Alberti, Harrison Nelson, and Fred Hanson, Department of Antibiotics Research, represent those who developed a biochemical process, later set aside, for hydrocortisone. It was this method which produced the first hydrocortisone on a large scale.

Many answers still depend on experiments, done with painstaking care. In a Chemistry lab, Bob Jackson and Anna Mae Searcy concentrate on Alan Nathan's reading of a melting point.

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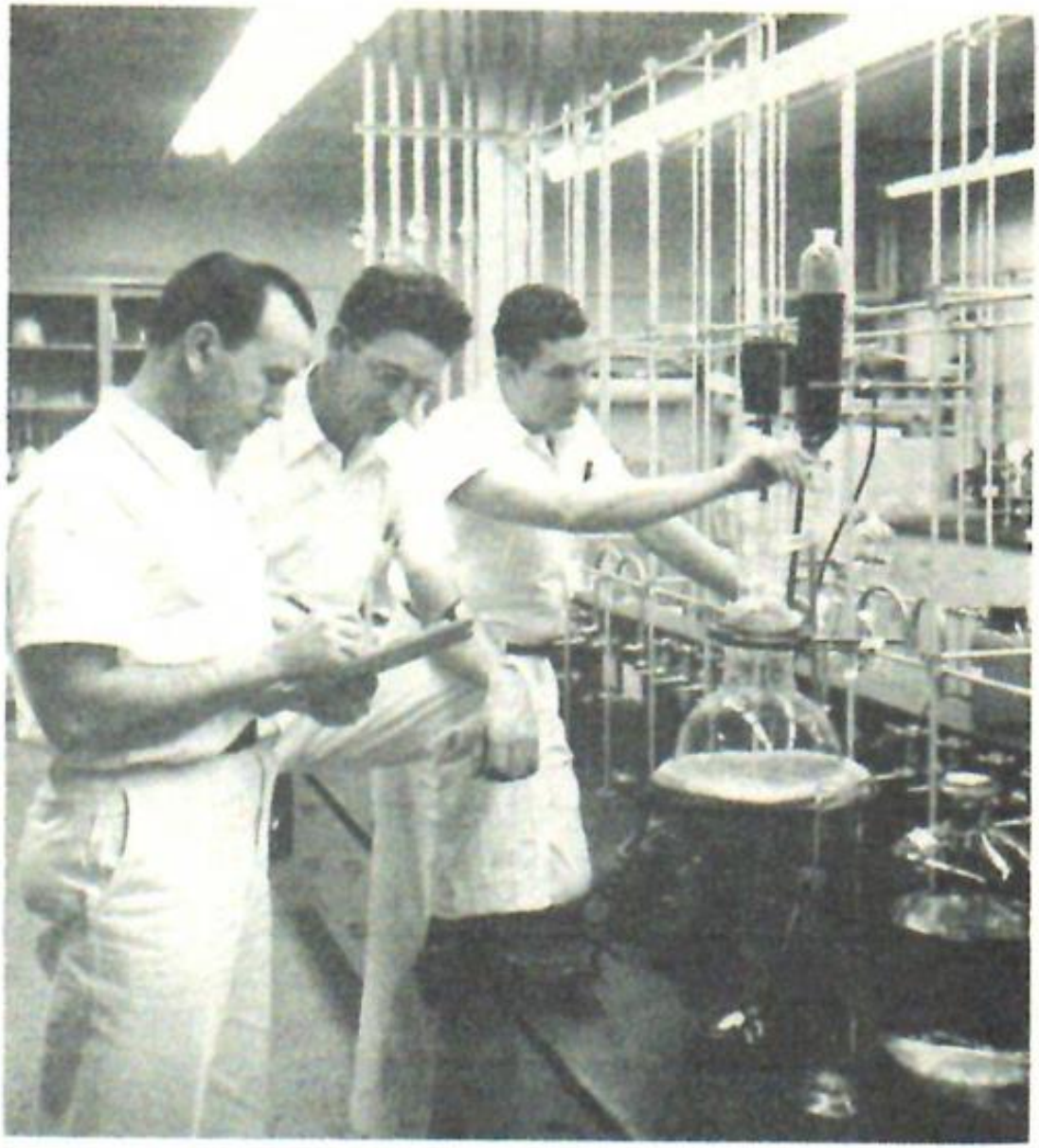
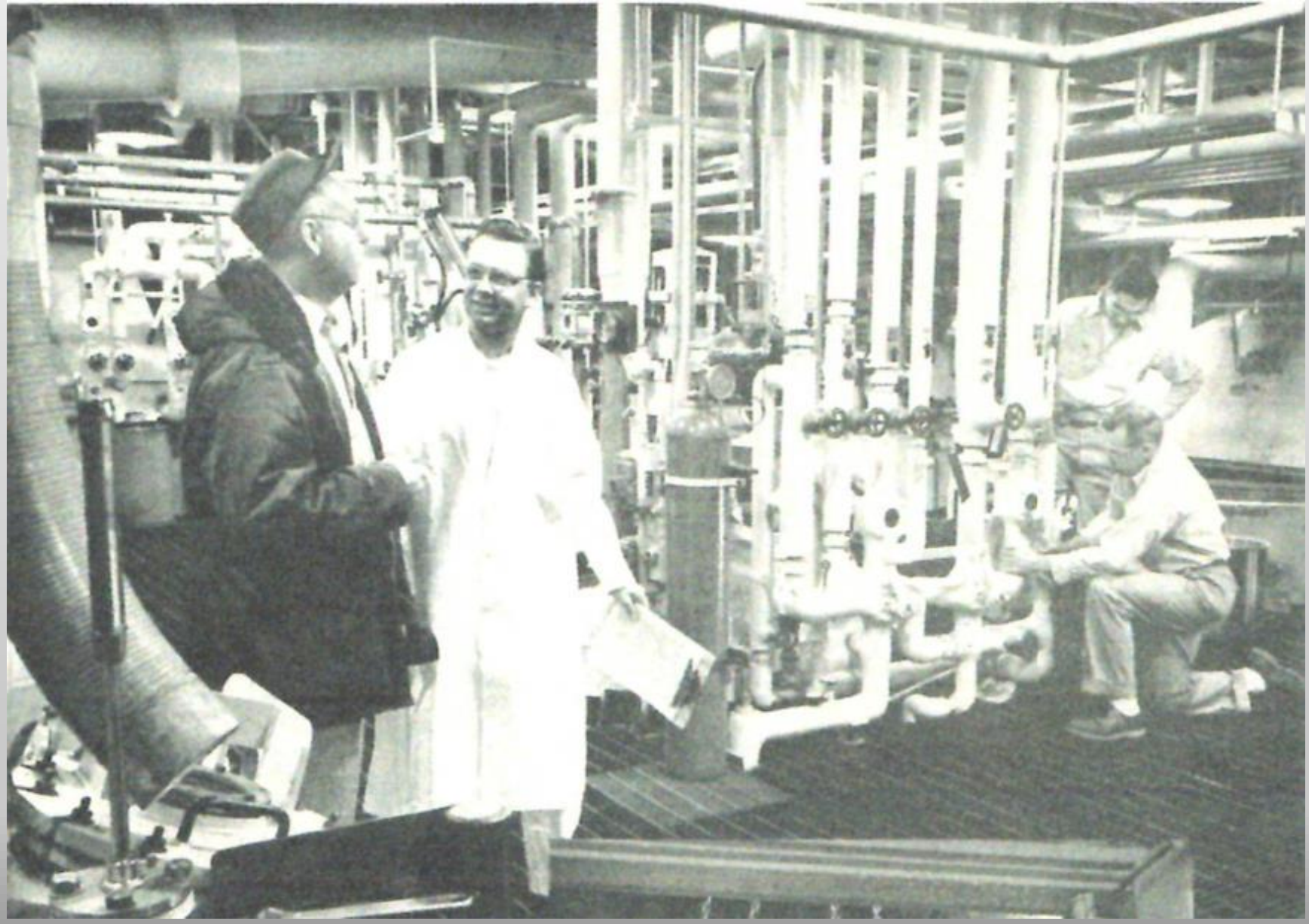


Once crystals were obtained in small-scale experiments, Paul Marlatt, Don Myers, and Bill Wetherall tackled developmental work needed to adapt methods to larger-scale experiments.

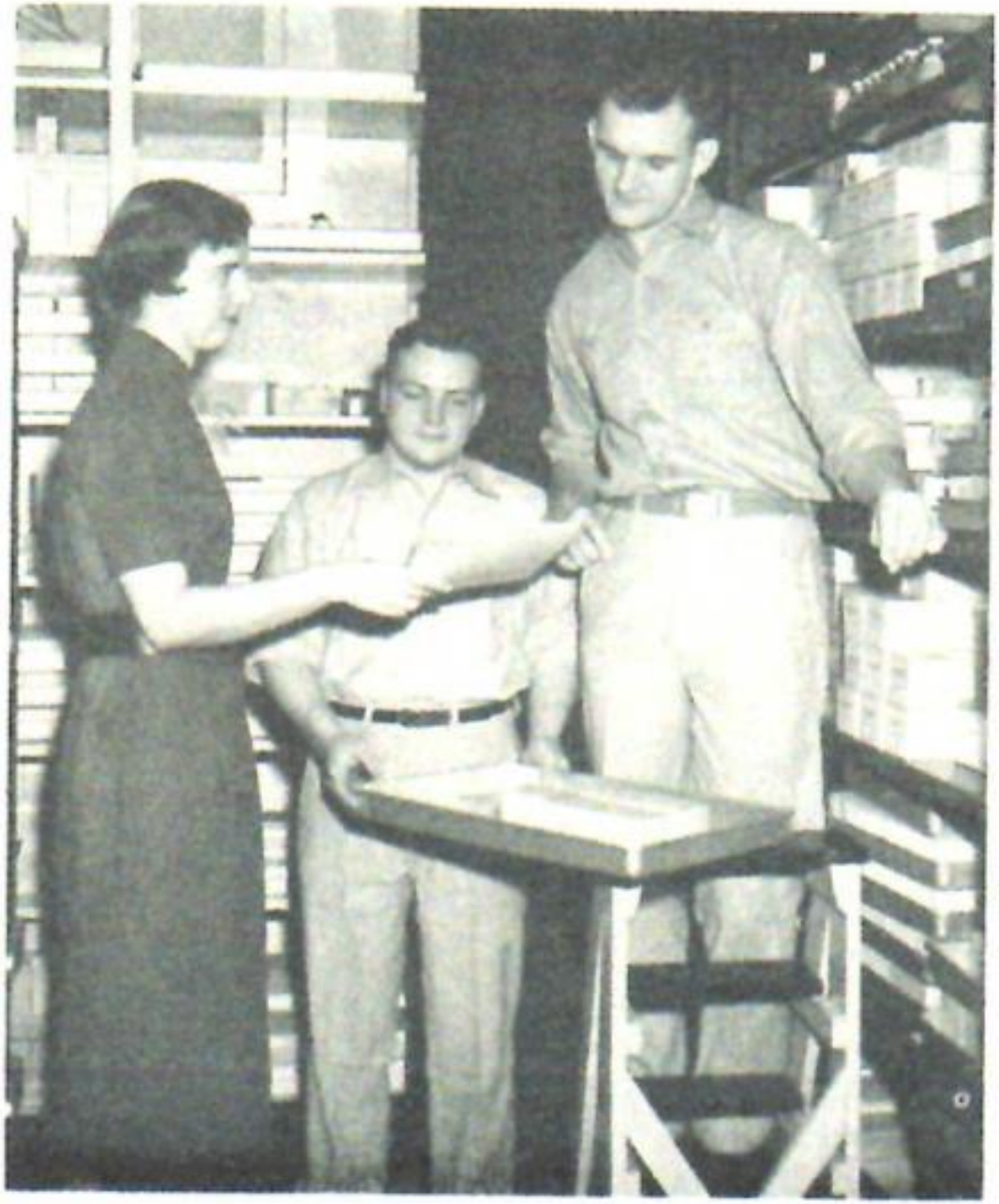
Assays tell the story of an experiment's success, for it is this tool that gives the final evaluation of a material's identity, purity, etc. In the case of a new compound such as an hydrocortisone intermediate, however, assays, too, must be devised. Some of this research was done by Tom Chulski, Physics Department.



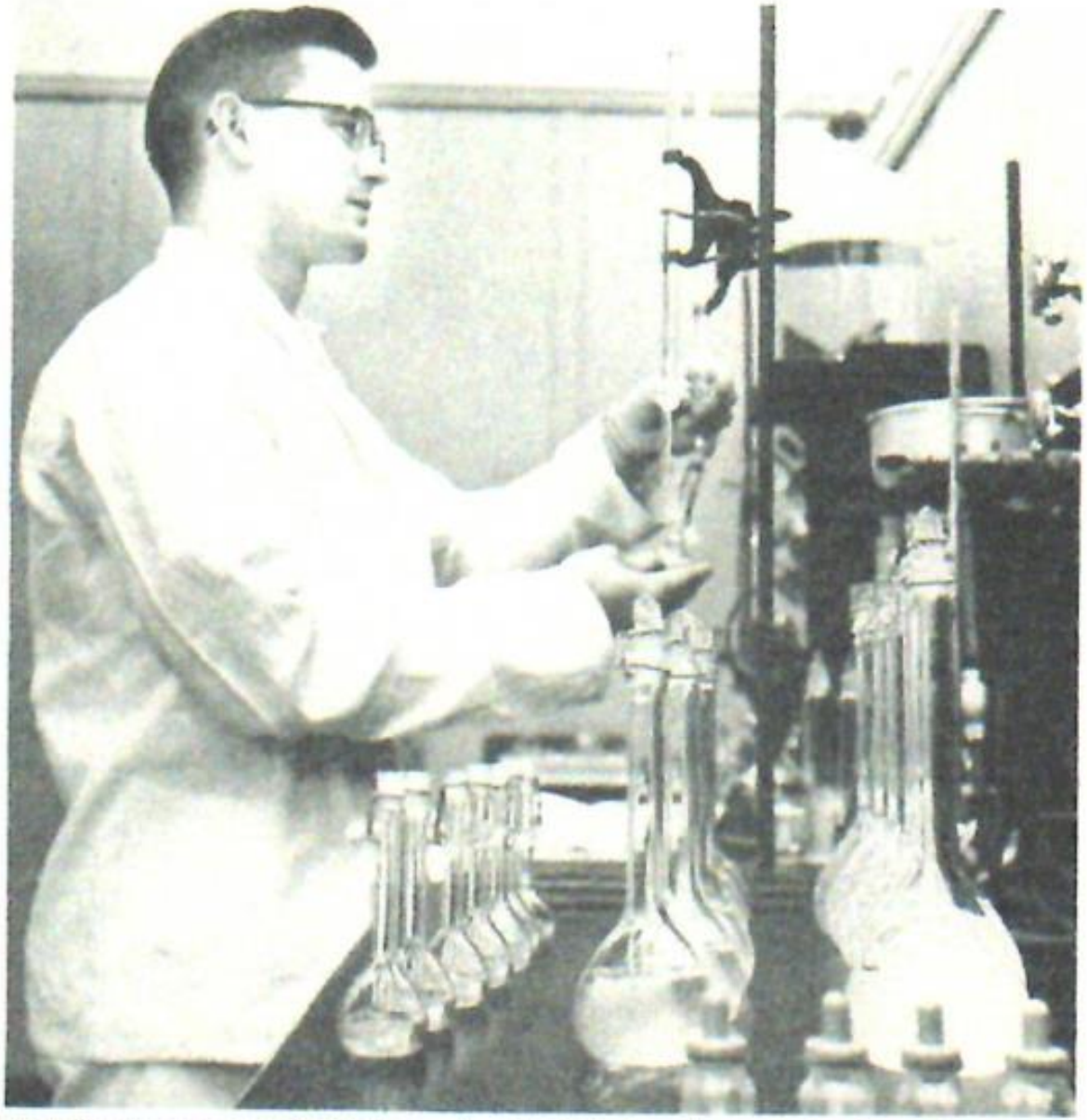
Sven Rundman, Lee Macdonald, ointments

Jerry Pleyte . . . tablets

Jack Dale . . . sterile preparations



Before any preparation may go for clinical investigation, its safety must be assured by Department of Pharmacology Research. Purpose of clinical investigation is evaluation by specialists in the field. On the basis of their appraisal three things may happen to a formulation: acceptance, rejection, further developmental work and more testing. Marian Dykshoorn, Don Musselman, and Dale Redeker have already sent hundreds of *Cortef* samples to clinics all over the country. By meeting the rigors of this investigation, nine *Cortef* products, to date, have received the nod for full-scale production.



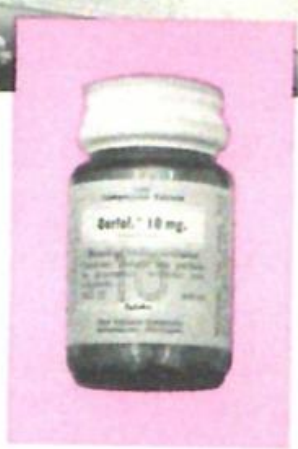
Cortef ointments gave Control some trouble. Colorimetric assays (to determine amount of *Cortef*) were developed and Bill West now runs a series almost daily.

In Sterile area, George Kramer runs suspension through colloid mill to disperse particles.

Neo-Cortef drops
1.5%

Thank You Sponsors

Leo Lemmer portrays early stage in tablet manufacture—blending powdered materials in 600 lb. mixer.



Cortef tablets 5 mg., 10 mg., 20 mg.

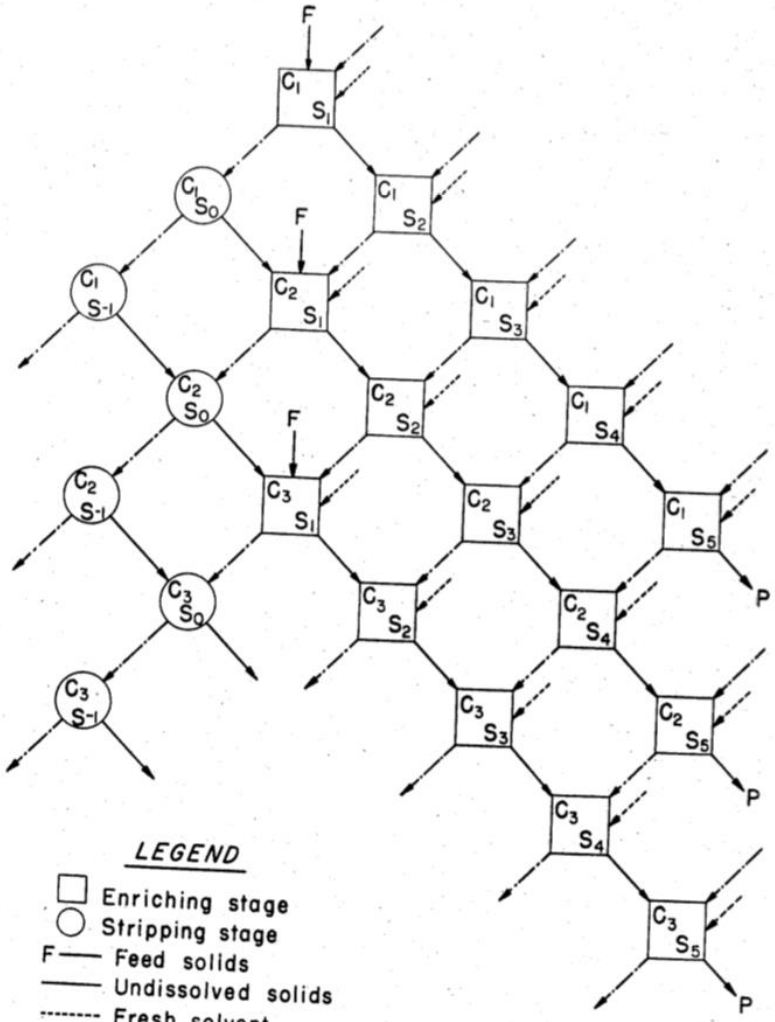
Representing ointment production, Tom Richmond weighs assembled *Neo-Cortef* ingredients.

Cortef ointments 1%, 2.5%
Neo-Cortef ointments 1%, 2.5%
Neo-Cortef ophthalmic ointment 1.5%

June 17, 1958 J. W. GREINER ET AL 2,839,544

COUNTERCURRENT EXTRACTION OF STEROIDS

Filed Sept. 4, 1956

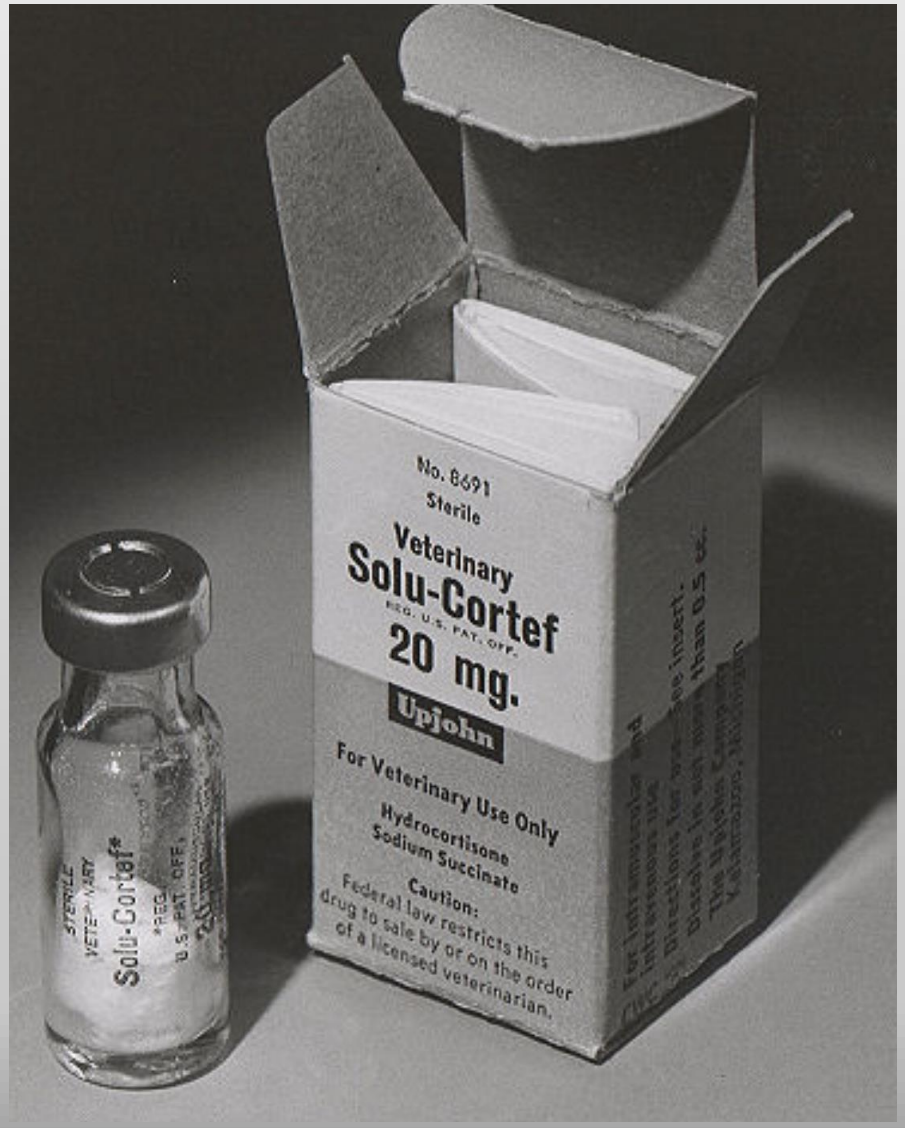


LEGEND

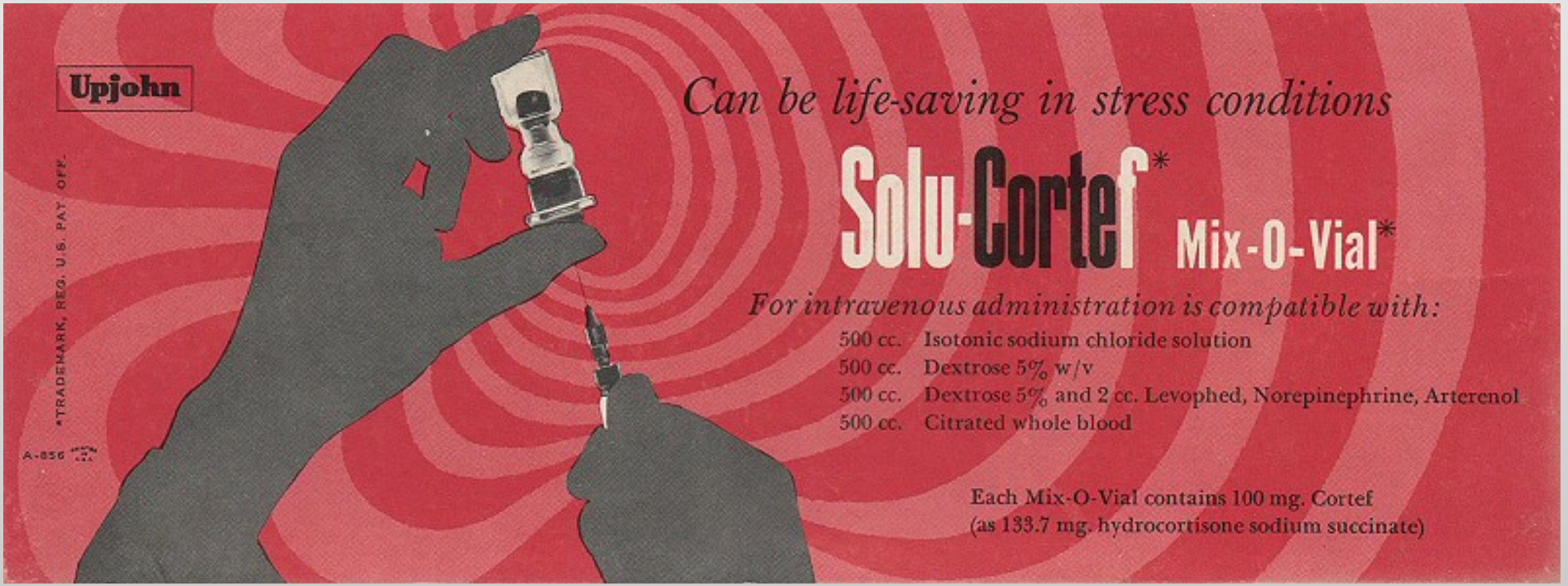
- Enriching stage
- Stripping stage
- F —— Feed solids
- —— Undissolved solids
- ------- Fresh solvent
- —·—·— Mother liquor
- C = Cycle
- S = Stage
- P = Product

INVENTOR.
J. WARD GREINER
GLEN A. FEVIG
BY
ATTORNEY


Cortisone Acetate, 15 mg. per Gm. (1.5%)
Medrol
Cortef 100 mg.
Solu-Medrol 40 mg.
Emergency Kit
Medrol
Medrol
4 mg.
Depo-Provera


No. 8691
Sterile
Veterinary
Solu-Cortef
REG. U.S. PAT. OFF.
20 mg.
Upjohn
For Veterinary Use Only
Hydrocortisone
Sodium Succinate
Caution:
Federal law restricts this
drug to sale by or on the order
of a licensed veterinarian.
Solu-Cortef*

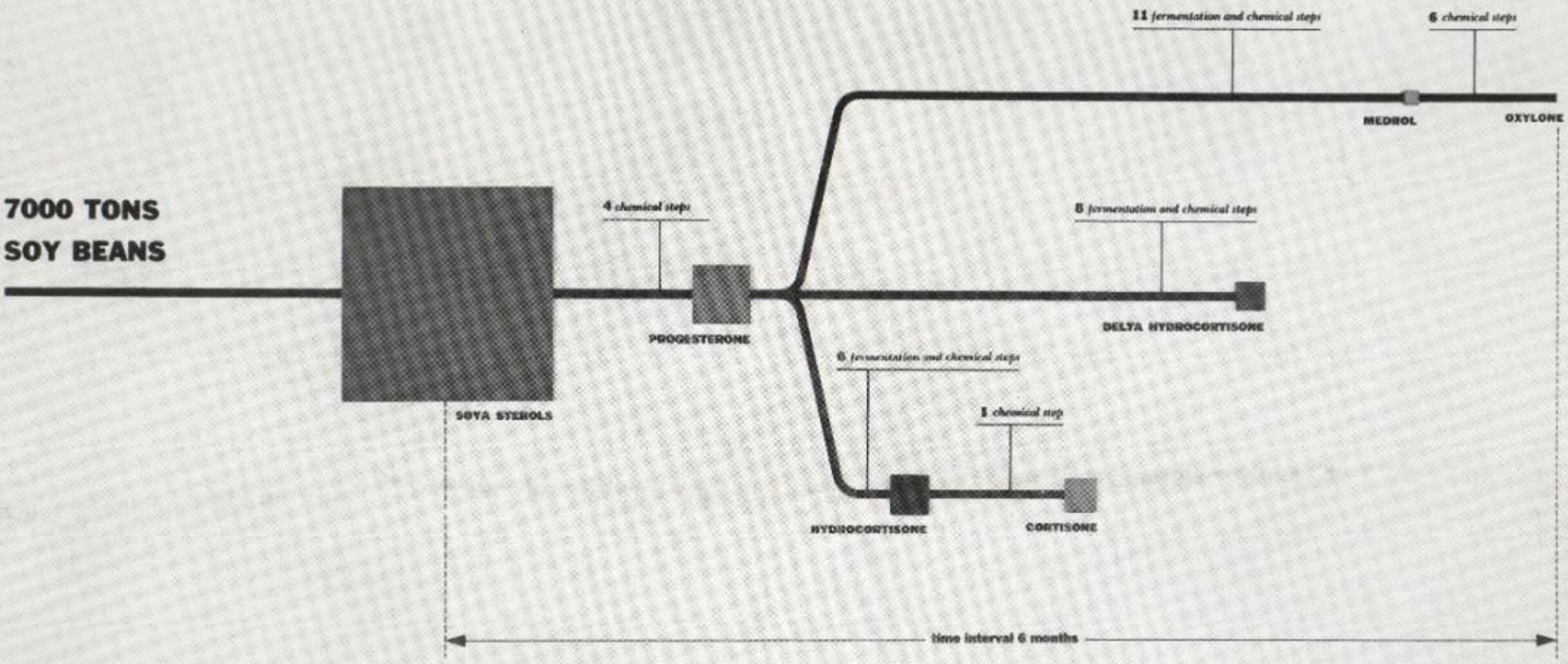

Sterile
No. 8699
Veterinary
Mix-O-Vial*
Solu-Delta-
Cortef
100 mg.
Upjohn
Prednisolone sodium
succinate
For intravenous or intra-
muscular use
Caution:
Federal law restricts this drug
to sale by or on the order of
a licensed veterinarian.
Protect from light
Store at room temperature


Upjohn
*TRADEMARK, REG. U.S. PAT. OFF.
A-856
Can be life-saving in stress conditions
Solu-Cortef*
Mix-O-Vial*
For intravenous administration is compatible with:
500 cc. Isotonic sodium chloride solution
500 cc. Dextrose 5% w/v
500 cc. Dextrose 5% and 2 cc. Levophed, Norepinephrine, Arterenol
500 cc. Citrated whole blood
Each Mix-O-Vial contains 100 mg. Cortef
(as 133.7 mg. hydrocortisone sodium succinate)

Upjohn

Production of a steroid

The production of a steroid originates with processing soy beans. Approximately 7000 tons of soy beans are required to make 1 pound of Oxylone.



CONTROL . . . THE MEASURE OF ACCEPTANCE

These are some of the steroid products we produce. They must pass 307 to 609 control checks for purity and potency before they can be used.

Continuous Microbiological Transformation of Steroids

F. Reusser, H. J. Koepsell, and G. M. Savage

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

Received for publication October 26, 1960

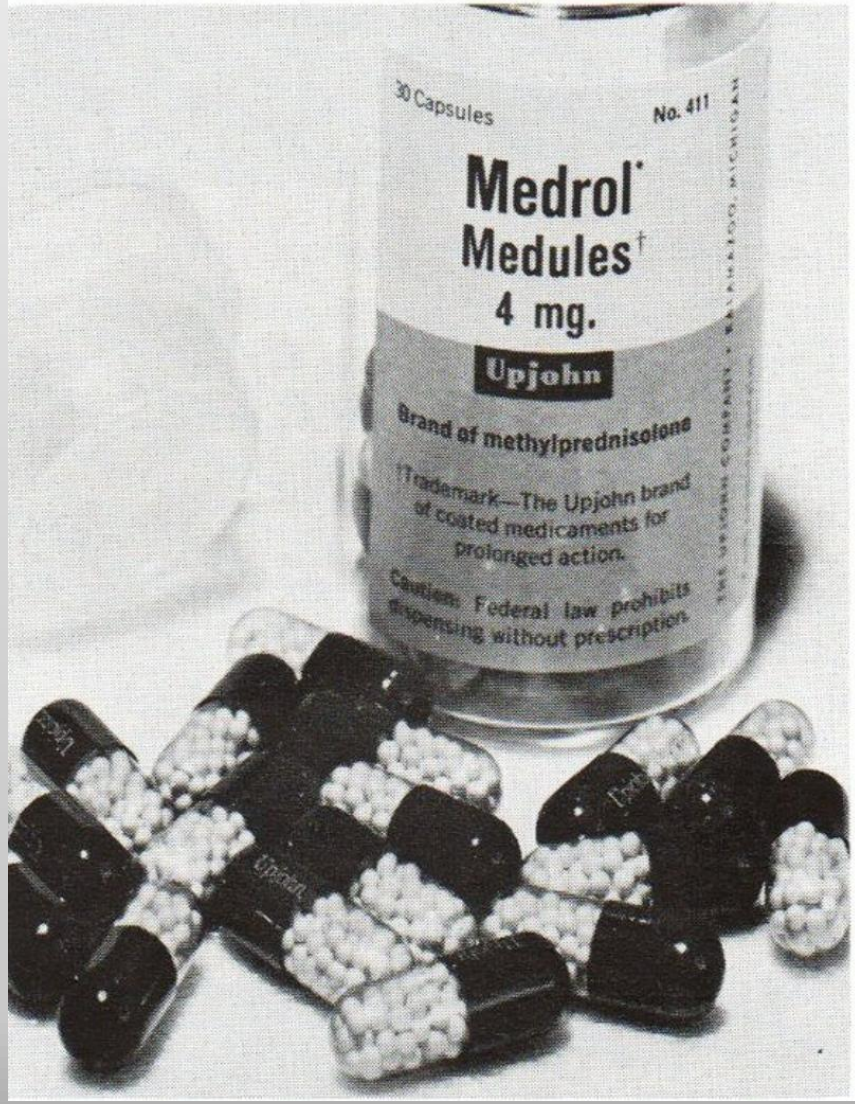
Abstract

Reusser, F. (The Upjohn Company, Kalamazoo, Mich.), H. J. Koepsell, and G. M. Savage. Continuous microbiological transformation of steroids. Appl. Microbiol. **9:** 346–348. 1961.—Continuous fermentation trials on the bioconversions of pregnadiene to pregnatriene by *Septomyxa affinis* and progesterone to 11α-hydroxyprogesterone by *Rhizopus nigricans* were conducted successfully in an eight-stage pilot plant reactor. The first stage was used as the mycelial growth stage while the steroid solutions were added continuously to stage 2, thus using the remaining stages as conversion vessels. Recoveries of 50 to 60% oxidized steroid (based on total steroid supplied) were obtained in both cases upon a contact time of 5 hr between mycelium and steroid. Longer contact times resulted in a gradual net loss of steroid. It was concluded that two-stage reactors (one growth stage and one conversion stage) were adequate for efficient continuous operation of such processes. The reaction volumes of both stages have to be kept in proper balance to insure optimal holdup times for both the cell growth and conversion steps.

Materials and Methods

Continuous Culture Apparatus

The design of the continuous culture apparatus will be described in another paper and only details pertinent to this work will be given here. The apparatus used was a multistage reactor of small pilot plant style and was fabricated of stainless steel. It consisted of eight individual stages connected together. The first stage had an operating volume of 20 liters, and each subsequent stage had a volume of 10 liters. Each stage was provided with the accessories of conventional tanks such as agitator, supply of sterile air, sample valves, and temperature controls. The level in each stage was kept constant by horizontal overflow to the next stage and finally to the drain. Air was sterilized by filtration through glass wool filters and its flow was measured by rotameters and controlled by needle valves. Continuous feed of sterile medium was provided into stage 1 by an injection device which delivered a constant amount of medium at short, variable time intervals. Steroid dissolved in suitable water-soluble solvents was added into stage 2 at a controlled rate by the use of a peristaltic-action metering pump. Temperatures were controlled by circulating thermostatically controlled


30 Capsules
No. 411
Medrol
Medules†
4 mg.
Upjohn
Brand of methylprednisolone
†Trademark—The Upjohn brand of coated medicaments for prolonged action.
Caution: Federal law prohibits dispensing without prescription


Veriderm†
Neo-Medrol
Acetate
0.25%
Upjohn
Exp. date: June 1, 1962
Lot No. ME445
Veriderm†
Medrol
Acetate
0.25%
Upjohn
Exp. date: June 1, 1962
Lot No. ME414

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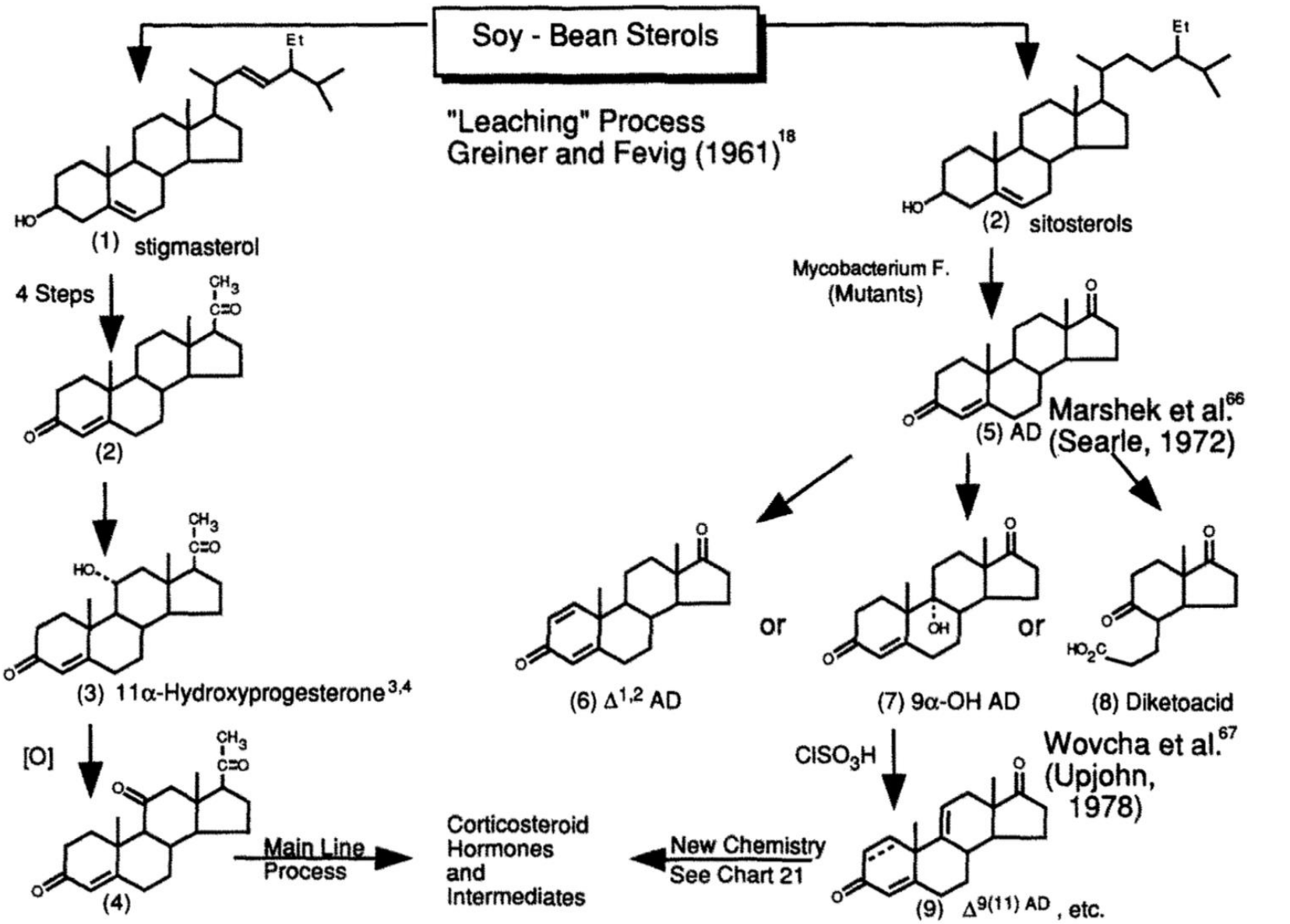

Soy - Bean Sterols
"Leaching" Process
Greiner and Fevig (1961)[18]
(1) stigmasterol
(2) sitosterols
4 Steps
(2)
Mycobacterium F.
(Mutants)
(5) AD
Marshek et al.[66]
(Searle, 1972)
(3) 11α-Hydroxyprogesterone[3,4]
(6) Δ1,2 AD
or
(7) 9α-OH AD
or
(8) Diketoacid
[O]
(4)
Main Line
Process
Corticosteroid
Hormones
and
Intermediates
New Chemistry
See Chart 21
ClSO3H
Wovcha et al.[67]
(Upjohn,
1978)
(9) Δ9(11) AD, etc.

Chemical reactors used in the production of steroids require close surveillance.

Synthesis of 6α-Fluoromethyl Steroids

P. F. Beal, R. W. Jackson, and J. E. Pike

Research Laboratories of The Upjohn Co., Kalamazoo, Mich.

Received November 22, 1961

The syntheses of 6α-fluoromethylprednisolone and the 9α-fluoro analog are reported, based on the application of the "oxo" reaction to 17,20;20 21-bismethylenedioxy-5-pregnene-3β,11β-diol 3-acetate (II), followed by conversion of the 6α-hydroxymethyl group to the fluoromethyl group by the action of potassium fluoride on the 6α-tosyloxymethyl derivative.

The modification of the hydrocortisone molecule, with the object of improving the anti-inflammatory activity, has led to the preparation of methyl and halogen analogs of steroids.[1] Other structural changes have included the introduction of double bonds, hydroxyl groups, and ring enlargement or contraction.[1] Since the substitution at C-6 by both methyl and fluorine to give the 6α-substituted derivatives has led to an enhancement of biological activity, it was decided to introduce other groups at this position. A valuable method

cordingly, cortisone was converted to cortisone BMD (I) as described earlier.[9] This latter was treated with isopropenyl acetate under acidic conditions to give the corresponding enol acetate[10] which on prolonged reduction with sodium borohydride, followed by reacetylation at C-3 with acetic anhydride in pyridine gave 17,20;20,21-bismethylenedioxy-5-pregnene-3β,11β-diol 3-acetate (II). Reaction of II with carbon monoxide and hydrogen at 91 kg./cm.² total pressure in the presence of cobalt carbonate at 180° for eighteen

Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism

Volume 531, Issue 3, 22 December 1978, Pages 308-321

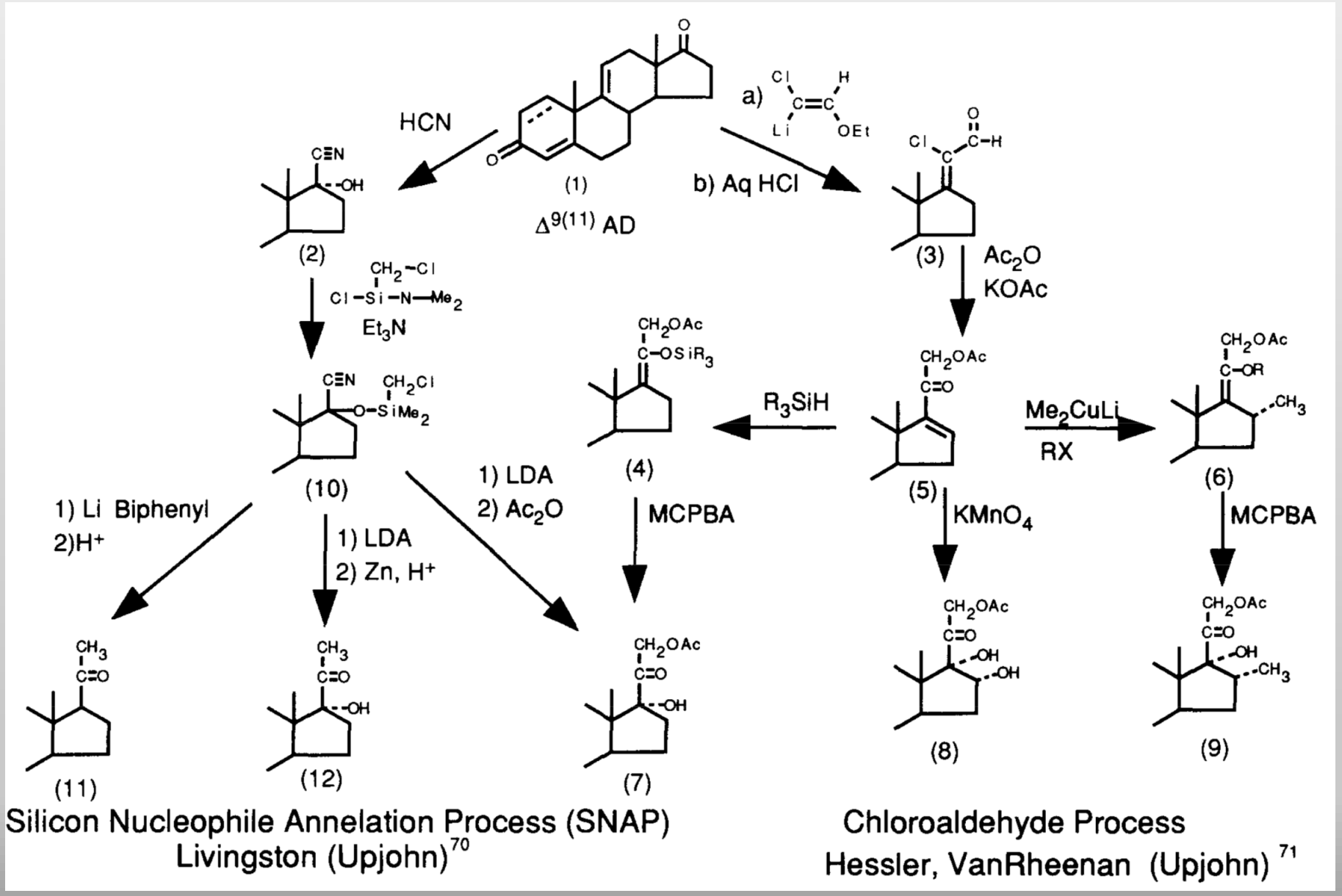
Bioconversion of sitosterol to useful steroidal intermediates by mutants of *Mycobacterium fortuitum* ☆

Merle G. Wovcha [a], Frederick J. Antosz [b], John C. Knight [b], Leo A. Kominek [a], Thomas R. Pyke [a]

APPLICATION OF SILICON CHEMISTRY IN THE CORTICOSTEROID FIELD

Douglas A. Livingston

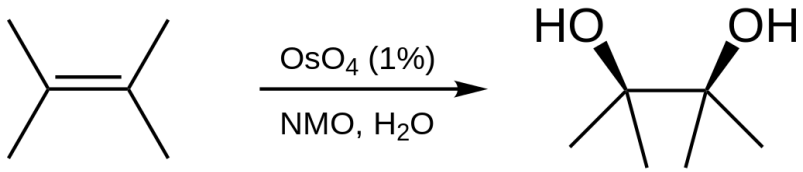
Figure 6. The "Sitosterol Pile" (with the author skiing in Michigan)


HCN
(1)
Δ9(11) AD
a)
b) Aq HCl
(2)
(3)
Ac2O
KOAc
Et3N
(10)
(4)
(5)
(6)
R3SiH
Me2CuLi
RX
1) LDA
2) Ac2O
MCPBA
KMnO4
1) Li Biphenyl
2)H+
1) LDA
2) Zn, H+
(11)
(12)
(7)
(8)
(9)
Silicon Nucleophile Annelation Process (SNAP)
Livingston (Upjohn)70
Chloroaldehyde Process
Hessler, VanRheenan (Upjohn) 71

Upjohn dihydroxylation

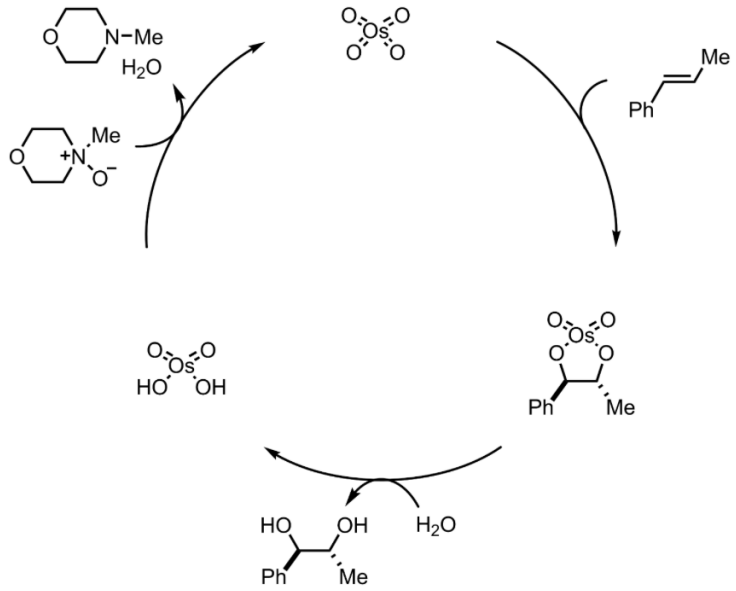
From Wikipedia, the free encyclopedia

The **Upjohn dihydroxylation** is an organic reaction which converts an alkene to a *cis* vicinal diol. It was developed by V. VanRheenen, R. C. Kelly and D. Y. Cha of the Upjohn Company in 1976.[1] It is a catalytic system using *N*-methylmorpholine *N*-oxide (NMO) as stoichiometric re-oxidant for the osmium tetroxide. It is superior to previous catalytic methods.



Upjohn dihydroxylation	
Named after	The Upjohn Company
Reaction type	Addition reaction
Identifiers	
Organic Chemistry Portal	upjohn-dihydroxylation

Mechanism of the Upjohn Dihydroxylation



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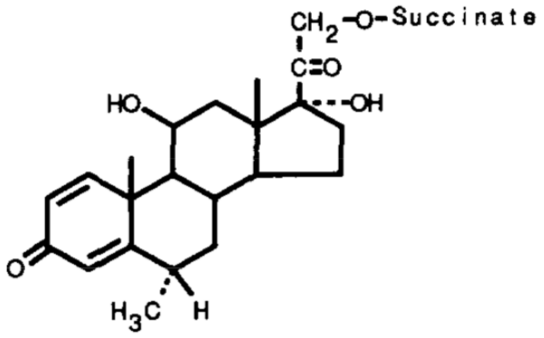

Methylprednisolone Succinate;
Solu-Medrol ®

PHARMACY RESEARCH
November 1980

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Journal of Chromatography A

Volume 316, 1984, Pages 461-472

Analysis of steroids in bulk pharmaceuticals by liquid chromatography with light-scattering detection

Paul A. Asmus, John B. Landis

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001, U.S.A.
TELEPHONE (616) 323-4000

PHARMACEUTICAL CHEMICAL MARKETING DIVISION

BULK PRODUCT LIST

Corticosteroid

- Betamethasone
- Betamethasone Phosphate
- Betamethasone Valerate
- Cortisone Acetate
- Dexamethasone
- Dexamethasone Acetate
- Dexamethasone Phosphate
- Fludrocortisone Acetate
- Fluorometholone
- Hydrocortisone
- Hydrocortisone Acetate
- Hydrocortisone Hemisuccinate
- Prednisolone Anhydrous
- Prednisolone Hydrous
- Prednisolone Acetate
- Prednisone
- Prednisone Acetate
- Triamcinolone
- Triamcinolone Acetonide

Steroid Intermediates

- Androstenedione (AD)
- 11α Hydroxyprogesterone
- 17α Hydroxyprogesterone
- 17α Acetoxyprogesterone
- DBXI [17α, 21-Dihydroxy-16β-methyl-9β, 11β-epoxy-pregna-1,4-diene-3,20-dione]
- SD-V [17α, 21-Dihydroxy-16α-methyl-pregna-4,9(11)-diene-3,20-dione,21-acetate]
- SD-VI [17α, 21-Dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione]
- SD-VII 17α, 21-Dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione,21-acetate]
- T-1D [16α, 17α, 21-Trihydroxypregna-1,4,9 (11)-triene-3,20-dione,21-acetate]
- 3TR [21-Hydroxypregna-1,4,9(11)-16-tetraene-3,20-dione-21-acetate]
- 1-2 Dihydrotriamcinolone [9α Fluoro-11β, 16α, 17,21-tetrahydroxypregna-4-ene-3,20-dione]

Antibiotics

- Erythromycin
- Erythromycin Stearate
- Erythromycin Ethyl Succinate
- Neomycin Sulfate
- Novobiocin

Hormones

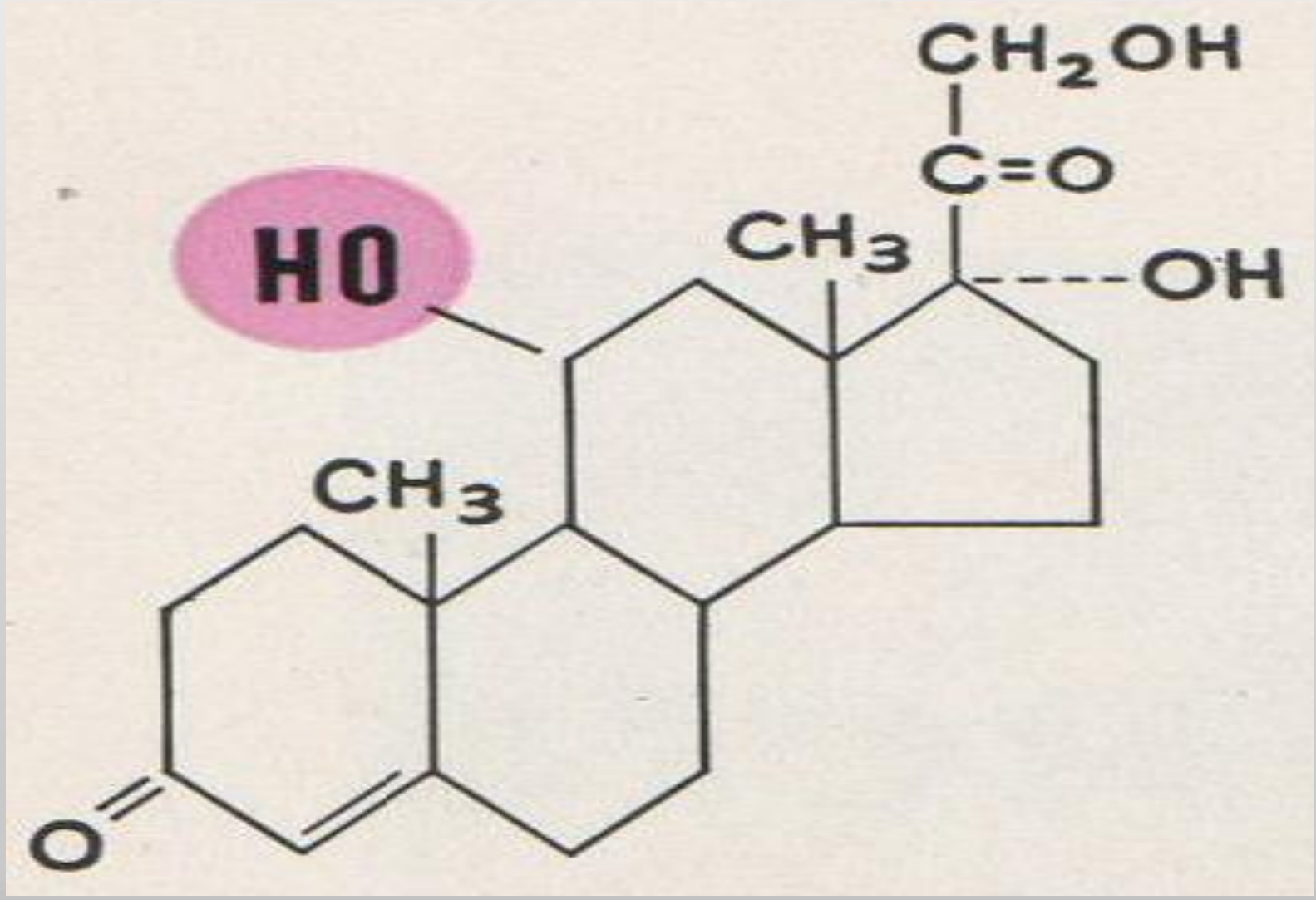
- Ethisterone
- Hydroxyprogesterone Caproate
- Methyltestosterone
- Progesterone
- Testosterone
- Testosterone Cypionate
- Testosterone Enanthate
- Testosterone Propionate

Sterols

- Sitosterol
- Stigmasterol

Specialty Chemicals

- Cycloheximide
- Streptozocin


CH2OH
C=O
HO
CH3
OH
CH3
O

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UPJOHN
Medrol
Medules
4 mg.
Upjohn
NATIONAL HISTORIC
CHEMICAL LANDMARK
Kalamazoo
CH_2OH
C=O
HO
CH_3
OH
CH_3
O
1950-1990
Steroid
Chemistry
Solu-Cortef
20 mg.
Upjohn