LEAGUE OF NATIONS.

Confidential. O.C./Confidential/15.

Geneva, July 20th, 1936.

ADVISORY COMMITTEE ON TRAFFIC IN OPIUM AND OTHER DANGEROUS DRUGS.

DESOMORPHINE (DIHYDRODESOXYMORPHINE-D).

Statement made by the Representative of the United States of America during the Twenty-first Session (May 1936).

Note by the Director of the Opium Traffic Section.

In accordance with the decision of the Advisory Committee, the Director has the honour to communicate herewith the statement made by the Representative of the United States of America on May 22nd, 1936, together with the annexes.

The members of the Committee will recall the information which I have presented at previous sessions in regard to the cooperative study undertaken in the United States under the leadership of the National Research Council in conjunction with the United States Public Health Service with a view to developing non-habit-forming substitutes for morphine and its derivatives. It will also be recalled that I reported particularly the discovery, by Dr. Lyndon F. Small, of an opium derivative which was given the name dihydrodesoxymorphine-D and stated that its manufacture for trade would not be permitted in the United States until thorough investigation of its therapeutic and scientific value and of its addictive properties should be completed.

I am now in a position to state that studies of dihydrodesoxymorphine-D by groups of individuals representing various scientific organizations and agencies, including the United States Public Health Service, indicate that it is a dangerous substance which possesses high addiction potentiality. In order that the Committee may know who the scientists are that have reached this conclusion and may have before it a picture of the methods followed in studying the subject, I take this opportunity of reading a memorandum from the Committee on Drug Addiction organized by the National Research Council to cooperate with the American Government in the endeavor to develop non-habit-forming substitutes for morphine and its derivatives.

MEMORANDUM ON

Dihydrodesoxymorphine-D.

Cooperating Agencies. In an effort towards a partial solution of the problem of drug addiction various interests and agencies representing the best thought in this country have entered into a cooperative movement for the interchange of ideas and the coordination of effort. These agencies are:

The National Research Council
The United States Public Health Service
The United States Bureau of Narcotics
The United States Bureau of Prisons
The United States Bureau of Patents
The Massachusetts Department of Public Health
The Rockefeller Foundation
The Department of Pharmacology, University of Michigan
The Department of Pharmacology, Harvard University
The Department of Pharmacology, Western Reserve University
The Division of Pharmacology, U.S. National Institute of Health
The Division of Chemistry, U.S. Department of Agriculture
The Division of Chemistry, U.S. National Institute of Health
The Division of Chemistry, University of Virginia.

Funds and Committee. As an approach to the subject of drug addiction the Rockefeller Foundation allotted a sum of money to the National Research Council which organized a special Committee on Drug Addiction for the study of this problem under the chairmanship of Dr. Wm. Charles White with members as follows:

Hon. H.J. Anslinger
U.S. Commissioner of Narcotics

Dr. Francis G. Blake
Professor of Medicine and Dean, School of Medicine, Yale University.

Prof. Charles W. Edmunds
Professor of Materia Medica and Therapeutics
University of Michigan

Dr. Ludvig Hektoen
Former Director, John McCormack Institute of Infectious Diseases

Prof. Claude S. Hudson
Professor and Chief, Division of Chemistry, U.S. National Institute of Health

Dr. Reid Hunt,
Professor of Pharmacology, Harvard University.

Frederick B. LaForge
Senior Chemist, U.S. Bureau of Chemistry & Soils.

Prof. Torald Sollmann
Professor of Pharmacology, Western Reserve University

Dr. Walter L. Treadway
Assistant Surgeon General in Charge
Division of Mental Hygiene,
U.S. Public Health Service

Dr. Carl Voegtlin,
Professor of Pharmacology and Chief,
Division of Pharmacology
U.S. National Institute of Health

Dr. Wm. Charles White (Chairman)
Former Chairman, Division of Medical Sciences, National Research Council
Chairman, Committee on Medical Research, National Tuberculosis Association.

Divisions of Work — The work of this committee is divided into three parts -

1. A chemical laboratory for the chemical analysis and synthesis of the opium alkaloids at the University of Virginia.

2. A laboratory for the pharmacological study of these substances at the University of Michigan.

3. Units for the clinical study of these substances in the hospitals of the Division of Mental Hygiene of the U.S. Public Health Service and in the hospitals of the Department of Public Health of Massachusetts.

University of Virginia. — The chemical division for the chemical analysis and synthesis of the opium alkaloids at the University of Virginia is under the direction of Lyndon F. Small, Research Associate in Organic Chemistry, and the following staff:

Erich Mosettig, Research Associate in Alkaloid Chemistry
Alfred Burger, " "
Jacob van de Kamp, " "
Lyon Southworth, " "
Ulysse Cormier, " "
R. E. Lutz, " "
John W. Krueger, " "
H. M. Fitch, " "
R. A. Robinson, " "
Burt Faris, " "

Some two hundred fifty substances, new and old, have been produced by chemical analysis or synthesis.

University of Michigan — The substances produced by the chemists are sent to the pharmacological laboratory at the University of Michigan where they are tested for their effect on animals. The staff here consists of:

Charles W. Edmunds, Professor of Materia Medica and Therapeutics
Nathan B. Eddy, Research Professor of Pharmacology
H. M. Krueger, Research Associate
C. I. Wright, " "
Elmer Mason, " "
William Sheldon, " "
Margaret Sumwalt, " "
Bertha Ahrens, " "
Freda Mohrmah, " "
A. T. Miller, " "

Clinical Studies at

When any substance gives indication of being valuable as a possible non-habit-forming substitute for morphine or its derivatives it is studied clinically in patients who are either addicted or in patients who are likely to become so as a result of the disease from which they suffer. Such studies have been conducted through the co-operation of the Division of Mental Hygiene of the U.S. Public Health Service on clinical material made available to that service.

United States Narcotic Farm

The main clinical studies in addicts are being made at the U.S. Narcotic Farm at Lexington, Kentucky. The staff at this institution is very expert and consists of:

Dr. Lawrence Kolb,
Medical Officer in Charge.
Dr. Justin K. Fuller,
Clinical Director.
Dr. C.K. Himmelsbach,
Pharmacologist.
Dr. Victor Vogel,
Psychiatrist.
Dr. Ralph R. Brown,
Psychologist.
Dr. E.G. Williams,
Pathologist and Director of Laboratories.
Dr. Fred W. Oberst,
Biochemist.

Pondville Hospital.

The clinical studies on non-addicts are made in the Massachusetts State Hospital for the study and Treatment of Cancer, the staff of which is as follows:

Dr. Henry D. Chadwick,
Commissioner of Public Health of Massachusetts.
Dr. Alton S. Pope,
Assistant Commissioner and Director of Tuberculosis.
Dr. George Parker,
Superintendent.
Dr. E.M. Daland,
Chief of Staff.
Dr. Ira T. Nathanson,
Clinician.
Dr. Wm. H. Roper,
Clinician.

Middlesex County Sanatorium. The clinical studies on non-addicts are also made in the State Tub rculosis Sanatorium the staff of which is as follows:

Dr. Henry D. Chadwick,
Commissioner of Public Health of Massachusetts.
Dr. Alton S. Pope,
Director of Tuberculosis for Massachusetts.
Dr. Sumner H. Remick,
Superintendent.
Dr. Donald S. King,
Associate Medical Director.
Dr. L.F. Davenport,
Clinician.

Dihydro-desoxy-morphine-D. Dihydrodesoxymorphine-D is one of the substances developed in the routine chemical analysis and synthesis of morphine and its derivatives.

Pharmacological Action. This drug was found by Dr. Eddy and his group to have analgesic properties approximately ten times as great as morphine in animals and so far as monkeys were concerned, in his judgment, to be free of addiction properties.

Patent Given U.S. At this point the committee, after conferences and preliminary studies, decided that steps should be taken to protect the public of the United States from the introduction of this drug if further studies should seem to make it an undesirable one. Accordingly Lyndon F. Small, the discoverer, obtained a patent and presented it to the United States Government in the person of the Secretary of the Treasury. This was done through the cooperation of the U.S. Public Health Service, the Bureau of Narcotics, and the Department of Justice.

Clinical Studies Made. Following the preliminary chemical and pharmacological work it became necessary to test the addiction property of dihydrodesoxymorphine-D in man. There are two methods available to-day of studying the addiction properties in man. One is to test the power of the drug to relieve the withdrawal symptoms of those already addicted, and the other is to study the reaction of non-addicts to this drug. In the latter case it is only possible to make this study on those individuals who are likely to become addicted, such as patients suffering from pain as in cancer or from cough as in tuberculosis. In a study on patients suffering with cancer or tuberculosis it must be remembered that pain and cough and the illness from which they result are complicating factors inthe study of the power of addiction.

Numerous studies were made at the clinical stations cooperating with the committee. The studies were made by expert clinicians, surgeons, and psychiatrists. The results have been carefully tabulated and passed on by a group of consultants and the members of the committee.

Results. The results of their observations and conclusions are as follows:

1. The analgesic effect of dihydrodesoxymorphine-D was stronger than dihydroheterocodein, dilaudid, heroin, morphine, codeine, isocodeine, and pseudocodeine.

2. Its reaction was more fleeting.

3. The dose had to be repeated more frequently than any of the other drugs mentioned above.

4. It was more powerful than any of the others in satisfying withdrawal symptoms but its effect in this was more fleeting.

5. Tolerance to dihydrodesoxymorphine-D developed more rapidly than to any of the others.

6. Its influence on the higher cerebral centres produced more excitement than any of the drugs mentioned above.

7. It had a marked depressant effect on the respiratory center and for this reason it was the opinion of the surgical group that it was not a satisfactory pre-operative or post-operative drug.

The American physicians are familiar with all of the claims made for this drug in some European publications for the control of pain both in prenarcosis and in post-operative conditions but, after their very careful studies, they have concluded that its addiction properties are greater than any drug now used and its ready solubility and the small dosage necessary may foster and encourage illicit traffic. The advantages of its use in the control of pain are off-set by its fleeting action. Its influence on the respiratory center makes it unsatisfactory for surgical use.

Recommendation of Committee on Drug Addiction. The Committee on Drug Addiction, after consideration of the results of the clincial studies, recommended by resolution that the drug, Dihydrodesoxymorphine-D, be not manufactured, distributed, or sold in the United States.

I may add that the United States Public Health Service concurs in the recommendations and resolutions of the National Research Council as set forth in this memorandum and has recommended that the manufacture, sale or distribution of dihydrodesoxymorphine-D in the United States be prohibited. Its import is already prohibited.

I suggest to the Committee the desirability of considering, in collaboration with the Health Committee, a recommendation to Governments that they should examine, in conjunction with the medical profession, the possibility and expediency of prohibiting the manufacture, importation, sale, distribution and use of dihydrodesoxymorphine-D, which is a dihydrogenated morphine in which the alcoholic hydroxyl group has been replaced by a hydrogen atom.

I am handing to the Secretariat a photostatic copy of American Letters Patent No. 1980972 which fully describes this drug and methods for its manufacture.

No.1980972

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

WHEREAS LYNDON FREDERICK SMALL, of Charlottesville, Virginia, assignor to GOVERNMENT OF THE UNITED STATES, represented by the Secretary of the Treasury,

Presented to the Commissioner of Patents a petition praying for the grant of letters patent for an alleged new and useful improvement in

MORPHINE DERIVATIVES AND PROCESSES FOR THEIR PREPARATION,

a description of which invention is contained in the specification of which a copy is hereunto annexed and made a part hereof, and complied with the various requirements of law in such cases made and provided, and

WHEREAS upon due examination made the said Claimant is adjudged to be justly entitled to a patent under the law.

Now therefore these LETTERS PATENT are to grant unto the said

Government of the United States, represented by the Secretary of the Treasury

For the term of SEVENTEEN years from the date of this grant

The exclusive right to make, use and vend the said invention throughout the United States and the Territories thereof.

In testimony whereof, I have hereunto set my hand and caused the seal of the PATENT OFFICE to be affixed at the City of Washington this thirteenth day of November, in the year of our Lord one thousand nine hundred and thirty-four, and of the Independence of the United States of America the one hundred and fifty-ninth.

Attest:

(Signed) H.S. Miller
Law Examiner.

(Signed) Conway P. Coe
Commissioner of Patents.

1,980,972

Patented Nov.13,1934.

UNITED STATES PATENT OFFICE

MORPHINE DERIVATIVE AND PROCESSES FOR ITS PREPARATION

Lyndon Frederick Small, Charlottesville, Va, assignor to Government of the United States, represented by the Secretary of the Treasury.

No Drawing. Application July 19th, 1934, Serial No. 736,108.

7 Claims. (Cl.260 - 25)

(Granted under the act of March 3,1883, as amended April 30, 1928; 370 O. G. 757)

The present invention is a new product of the morphine series and is superior in physiological action to most present known narcotics related to morphine, codeine and drugs of like action and which may serve to replace morphine, in pharmaceutical preparations and in medical applications.

The invention is more effective in producing analgesia, in effect on respiration and cough, and in general depressant action, but relatively free from convulsant, emetic and toxic effects, and is designed to replace morphine and other drugs of morphine-like action in therapeutic practice. It is intended to be administered by mouth, by rectum or by injection. In respect to effective dose it will be less costly - that is, the amount necessary for an effective dose would be less than morphine or codeine; consequently for an effective dose it would be less expensive than the equivalent amount of morphine or codeine.

The methods of producing the present product are simple in operation and relatively economical.

The invention, to be known chemically as dihydrodesoxy-morphine-D, represents a dihydrogenated morphine in which the alcoholic hydroxyl group has been replaced by a hydrogen atom.

The present product may be attained in three distinct ways: (1) by catalytic hydrogenation of the halogenomorphides; (2) by catalytic hydrogenation of the halogenocodides, followed by demethylation; (3) by catalytic hydrogenation of desoxy-morphine-C (see Journal of American Chemical Society, vol.55, page 2874 of 1933, particularly at page 2881) under special conditions.

The applicant is aware that German Patent No.414,598 of Knoll and Company claims the preparation of a substance of the formula of dihydrodesoxymorphine-D. Applicant has, however,

demonstrated that the product in the Knoll patent is actually a desoxymorphine which depresses the melting point of dihydrodesoxymorphine-D and is convertible to the latter by addition of two hydrogen atoms catalytically, and therefore can not be identical with it.

In producing the product of the invention by the first example mentioned above: Fifteen grams of alpha-chloromorphide, a well-known morphine drivative, dissolved in 150 cc of absolute methanol is shaken in the presence of 1 gram of palladium on barium sulphate in an atmosphere of hydrogen, whereby about 2064 cc. of hydrogen, more or less, is absorbed. The solution is then filtered and the solvent removed by distillation at atmospheric pressure, or preferably in vacuum at about 40° C. The resulting material is dissolved in water and the product precipitated out by slow addition of ammonia, sodiumcarbonate, or similar precipitants for phenolic substances, shaking into ether or other organic solvent, as chlorc form, benzene, etc. after each addition. The organic solvent is distilled to a small volume and traces of tetrahydrodesoxymorphine filtered out. The product remaining in the solvent crystallizes on rubbing with ethyl acetate. The yield is approximately 9.2 grams. The substance has the melting point 188-189° C. and has the specific rotation in absolute methanol

$$(a)D^{28} - 76.8^{o} \ (c = 1.614).$$

Analysis shows the composition to be $C_{17}H_{21}O_2N$.

As variations of this process, under the first example the well-known beta-chloromorphide, bromomorphide or iodomorphide may be used, and other noble metal catalysts or copper containing catalysts, or finely divided nickel in vario organic solvents as ethanol, benzene, etc., or in acid solutio may be employed as well as the neutral aqueous solution of the salts, or alkaline solution, but in a degree less satisfactory so far as experiments have shown, the neutral salts being more satisfactory than the alkaline solution.

The amounts of catalysts and solvent, above mentioned may be varied within wide limits without greatly changing the result. Also, hydrogen pressure below and especially above, atmospheric pressure may be employed.

The product may likewise be isolated advantageously in the form of salts, as oxalate, salicylate, hydrochloride, sulfate, etc. Dihydrodesoxymorphine D hydrochloride of formula

$$C_{17}H_{21}O_2N.HCl$$

has the specific rotation

$$(a)D^{27}-66.8^{o}(\text{water, } c=0.898).$$

Dihydrodesoxymorphine-D, sulfate of formula $(C_{17}H_{21}O_2N)_2H_2SO_4 + 2H_2O$, has the specific rotation

$$(a)D^{29}-57.9^{o}(\text{water, } c=1.425$$

These salts as well as numerous others such as the tartrate, phosphate and acetate are soluble in water and adapted to medical use.

In preparing the dihydrodesoxymorphine-D in accordance with the second example: Fifty grams of the well-known codeine derivative, alphachlorocodide, is dissolved in 160 cc. of dilute, preferably normal hydrochloric acid, 100 cc. of water and 2 grams of palladium on barium sulfate catalyst added, and the mixture shaken under hydrogen until absorption ceases. The amounts of these reagents and the strength of acid may be varied within wide limits without greatly changing the result. About 7600 cc of hydrogen is absorbed. The product of this hydrogenation, the known dihydrodesoxycodeine-D, is isolated after removal of the catalyst by treating the acid solution with excess of sodium carbonate, sodium hydroxide or other alkaline agents and extracting into ether or other organic solvents usually employed for extraction. The product is obtained in nearly quantitative yield when the organic solvent is distilled off, and is purified by crystallization from alcohol, acetone, benzene or other solvents, or may be purified advantageously as salts such as the tartrate, salicylate, sulfate and others. As variations of this process, other known halogenocodides as betachlorocodide, bromocodide or iodocodide may be used in organic solutions or in acid solutions, and alpha-chlorocodide may be used in organic solvents as ethanol, methanol, and others adapted as media for hydrogenation. Other catalysts, as the various known active forms of platinum, palladium, and nickel, and copper compounds may be employed. The dihydrodesoxycodeine-D is demethylated as follows: ten grams of dihydrodesoxycodeine-D is dissolved in 50 cc. of hydrobromic acid (48% HBr, sp. gr. 1.49) and boiled under a reflux condenser until the product is completely soluble in sodium hydroxide solution, requiring about 15 minutes. The reaction mixture is diluted with water, 500 cc. of ether, benzene, chloroform, etc. added and saturated sodium carbonate solution or ammonia in excess cautiously poured in. The precipitate of dihydrodesoxymorphine-D is extracted into the organic layer. Several more extractions yield a small additional amount of the drug. During the extraction, traces of tetrahydrodesoxymorphine, which is almost insoluble in organic solvents, are separated by filtration and discarded. The yield is about 8 grams of pure dihydrodesoxymorphine-D base. As variations of this demethylation, concentrated hydriodic acid may be used, or concentrated hydrochloric acid in a sealed tube at temperatures above 100°C. The amount and strength of the acids used for demethylation may be varied. The product may also be isolated as the crystalline hydrobromide or hydriodide salt when the acid solution is diluted.

In accordance with the third example mentioned above, of preparing the dihydrodesoxymorphine-D: A suspension of 2.27 grams of the well-known desoxymorphine-C hydrochloride (see Journal of American Chemical Society, vol. 55, page 2874 of 1933, particularly at page 2881) in 10 cc. of glacial acetic acid with 0.05 g. of platinum oxide or other platinum, palladium, nickel or copper containing catalyst is shaken under hydrogen until absorption ceases, the solution is freed from catalyst, diluted and treated with excess of ammonia, or sodium carbonate or bicarbonate or similar precipitants for phenolic substances. While the preferred quantities are here stated, the amounts of glacial acetic acid and catalyst may be varied within wide limits. The precipitate is extracted into ether or other organic solvent as

benzene or chloroform, and on distillation of the solvent, about 2.2 grams of oily material is obtained. This is rubbed with a little acetone, ethyl acetate or other organic solvent whereby the tetrahydrodesoxymorphine present crystallizes and can be filtered out. The mother liquor yields about 0.75 grams of dihydrodesoxymorphine-D which is purified by one of the methods described in connection with the first example.

As a variation of this process, the well-known desoxycodeine-C hydrochloride (see Journal American Chemical Society, vol. 53, page 2225 of 1931) or other desoxymorphine-C ethers may be hydrogenated, and the product so obtained de-etherified as described under the second example.

I have found that in the preparation of the product of this invention, the first and second examples constitute the more feasible and economical preparative methods while the third process is more difficult and involves considerable losses in material, giving a lower yield of the desired product.

The product of invention has a very great advantage over most narcotics in its extreme stability, so that solutions of its salts may be sterilized by boiling without any deterioration.

What I claim as new is:

1. A dihydromorphine derivative in which the alcoholic hydroxyl group of dihydromorphine has been replaced by hydrogen.

2. A new compound having the formula $C_{17}H_{21}O_2N$ and wherein two hydrogen atoms have been added to the alicyclic unsaturation in morphine and the alcoholic hydroxyl group replaced by a hydrogen atom.

3. The method of preparing a new product of the morphine series which includes catalytically hydrogenating a compound selected from the group consisting of halogenomorphides and desoxymorphine-C in the liquid phase.

4. The method of preparing a new product of the morphine series which includes catalytically hydrogenating a compound selected from the group consisting of the ethers of the halogenomorphides and of desoxymorphine-C in the liquid phase, and then de-etherifying the hydrogenation products.

5. The method of preparing a new product of the morphine series which includes catalytically hydrogenating solutions of the halogenomorphides in the presence of a catalyst selected from a group consisting of nickel, noble metals and copper-containing hydrogenation catalysts.

6. The method of preparing a new product of the morphine series which includes demethylation of dihydrodesoxycodeine-D by action of a hot concentrated acid selected from the group consisting of hydrobromic, hydriodic, and hydrochloric.

7. The method of preparing a new product of the morphine series which includes catalytic hydrogenation of organic acid solutions of desoxymorphine-C in the presence of a catalyst selected from a group consisting of nickel, noble metals and copper-containing hydrogenation catalysts.

LYNDON FREDERICK SMALL