PATENT SPECIFICATION

Inventor: RONALD SLACK

698,544

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Index at acceptance:—Class 2(iii), C1f3a(3: 4), C1f3(c5:d3), C1f4a(3: 4), C1f4(c5: d2), C1f4f(1: 4).

COMPLETE SPECIFICATION

Process for the Preparation of a Propane Derivative

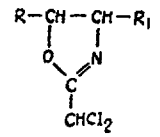
We, PARKE, DAVIS & COMPANY, a Corporation organised under the laws of the State of Michigan, United States of America, of Foot of Joseph Campau Avenue at the River, of Detroit, State of Michigan, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to the production of chemical compounds and in particular is concerned with the provision of a new and commercially useful synthesis of 2-dichloracetamido - 1-*para* - nitro-phenyl-propane 1:3-diol.

An optically active isomer of this acylamido-diol which is dextro-rotatory in ethanol solution is identical with the so-called natural product obtained by the fermentative growth of *Streptomyces Venezuelae* known under the generic name "Chloramphenicol"; it has marked anti-biotic activity and is an important therapeutic agent.

According to the present invention a process for the preparation of 2-dichloracetamido - 1 -*para*-nitrophenyl-propane 1:3-diol comprises treating a dichloromethyl oxazoline of 2-amino-1-*para*-nitrophenyl-propane 1:3-diol with dilute acid followed by neutralisation of the reaction mixture with a base at a temperature not greater than 30° C.

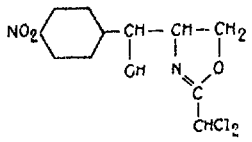
Thus, according to the present invention, 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol is obtained by treating with dilute acid, preferably dilute hydrochloric acid, an oxazoline of the formula:



I

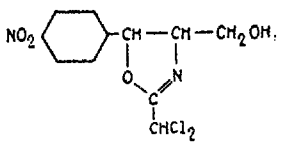
(where R represents a *para*-nitrophenyl group and R_1 represents a hydroxymethyl group or R represents a hydrogen atom and R_1 represents a *para*-nitrophenylhydroxymethyl group) and subsequently neutralising the reaction mixture with a base such as aqueous ammonia, at a temperature not exceeding 30° C.

These oxazolines have either the structure:



II

or the analogous structure:



III

Both of these oxazolines, as also the acylamido-diol to which, according to the invention, they are converted by careful hydrolysis contain two asymmetric carbon atoms and can exist in structural as well as optical isomeric forms. By analogy with the nomenclature adopted by Rebstock *et al* (J.A.C.S. Vol. 71 pp.

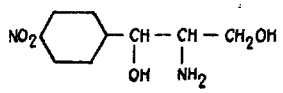
2458-2473) in connection with chloramphenicol and its isomers, the structural isomeric forms are herein referred to as "erythro" and "threo" respectively. Both the erythro and threo forms can exist as racemates of optically active isomers from which it will be appreciated that, strictly speaking, each compound can exist in six different forms and that, accordingly, for a given structural formula of conventional type as used herein, there are included the complete mixture of all six forms, the racemates of the erythro and threo series and the four individual isomers L-erythro, D-erythro, L-threo and D-threo. It should be noted that the configurational representation of the isomers as D and L bears no relation to the actual sign of the rotation but refers to the configuration about the alpha carbon atoms. The D-threo isomer of formula II has the same configuration with regard to the alpha carbon atom as the therapeutically active chloramphenicol isomer which has been designated D(—)-threo 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol.

The process of the present invention is preferably effected by warming the oxazoline with dilute mineral acid (dilute hydrochloric acid has given very satisfactory results) until dissolution is complete, cooling the reaction mixture and neutralising the same with ammonia. While, as indicated, ammonia is the base of choice other bases may also be employed e.g. alkali metal and alkaline earth metal hydroxides and strong organic bases such as triethylamine.

The step of neutralization is preferably effected at about room temperature. If conducted at a temperature substantially greater than 30° C., there is the possibility of hydrolysing the dichloracetamido group.

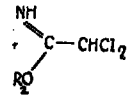
The process of this invention does not involve epimerisation. Thus, the DL- and D- threo oxazolines of formula II and III respectively yield the DL- and D- threo forms of 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol and, therefore, constitute preferred starting materials in the process. The DL racemic mixture may, of course, be resolved if desired. However, the DL- and L-erythro oxazolines are also of some importance since the erythro epimers of the aclyamido-diol which they produce when treated by the process of the invention can be converted by epimerisation into the threo forms.

The oxazolines hereinbefore referred to can be prepared by reacting a 2 - amino - 1-*para*-nitrophenyl-propane 1:3-diol of the formula:



IV

with an iminoether of the type:



V

(where R_2 represents the residue of an alcohol R_2OH) or with an acid addition salt of such ether. The resultant reaction mixture contains corresponding compounds of both types II and III which can be separated as, for example, by fractional crystallisation or chromatography. The production of the said oxazolines is described in co-pending Application No. 32127/49 (Serial No. ~~698,542~~ 698,542).

The amino-diol of formula IV, of course, contains two asymmetric carbon atoms and can exist in erythro and threo forms each of which can occur as racemate or D or L isomers. In the process of converting amino-diol into oxazoline above described there is no substantial inversion of erythro to threo form, or *vice versa*. There is, however, a substantial difference between the erythro and threo series as to the relative proportions of isomers of type II and type III produced. In the threo series, the proportion is substantially 2:3 while in the erythro series the product is substantially entirely erythro compound of type II with a minor percentage of erythro compound of type III.

The present invention includes the overall process of preparing 2-dichloracetamido - 1 - *para* - nitrophenyl-propane 1:3-diol (especially the DL- and D- threo forms) from 2-amino-1-*para*-nitrophenyl-propane 1:3-diol which comprises reacting the amino diol (preferably in the DL- or D- threo form) with a dichloracetimino ether or acid addition salt of such ether, separating from the reaction mixture either 2-~~dichloromethyl~~ - 4 - *para* - nitrophenyl dichloromethyl-hydroxymethyl-Δ^2-oxazoline or 2-dichloromethyl - 5 - *para* - nitrophenyl - 4 - hydroxymethyl-Δ^2-oxazoline and treating such oxazoline with dilute acid and subsequently neutralising the reaction mixture with a base as hereinbefore described.

The process of the present invention is illustrated by the following Examples:

EXAMPLE 1.

DL-Threo 2-dichloromethyl-4-*p*-nitro-

phenyl-hydroxymethyl-Δ^2-oxazoline was prepared as follows:

DL-Threo 2-amino-1-*p*-nitrophenyl-propane 1:3-diol as prepared by the method described by Rebstock *et al* (J.A.C.S. Vol. 71 pp. 2458-2473) (6.7 g.) was dissolved in warm dry pyridine (40 c.c.) and treated with dichloracetiminoethyl ether hydrochloride (6.7 g.). The mixture was allowed to stand at room temperature for some hours, and the pyridine hydrochloride was then removed by filtration. Evaporation of the solvent and crystallisation of the residue from methanol gave the oxazoline DL-threo 2-dichloromethyl-4-*p*-nitrophenyl-hydroxymethyl-Δ^2-oxazoline, m.p. 163-164° C. Found: C, 43.2; H, 3.3; N, 9.3; Cl, 23.0. $C_{11}H_{10}O_4N_2Cl_2$ requires C., 43.25; H, 3.18; N, 9.17; Cl, 23.2%.

0.6 Gm. of this oxazoline was treated with 3.0 c.c. of dilute hydrochloric acid and warmed gently to give a clear solution. Cooling followed by neutralisation with aqueous ammonia resulted in the precipitation of DL-threo 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol m.p. 153-154° C. after crystallisation from ethyl acetate—light petroleum mixture or from water containing a little methanol.

The optically pure D-threo oxazoline, m.p. 143—144° C., prepared from D(—)-threo 2-amino-1-*para*-nitrophenyl-propane 1:3-diol in manner analogous to the DL racemate hydrolysed similarly to give D(—)-threo 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol, m.p. 152—153° C.

EXAMPLE II.

DL-Erythro 2-dichloromethyl-4-*p*-nitrophenyl-hydroxymethyl-Δ^2-oxazoline was prepared as follows:

1.93 g. of racemic erythro 2-amino-1-*p*-nitrophenyl-propane 1:3-diol hydrochloride of m.p. 206—208° C. were dissolved in 15 c.c. of anhydrous pyridine. To this solution was added 1.8 g. of dichloracetiminoethyl ether hydrochloride of m.p. 80° C. The solution was left for 2 hours at room temperature when pyridine hydrochloride precipitated. The mixture was then poured into 100 c.c. of water. A product crystallised rapidly and was filtered off, washed with water and dried at 100° C. It was racemic erythro 2-dichloromethyl-4-*p*-nitro-phenylhydroxymethyl-Δ^2-oxazoline, m.p. = 167—168° C.

0.5 Gm. of the racemic oxazoline were dissolved at about 50° C. in 10 ccs of N/10 hydrochloric acid. On cooling there were added 2 ccs. of aqueous ammonia when DL-erythro 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol melting (on re-crystallisation) at 170—172° C. precipitated.

EXAMPLE III.

D-threo 2-dichloromethyl-5-*para*-nitrophenyl-4-hydroxymethyl-Δ^2-oxazoline was prepared as follows:

D(-)-Threo 2-amino-1-*p*-nitrophenyl-propane 1:3-diol as prepared by the method described by Rebstock *et al* (J.A.C.S. Vol. 71 pp. 2458—2473) (1.65 g.) was dissolved in warm dry pyridine (10 c.c.) and treated with dichloracetiminoethyl ether hydrochloride (1.8 g.). The mixture was allowed to stand at room temperature for some hours, and the pyridine hydrochloride was then removed by filtration. Evaporation of the solvent and treatment with methanol gave a preciptate which was filtered off. The filtrate was evaporated to dryness and the residue fractionally crystallised from benzene to give the oxazoline D-threo 2-dichlormethyl-5-*p*-nitrophenyl-4-hydroxymethyl-Δ^2-oxazoline, m.p. 132—133° C. and $(\alpha)_D^{20} = -13.65°$ (C = 6.5% in ethyl acetate). Found: C, 42.9; H, 3.18; N, 9.15; Cl, 23.2. $C_{11}H_{10}O_4N_2Cl_2$ requires C, 43.25; H, 3.18; N, 9.17; Cl, 23.2%.

0.5 Gm. of this oxazoline were treated with sufficient warm, dilute hydrochloric acid to effect complete solution. Rapid cooling, followed by addition of concentrated aqueous ammonia to neutrality gave D-threo 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol. Recrystallisation from a mixture of ethyl acetate and light petroleum gave the pure compound, m.p. 151° C. $(\alpha)_D^{20} = +25°$ (in ethyl acetate).

EXAMPLE IV.

0.75 Gm. of DL-threo 2-dichloromethyl-5-*para*-nitrophenyl-4-hydoxymethyl-Δ^2-oxazoline m.p. 128—129° C., prepared in manner analogous to the D-isomer of Example III, were treated with 12 ccs. of dilute hydrochloric acid and the mixture warmed gently to give a clear solution. Treatment with aqueous ammonia as described in Example III gave an almost theoretical yield of DL-threo 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol m.p. 150° C., after recrystallisation from a mixture of ethyl acetate and light ~~recrystallisation from a mixture of ethyl acetate and light~~ petroleum.

What we claim is:—

1. Process for the preparation of 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol which comprises treating a dichloromethyl oxazoline of 2-amino-1-*para*-nitrophenyl-propane 1:3-diol with dilute acid followed by neutralisation of the reaction mixture with a

phenyl-hydroxymethyl-Δ^2-oxazoline was prepared as follows:

DL-Threo 2-amino-1-*p*-nitrophenyl-propane 1:3-diol as prepared by the method described by Rebstock *et al* (J.A.C.S. Vol. 71 pp. 2458-2473) (6.7 g.) was dissolved in warm dry pyridine (40 c.c.) and treated with dichloracetiminoethyl ether hydrochloride (6.7 g.). The mixture was allowed to stand at room temperature for some hours, and the pyridine hydrochloride was then removed by filtration. Evaporation of the solvent and crystallisation of the residue from methanol gave the oxazoline DL-threo 2-dichloromethyl-4-*p*-nitrophenyl-hydroxymethyl-Δ^2-oxazoline, m.p. 163-164° C. Found: C, 43.2; H, 3.3; N, 9.3; Cl, 23.0. $C_{11}H_{10}O_4N_2Cl_2$ requires C., 43.25; H, 3.18; N, 9.17; Cl, 23.2%.

0.6 Gm. of this oxazoline was treated with 3.0 c.c. of dilute hydrochloric acid and warmed gently to give a clear solution. Cooling followed by neutralisation with aqueous ammonia resulted in the precipitation of DL-threo 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol m.p. 153-154° C. after crystallisation from ethyl acetate—light petroleum mixture or from water containing a little methanol.

The optically pure D-threo oxazoline, m.p. 143—144° C., prepared from D(—)-threo 2-amino-1-*para*-nitrophenyl-propane 1:3-diol in manner analogous to the DL racemate hydrolysed similarly to give D(—)-threo 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol, m.p. 152—153° C.

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0.5 Gm. of the racemic oxazoline were dissolved at about 50° C. in 10 ccs of N/10 hydrochloric acid. On cooling there were added 2 ccs. of aqueous ammonia when DL-erythro 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol melting (on re-crystallisation) at 170—172° C. precipitated.

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0.5 Gm. of this oxazoline were treated with sufficient warm, dilute hydrochloric acid to effect complete solution. Rapid cooling, followed by addition of concentrated aqueous ammonia to neutrality gave D-threo 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol. Recrystallisation from a mixture of ethyl acetate and light petroleum gave the pure compound, m.p. 151° C. $(\alpha)_D^{20} = +25°$ (in ethyl acetate).

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0.75 Gm. of DL-threo 2-dichloromethyl-5-*para*-nitrophenyl-4-hydoxymethyl-Δ^2-oxazoline m.p. 128—129° C., prepared in manner analogous to the D-isomer of Example III, were treated with 12 ccs. of dilute hydrochloric acid and the mixture warmed gently to give a clear solution. Treatment with aqueous ammonia as described in Example III gave an almost theoretical yield of DL-threo 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol m.p. 150° C., after recrystallisation from a mixture of ethyl acetate and light petroleum.

What we claim is:—

1. Process for the preparation of 2-dichloracetamido-1-*para*-nitrophenyl-propane 1:3-diol which comprises treating a dichloromethyl oxazoline of 2-amino-1-*para*-nitrophenyl-propane 1:3-diol with dilute acid followed by neutralisation of the reaction mixture with a

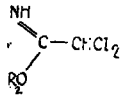
* C L M S *

base at a temperature not greater than 30° C.

2. Process according to claim 1 wherein the oxazoline starting material is a 2 - dichloromethyl - 4-*para*-nitrophenyl-hydroxymethyl-Δ^2-oxazoline.

3. Process according to claim 1 or 2 wherein the neutralisation is carried out using aqueous ammonia.

4. Process according to claim 1 which comprises reacting 2-amino-1-*para*-nitrophenyl-propane 1:3-diol with an imino ether of the type



or with an acid addition salt thereof (where R_2 represents the residue of an alcohol R_2OH) and treating the reaction product so produced with dilute acid followed by neutralisation of the reaction mixture with a base at a temperature not greater than 30° C.

5. Process according to any of the preceding claims in which the starting material has the threo structural form.

For the Applicants,
J. A. KEMP & CO.,
Chartered Patent Agents,
Bank Chambers, 329 High Holborn,
London, W.C.1.

PROVISIONAL SPECIFICATION
No. 32129 A.D. 1949.

Process for the Preparation of a Propane Derivative

We, PARKE, DAVIS & COMPANY, a Corporation organised under the laws of the State of Michigan, United States of America, of Foot of Joseph Campau Avenue at the River, of Detroit, State of Michigan, United States of America, do hereby declare the nature of this invention to be as follows:—

This invention is for improvements in or relating to the production of a therapeutically useful organic compound, namely N - dichloroacetyl - 1 - *p* - nitrophenyl-2-amino-propane-1:3-diol which has been demonstrated to have an important place in therapeutics and which is known under the common name "Chloramphenicol".

It is the object of the present invention to provide a new and useful synthesis of chloramphenicol.

The process of the present invention consists in treating 2-dichloromethyl-4-[(*p* - nitrophenyl) - hydroxymethyl] - oxazoline under conditions such that fission of the oxazoline ring occurs between the ring oxygen atom and the adjacent methylene group.

According to a feature of the invention, such fission is effected by treating the oxazoline with dilute acid, conveniently hydrochloric acid, and warming until dissolution is complete. Cooling, followed by basification with a suitable base such as ammonia, results in precipitation of the desired product.

The oxazoline starting material may be obtained by treating 1-*p*-nitrophenyl-2-amino-propane-1:3-diol with dichloroacetimino ethyl ether (see the specification of co-pending Application No. 32127/49 of even date) (Serial No. 698,542) itself obtainable from dichloroacetonitrile by treatment with dry hydrogen chloride and dry alcohol in an inert solvent (see the specification of co-pending Application No. 32128/49 of even date) (Serial No. 698,543).

The present invention includes the over-all process hereinbefore described in which th starting material is dichloroacetonitrile.

The present invention is illustrated by the following Example:

0.6 Gm. of *dl* - 2 - dichloromethyl-4-[(*p*-nitrophenyl)-hydroxymethyl] oxazoline, prepared by the method of the Example in the specification of co-pending Application of 32127/49 (Serial No. 698,542) of even date herewith, was treated with 3.0 c.c. of dilute hydrochloric acid and warmed gently to give a clear solution. Cooling followed by neutralisation with aqueous ammonia resulted in the precipitation of N-dichloroacetyl-1-*p*-nitrophenyl - 2 - amino-1:3-propane diol, m.p. 153—154° C., after crystallisation from ethyl acetate—light petroleum mixture or from water containing a little methanol.

The optically pure *l*-oxazoline, m.p. 134—135° C., also described in the aforesaid Example, hydrolysed similarly to give *l*-N-dichloroacetyl-1-p-nitrophenyl-2-amino-propane-1:3-diol, m.p. 152—153° C.

Dated this 14th day of December, 1949.

For the Applicants,
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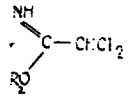
base at a temperature not greater than 30° C.

2. Process according to claim 1 wherein the oxazoline starting material is a 2 - dichloromethyl - 4-*para*-nitrophenyl-hydroxymethyl-Δ^2-oxazoline.

3. Process according to claim 1 or 2 wherein the neutralisation is carried out using aqueous ammonia.

4. Process according to claim 1 which comprises reacting 2-amino-1-*para*-nitrophenyl-propane 1:3-diol with an imino ether of the type



or with an acid addition salt thereof (where R_2 represents the residue of an alcohol R_2OH) and treating the reaction product so produced with dilute acid followed by neutralisation of the reaction mixture with a base at a temperature not greater than 30° C.

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The process of the present invention consists in treating 2-dichloromethyl-4-[(*p* - nitrophenyl) - hydroxymethyl] - oxazoline under conditions such that fission of the oxazoline ring occurs between the ring oxygen atom and the adjacent methylene group.

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For the Applicants,
J. A. KEMP & CO.,
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PROVISIONAL SPECIFICATION
No. 9063 A.D. 1950.

Process for the Preparation of a Propane Derivative

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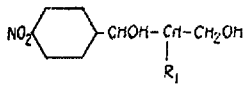
This invention is for improvements in or relating to the production of therapeutically, or otherwise, useful compounds of the type:

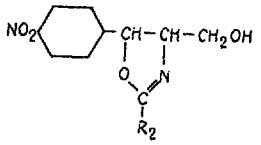


I

where R_1 represents a halogen substituted lower aliphatic acylamino group.

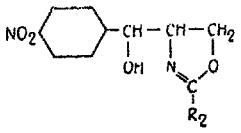
The object of the present invention is to provide a new and useful synthesis of the foregoing compounds.

According to the present invention, the compounds of general formula I are prepared by treating an oxazoline selected from the class consisting of the compounds of the general formulae:



II

or

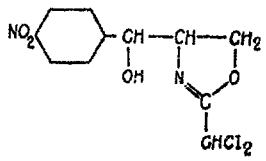


III

(R_2 being the radical necessary with the group -NHCO to complete the radical R_1) under conditions such that fission of the oxazoline ring occurs between the ring oxygen atom and an adjacent ring carbon atom.

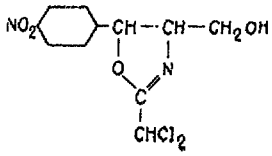
The oxazoline starting materials are conveniently prepared by the process described in the specification of co-pending Application No. 32127/49 (Serial No. 698,542) and, as mentioned in that specification, exist in structural as well as optical isomeric forms. The structural isomeric forms are—for the reasons advanced in the aforesaid specification—herein designated the "erythro" and "threo" forms respectively. Both the erythro and the threo forms can exist as racemates of optically active isomers from which it will be appreciated that, strictly speaking, all of the compounds of the present invention can exist in six different forms, and that, accordingly, for a given structural formula of conventional type as used herein, there are included the complete mixture of all six forms, the racemates of the erythro and threo series and the four individual isomers, *d*-erythro, *l*-erythro, *d*-threo and *l*-threo.

In the specification of co-pending Application No. 32129/49 (Serial No. 698,544) we have described a synthesis of the (at present) most important member of the class of compounds having the general formula I which consists in treating 2 - dichloromethyl - 4-[(*p*-nitrophenyl)-hydroxymethyl]-oxazoline under conditions such that fission of the oxazoline ring occurs between the ring oxygen atom and the adjacent methylene group, such fission being preferably effected by treating the oxazoline with dilute acid, conveniently hydrochloric acid, and warming until dissolution is complete. Cooling, followed by basification with a suitable base such as ammonia, results in precipitation of the desired product, namely, N - dichloracetyl - 1 - *p*-nitrophenyl-2-amino-propane-1:3-diol otherwise known as chloramphenicol. It has now been confirmed that the specific oxazoline employed in the Example of the aforesaid specification is the *dl*-threo compound of the structure:



IV

It has furthermore been found that the corresponding oxazoline of the formula:



V

can in a similar manner be converted into the same final product.

Where a particular racemic form of the final product of type I is desired, it will usually be advantageous that the oxazoline starting material has the same isomeric form. Where individual optical isomers are required, the corresponding racemic mixture of oxazoline isomers may be employed with subsequent resolution of the isomers of the final product or the oxazoline racemic mixture can be resolved in a preliminary stage.

It will, of course be appreciated that by making use of the process of epimerisation it is also possible, for the purpose of preparing the threo series of type I, to employ the erythro oxazoline series. Thus the specific oxazoline IV and the corresponding compound V which can exist in six isomeric forms as hereinbefore explained may be available in a total of eight different forms for the production of the threo forms of the final product.

Dated this 12th day of April, 1950.

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