AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller-General, dated the fourth day of November, 1958, under Section 14, of the Patents Act, 1949.

PATENT SPECIFICATION

Inventor: BASIL JASON HEYWOOD

692,265

Date of filing Complete Specification (under Section ~~16 of the Patents and Designs Acts, 1907 to 1946~~ 3(3) of the Patents Act 1949) May 21, 1951.

Application Date: May 19, 1950. No. 12622/50.

Application Date: July 21, 1950. No. 18308/50.

Complete Specification Published: June 3, 1953.

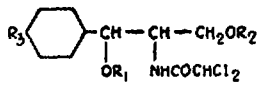
Index at acceptance:—Class 2(iii), C1f1a(3:4), C1f1b, C1f1c(2:4:5:6:7), C1f1d(2:3), C1f4a(3:4), C1f4b, C1f4c(2:4:5:6:7), C1f4d(2:3), C1f4f(1:4), C2a(3:13), C2r15.

COMPLETE SPECIFICATION

Improvements in or relating to Dichloracetamides

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, 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 present invention relates to the preparation of dichloracetamides and is particularly concerned with the preparation of N-dichloracetyl derivatives of the general formula:



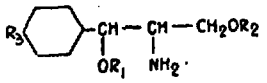
I

in which: R_1 and R_2 are each a hydrogen atom or together constitute a $—CHR_4—$ group in which R_4 represents a hydrogen atom or an alkyl group containing not more than 4 carbon atoms, or an aryl group and R_3 represents a hydrogen atom or a nitro group. In a preferred form of this invention, R_1 and R_2 each represent a hydrogen atom.

Various processes have heretofore been employed for the preparation of certain of these compounds; thus, for example, the acid chloride, anhydride, or esters of dichloracetic acid are known to react with the appropriate amines to give compounds of type I in which R_1 and R_2 represent hydrogen atoms.

It is the object of the present invention to provide improved syntheses of the aforesaid compounds which offer commercial advantage over those hitherto employed.

In accordance with this invention, the N-dichloracetyl derivatives of the type I are prepared by reacting the corresponding amines of the type:



II

with chloral cyanhydrin, or with chloral and an alkali metal cyanide, or with chloral hydrate and an alkali metal cyanide, in the presence of an acid-binding agent. If desired, the chloral cyanhydrin may first be treated with an acid-binding agent and the reaction product so-obtained used as the dichloracetylating agent.

In accordance with a feature of this invention, the alkali metal cyanide is employed in quantity less than one molecular equivalent of the reacting amine.

In carrying the present invention into effect, the acid-binding agent used may be an inorganic or a tertiary organic base or an excess of the reacting amine or, when such is to be present in the reaction mixture as catalyst, an excess of alkali metal cyanide catalyst. The preferred acid-binding agents are strong tertiary organic bases such as triethylamine when chloral cyanhydrin is employed directly as the dichloracetylating agent, whereas when chloral or chloral hydrate is used inorganic bases such as precipitated calcium carbonate, magnesium oxide and sodium carbonate have been found to be most advantageous.

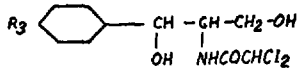
The reaction medium may be aqueous or non-aqueous and, of organic solvents, both dioxan and pyridine have been found to be very suitable, the preferred reaction medium when chloral or chloral hydrate is employed

being water and, when chloral cyanhydrin is employed, dioxan.

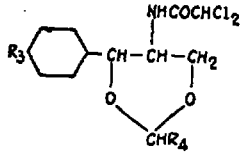
When chloral cyanhydrin is employed as such, the reaction is preferably effected at a temperature of 0—25°C. while, when chloral or chloral hydrate is employed in the presence of cyanide catalyst, it is preferred to increase the reaction temperature to 60—100°C.

In addition to the high degree of purity and the excellent yields in which the products are obtained, a further advantage of the process of the present invention is that, using chloral cyanhydrin direct, the reaction proceeds at normal temperatures thus enabling simpler procedures to be used than those of the methods previously employed.

The products of this invention can be regarded as comprising the compounds of the type III and those of type IV.



III



IV

These compounds, like the amines from which they are prepared, each contain two asymmetric carbon atoms and can exist in structural as well as optical isomeric forms. The term "structural" refers to the spatial relationship of the polar groups respectively attached to the two asymmetric carbon atoms. In conformity with the nomenclature adopted by M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Bartz, and L. M. Long and H. D. Troutman in the Journal of the American Chemical Society 1949, Volume *71*, pages 2458 to 2475, the diastereoisomeric forms are designated "erythro" and "threo" respectively.

Both the erythro and the threo forms can exist as racemates of optically active isomers whence it follows that each compound can exist in six different forms and, accordingly, a given structural formula of the conventional type as used herein, represents any of the forms, the racemates of the erythro and threo series and four individual isomers, D-erythro, L-erythro, D-threo and L-threo or a mixture of two or more of these forms unless otherwise stated.

An especially important feature of the present invention consists in the production of DL- and L-erythro compounds of type III employing the corresponding amines of type II, which compounds of type III are valuable intermediates for the production of the therapeutically active D-threo 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol, commonly known as chloramphenicol, and the DL-mixture containing the same. The compounds of type IV may be converted into those of type III by hydrolysis. An important feature of the present invention consists in the production of the therapeutically active D-threo-2-dichloracetamido-1-*p*-nitrophenyl propane-1:3-diol, commonly known as chloramphenicol, employing the corresponding D-threo amine of type II.

The present invention is illustrated by the following Examples.

EXAMPLE I

To a stirred and refluxing mixture of DL-erythro 5 - amino-4-phenyl-2-methyl-1:3-dioxan (19.3 g.) precipitated calcium carbonate (12.0 g.) sodium cyanide (0.95 g.) and water (45 c.c.), a solution of chloral hydrate (23.4 g.) in water (10 c.c.) was added cautiously over ten minutes. The reaction mixture was stirred and refluxed for ten minutes further and then allowed to cool. Sufficient hydrochloric acid was added to the stirred reaction mixture to render it acid to Congo Red. The DL-erythro 5-dichloracetamido-4-phenyl-2-methyl-1:3-dioxan (25.5 g.) 85% of theory was filtered off and dried at 100°C. The amide may be crystallised from methanol when it separates in colourless crystals m.p. 220—222°C.

EXAMPLE II

To a stirred mixture at 95°C. of DL-erythro 5 - amino-4-phenyl-2-methyl-1:3-dioxan (3.94 g.), dioxan (5 c.c.), water (5 c.c.), sodium cyanide (0.2 g.) and sodium acetate crystals (4.5 g.) was added a solution of chloral hydrate (4.67 g.) in water (2 c.c.) over 30 seconds. The emulsion was stirred at 95—100°C. for 10 minutes and then seeded with crystals of the desired product, when the mass crystallised. The mixture was cooled to 15°C., made acid to Congo Red and the reaction product isolated. The product, DL-erythro 5-dichloracetamido-4-phenyl-2-methyl-1:3-dioxan, melted at 216—217°C. One crystallisation of this product from methanol gave a pure product, melting at 224°C.

EXAMPLE III

In place of 19.3 g. of DL-erythro 5-amino-4-phenyl-2-methyl-1:3-dioxan used in Example I, 21.2 g. of DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol were employed. The dichloracetyl derivative, DL-threo 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was filtered off as in Example I and a further quantity obtained by extraction of the aqueous filtrate with ethyl acetate and evaporation of the extract. The total yield was 28.1 g. which is 87% of theory. Crystallisation from a mixture of ethyl acetate and petroleum ether gave an almost colourless product melting at 150°C.

EXAMPLE IV

A mixture of DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol, (0.53 g.), magnesium oxide (0.125 g.), sodium cyanide (0.05 g.) and water (2.5 c.c.) was stirred and heated to the boiling point. A solution of chloral hydrate (0.582 g.) in water (1 c.c.) was added over ½ minute and the reaction was allowed to stir and reflux for 10 minutes. The cooled reaction mixture was made acid to Congo Red by the addition of hydrochloric acid and the crystalline product filtered off, washed with a little water and dried. The yield of DL-erythro 2 - dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol obtained was 65% of theory.

EXAMPLE V

To a mechanically stirred solution at 40°C. of DL - erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol (0.53 g.), sodium carbonate (anhydrous 0.325 g.), sodium cyanide (0.05 g.) and water (2.5 c.c.) was added over ½ minute a solution of chloral hydrate (0.625 g.) in water (1 c.c.). The product, DL-erythro 2-dichloracetamido - 1 - *p*-nitrophenylpropane 1:3-diol, was isolated in the same way as described in Example IV.

EXAMPLE VI

The sodium cyanide (0.05 g.) employed in Example V, was replaced by potassium cyanide (0.066 g.), and gave the same reaction product.

EXAMPLE VII

Proceeding as in Example V but replacing the DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol by the optically active dextro rotatory L isomer hydrochloride [$(\alpha)_D$ = +15.8° (c=6% in water)], there was obtained L-erythro 2 - dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol, m.p. 173—5°C.

EXAMPLE VIII

To a stirred solution of DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol (0.53 g.) and potassium cyanide (0.216 g.) in water (2.5 c.c.) at 40°C. was added a solution of chloral hydrate (0.496 g.) in water (2.5 c.c.). The reaction mixture was stirred for 10 minutes and then the product isolated as described in Example IV. The yield obtained of DL-erythro 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was 72% of theory.

EXAMPLE IX

To a stirred suspension of DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol (0.53 g.), magnesium oxide (0.756 g.), sodium cyanide (0.061 g.) and water at 40°C. was added over 10 minutes a solution of chloral hydrate (0.62 g.) in water (1 c.c.). The DL-erythro 2 - dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol obtained was isolated as described in Example IV. The yield was 60% of theory.

The reaction can be carried out at 100°C. with a slightly improved yield.

EXAMPLE X

A mixture of DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol (2.12 g.) chloral hydrate (2.20 g.) dry pyridine (5 c.c.) and sodium cyanide (0.7 g.) was heated on the steam bath for some hours. The solution was poured into water and the precipitated solid filtered off and dried at 100°C. After crystallisation from ethyl acetate-petroleum ether mixture, the DL-threo 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol so obtained melts at 150—151°C.

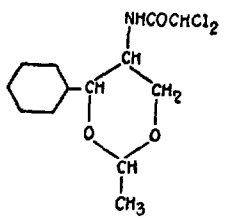
The reaction medium, pyridine, used in this Example can be replaced by dioxan with a similar result.

EXAMPLE XI

DL - erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol hydrochloride (2.5 g.) of m.p. 208—211°C. was suspended in anhydrous dioxan (12 c.c.) with anhydrous pyridine (1.9 c.c.). After cooling to +10°C., chloral hydrate (2.56 g.) was added. The temperature rose to +15°C., and after recooling to +8°C., sodium cyanide (0.87 g.; 95% purity) was added; the temperature rose to 30°C. The milky solution obtained was agitated for two hours at ordinary temperature, then diluted with distilled water (40 c.c.) and left to stand for one hour in an ice-bath. The product which crystallised was separated off, washed with water and dried *in vacuo*. A crude product (2.4 g.) of m.p. 150—160°C. was obtained which on recrystallisation and decolourisation with charcoal in boiling water (50 c.c.) gave DL-erythro 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol, m.p. 169.5—170.5°C.

EXAMPLE XII

Chloral cyanhydrin (10.9 g.) was dissolved in dioxan (20 c.c.) and cooled in an ice-water bath while DL-erythro 5-amino-4-phenyl-2-methyl-1:3-dioxan (9.65 g.) (m.p. 73—75°C.) was added over five minutes. To the cooled solution was added slowly triethylamine (10 g.). The almost solid suspension was allowed to stand at normal temperature for 14 hours and then poured on to ice and water. After standing for some time, the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid and the solid was filtered off. The yield of DL-erythro 5-dichloracetamido - 4 - phenyl-2-methyl-1:3-dioxan was 90% of theory. After purification the melting point was 220—224°C. The product is believed to have the formula:



EXAMPLE XIII

Chloral cyanhydrin (10.9 g.) was dissolved in dioxan (20 c.c.) and cooled in an ice-water bath while DL-threo 5-amino-4-phenyl-2-methyl-1:3-dioxan (9.65 g) (b.p. 85—87°C./0.04 mm.; picrate m.p. 223°C.) was added over five minutes. To the cooled solution was added slowly triethylamine (10 g.) and the suspension was then allowed to stand at normal temperature for ten hours. The suspension was poured on to ice and water and, after allowing to stand for a few hours, the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid. The dichloracetyl derivative was filtered off and washed with water. The yield (15.18 g.) of DL-threo 5-dichloracetamido-4-phenyl-2-methyl-1:3-dioxan was 100%. The purified product melted at 131—131.5°C. This product is also represented by the same structural formula as shown in Example XII, although of course, they are different chemical compounds.

EXAMPLE XIV

DL - erythro 5-amino-4-phenyl-2-methyl-1:3-dioxan (1.93 g.) (m.p. 73—75°C.) was dissolved in 2N hydrochloric acid (5 c.c.) and water (10 c.c.). The solution was cooled to 0° C. and chloral cyanhydrin (2.25 g.) added. To this stirred and cooled solution was added 2N sodium hydroxide over half an hour. The suspension was allowed to stand overnight when the crystalline solid was filtered off, washed with water and dried. The yield (2.0 g.) of DL-erythro 5-dichloracetamido-4-phenyl-2-methyl-1:3-dioxan was 66% of theory.

EXAMPLE XV

DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol (4.24 g.) was dissolved in pure hot dioxan (25 c.c.) and the solution allowed to crystallise in an ice-water bath. When the temperature had reached 10°C. solid chloral cyanhydrin (4.5 g.) was added, followed, after standing for five minutes, by the addition over a period of about 5 minutes of a solution of triethylamine (5.5 c.c.) in dioxan (12 c.c.). The last addition caused an exothermic reaction to take place and the temperature was maintained below 30°C. by cooling in an ice-water bath. The pale brown suspension was allowed to stand overnight at normal temperature and then poured on to ice (100 g.) and water (200 g.). After standing for four hours, the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid. The dichloracetyl derivative was filtered off and washed with water. The aqueous filtrate was extracted with ethyl acetate and, after concentration to small volume, a little petroleum ether added which caused a further quantity of the dichloracetyl derivative to separate. The yield (6.40 g.) of DL-threo 2-dichloracetamido-1-*p*-nitrophenyl-propane 1:3-diol (commonly known as racemic Chloramphenicol) was 99% of theory and it melted at 149—151°C. It was obtained as an almost colourless crystalline solid.

EXAMPLE XVI

The triethylamine (5.5 c.c.) in dioxan (12 c.c.) used in Example XV was replaced by anhydrous sodium carbonate (2.6 g.). The yield of DL-threo 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was not, however, as great as that obtained in Example XV.

EXAMPLE XVII

Chloral cyanhydrin (4.3 g.) was added to dry pyridine (15 c.c.) and immediately afterwards DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol (4.2 g.) was added to the cooled solution. The internal temperature rose to 40°C. and the mixture was heated on a steam bath for 15 minutes. The light brown solution was poured on to water and ice and, after standing for one hour, acidified with concentrated hydrochloric acid. The DL-threo 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was filtered off and crystallised from a mixture of ethyl acetate and petroleum ether. The product was identical with that of Example XV.

EXAMPLE XVIII

DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol hydrochloride (2.49 g.) was dissolved in water (15 c.c.). Chloral cyanhydrin (2.5 g.) was dissolved in this solution and, after cooling to 0°C., triethylamine (3.0 g.) was added drop by drop over five minutes with shaking between each addition. An oil was deposited which solidified after shaking for half an hour. The suspension was allowed to stand for four hours and then made acid to Congo Red by the addition of concentrated hydrochloric acid. The DL-threo 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was filtered off, washed with water and dried. The yield (3.15 g.) was 97% of theory. The product is the same as that of Example XV.

EXAMPLE XIX

A mixture of L-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol hydrochloride (12.6 g.) (m.p. 194—8°C. $(\alpha)_D = +15.8°$, (c=6% in water)), dry dioxan (65 c.c.) and dry triethylamine (6.2 c.c.) was allowed to stand at laboratory temperature for one hour. Chloral cyanhydrin (11.8 g.) was added over five minutes and the mixture cooled in an ice bath. Three amounts of triethylamine (5 c.c., 5 c.c., and 2.5 c.c.) were added with good stirring at intervals of five minutes. The slightly brown crystalline magma was allowed to stand at laboratory temperature overnight. The triethylamine hydrochloride was filtered off and washed with dioxan. The combined filtrates were evaporated to about 50 c.c. under reduced pressure and, after cooling, the solid collected and washed three times with water. The dioxan filtrate and the aqueous washings were combined and extracted with ethyl acetate to yield, on concentration, a second yield of pro-

duct. The total yield obtained of L-erythro 2-dichloracetamido - 1 - *p*-nitrophenylpropane 1:3-diol, m.p. 178°C. $(\alpha)_D = -25.8°$ (c=4% in acetone), was 12.8 g. or 78% of theory.

EXAMPLE XX

DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol (4.24 g.) of m.p. 108—109°C. was dissolved in anhydrous dioxan (25 c.c.) by heating to 70°C. The solution was cooled to +10°C. and at this temperature chloral cyanhydrin (4.5 g.) was added. After 5 minutes a solution of anhydrous triethylamine (4.0 g.) in dioxan (12 c.c.) was run in, keeping the temperature at about 30°C. The mixture was stirred for 2 hours at ordinary temperature, then left to stand overnight. The product which crystallised was filtered off and the filtrate evaporated under reduced pressure. The residue of the filtration and the residue of the evaporation were taken up in water (35 c.c.), and, after acidifying with sulphuric acid and filtering, the crude product obtained (6.64 g.) was recrystallised in water. There were obtained 4.66 g. of DL-erythro 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol of m.p. 169—171°C. By extraction of the mother liquors a second yield (0.44 g.) was obtained of m.p. 168—170°C.

EXAMPLE XXI

DL - erythro 2 - amino - 1 - *p* - nitrophenylpropane 1:3-diol hydrochloride (4.97 g.) were suspended in anhydrous dioxan (25 c.c.). Anhydrous triethylamine (2.0 g.) was added and after stirring for 1 hour at about 70°C. the mixture was cooled to +10°C. and treated as in Example XX with chloral cyanhydrin (4.5 g.) and anhydrous triethylamine (4.0 g.) in dioxan (12 c.c.). A first yield was obtained of 3.84 g. of DL-erythro 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol, m.p. 167—168°C., and a second yield (0.19 g.) of m.p. 162—166°C.

EXAMPLE XXII

DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol (5.3 g.) was dissolved in dry pyridine (25 c.c.) and the solution then cooled to 0°C. Chloral cyanhydrin (5.5 g.) was added carefully, keeping the temperature at 0°C. Anhydrous sodium carbonate (3.25 g.) was added, and the reaction mixture allowed to stand at normal temperature overnight. The next day the pyridine suspension was poured into water, made acid to Congo Red and the DL-erythro 2-dichloracetamido - 1 - *p*-nitrophenylpropane 1:3-diol obtained filtered off, washed with water and dried.

EXAMPLE XXIII

DL-erythro 2-amino-1-phenylpropane 1:3-diol (0.4 g.: m.p. 103°C.) was dissolved in dry dioxan (8.0 c.c.) at 50—60°C. and the solution was then cooled to laboratory temperature. Chloral cyanhydrin (0.6 g.) was added, followed by triethylamine (1.5 c.c.). The reaction mixture was cooled during the additions. After standing overnight, the reaction mixture was poured into ice-water (50 g.). At first a solution was obtained but on standing for 5—10 minutes, the product separated in a colourless felt-like mass of crystals. After standing for two hours, the mixture was made acid to Congo Red by the addition of concentrated hydrochloric acid. The crystals were filtered off and dried at 100°C. A further amount of product was obtained by extracting the filtrate with chloroform. The total yield obtained of DL-erythro 2-dichloractamido-1-phenylpropane 1:3-diol (m.p. 156—158°C.) was 0.60 g., or 90% of theory.

EXAMPLE XXIV

DL-erythro 2-amino-1-phenylpropane 1:3-diol (1.67 g.) was dissolved in pure hot dioxan (32 c.c.), and then the solution cooled in an ice-bath. Solid chloral cyanhydrin (2.5 g.) was added, followed, after standing for five minutes, by triethylamine (6.0 c.c.) added over five minutes. The colourless suspension so formed was allowed to stand overnight at normal temperature and then poured on to ice (50 g.) and water (50 c.c.). After standing for two hours the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid. The dichloracetyl derivative was filtered off and washed with water. An improved yield was obtained by extracting the aqueous filtrate with ethyl acetate. The total yield (2.56 g.) of DL-erythro 2-dichloracetamido - 1 - phenylpropane 1:3-diol was 92% of theory. It was obtained as colourless needles.

EXAMPLE XXV

A solution of chloral cyanhydrin (5.64 g.) dissolved in dry dioxan (25 c.c.) at 10°C. was treated slowly with a solution of triethylamine (6.87 g.) dissolved in dry dioxan (30 c.c.) at such a rate that the temperature did not rise above 15°C. The precipitated triethylamine hydrochloride was filtered off and washed with dry dioxan. To the filtrate was added a solution of DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol (5.3 g.) in dry dioxan (250 c.c.), and the reaction allowed to proceed at normal temperatures overnight.

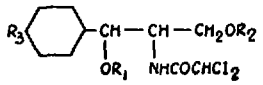
The next day the solution was poured into a large excess of water and the solution made acid to Congo Red. The desired product, DL-erythro 2-dichloractamido - 1 - *p*-nitrophenylpropane 1:3-diol was extracted with ethyl acetate (6 extractions). After concentration of the ethyl acetate solution to 40 c.c., the crude product crystallised on cooling (7.7 g., 95% of theory). Crystallisation of the crude product from dioxan gave the pure product, m.p. 176°C.

Racemic threo and erythro 5-amino-4-phenyl - 2 - methyl-1:3-dioxan employed as starting materials in certain of the foregoing Examples were prepared as follows: benzaldehyde and 2-nitroethanol were condensed together as described by Controulis, Rebstock and Crooks in the Journal of the American

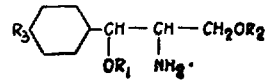
Chemical Society of 1949, Volume *71*, page 2463, and the sodium salt converted to 2-nitro-1-phenylpropane 1:3-diol by means of acetic acid in the presence of ether. The threo and the erythro isomers of 2-nitro-1-phenylpropane 1:3-diol were separated by crystallisation. Each isomer was converted to the DL-5-nitro-4-phenyl-2-methyl-1:3-dioxan by treatment of the ethereal solution of the diol with acetaldehyde in the presence of an acid catalyst such as *p*-toluene sulphonic acid. Catalytic reduction of the threo and erythro nitrodioxans gave the desired amines.

WHAT WE CLAIM IS:—

1. A process for the preparation of the stereoisomeric compounds, or mixtures thereof, of the general formula:



in which R_1 and R_2 are each a hydrogen atom or together constitute a $—CHR_4—$ group in which R_4 represents a hydrogen atom or an alkyl group having not more than 4 carbon atoms, or an aryl group and R_3 represents a hydrogen atom or a nitro group, which comprises reacting the corresponding amines of the type:



with chloral cyanhydrin, or with chloral and an alkali metal cyanide, or with chloral hydrate and an alkali metal cyanide, in the presence of an acid-binding agent.

2. A process according to claim 1 in which the cyanide is employed in quantity less than one molecular equivalent of the reacting amine.

3. A process according to claim 1 in which chloral cyanhydrin is employed and the acid-binding agent is an inorganic base or a tertiary organic base or an excess of the said amine.

4. A process according to claim 1 in which chloral or chloral hydrate and a cyanide are employed and the acid-binding agent is calcium carbonate, magnesium oxide or sodium carbonate, or is in the form of an excess of the alkali metal cyanide.

5. A process according to claim 1 in which chloral cyanhydrin is directly employed and in which the reaction is effected in an organic solvent medium at a temperature between 0° and 25°C.

6. A process according to claim 5 in which the organic solvent consists of dioxan.

7. A process according to claim 5 or 6 in which the acid-binding agent is triethylamine.

8. A process according to claim 1 or to any one of claims 5, 6 and 7 in which chloral cyanhydrin is first reacted with an acid-binding agent and the reaction product then reacted with the said amine.

9. A process according to claim 1 in which chloral or chloral hydrate and a cyanide are employed and the reaction is effected in aqueous medium at a temperature of 60° to 100°C.

10. A process according to any one of the preceding claims in which the reacting amine is DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

11. A process according to any one of claims 1 to 9 in which the reacting amine is D-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

12. A process according to any one of claims 1 to 9 in which the reacting amine is DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

13. A process according to any one of claims 1 to 9 in which the reacting amine is L-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

14. A process for the preparation of N-dichloracetyl derivatives as claimed in claim 1 and substantially as described in any of the foregoing Examples.

15. A process for the preparation of 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diols substantially as described in any one of Examples III to XI and Examples XV to XXII and Example XXV.

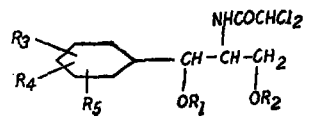
For the Applicants,
J. A. KEMP & CO.,
Chartered Patent Agents,
Bank Chambers,
329, High Holborn, London, W.C.1.

PROVISIONAL SPECIFICATION
No. 12622 A.D. 1950

Improvements in or relating to Dichloracetamides

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, Detroit, State of Michigan, United States of America, do hereby declare this invention to be described in the following statement:—

This present invention relates to the preparation of derivatives of organic amino alcohols and is particularly concerned with the preparation of N-dichloroacetyl derivatives of the general formula:



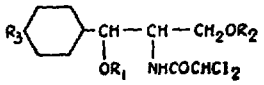
I

* C L M S *

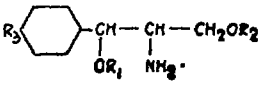
Chemical Society of 1949, Volume *71*, page 2463, and the sodium salt converted to 2-nitro-1-phenylpropane 1:3-diol by means of acetic acid in the presence of ether. The threo and the erythro isomers of 2-nitro-1-phenylpropane 1:3-diol were separated by crystallisation. Each isomer was converted to the DL-5-nitro-4-phenyl-2-methyl-1:3-dioxan by treatment of the ethereal solution of the diol with acetaldehyde in the presence of an acid catalyst such as *p*-toluene sulphonic acid. Catalytic reduction of the threo and erythro nitrodioxans gave the desired amines.

WHAT WE CLAIM IS:—

1. A process for the preparation of the stereoisomeric compounds, or mixtures thereof, of the general formula:



in which R_1 and R_2 are each a hydrogen atom or together constitute a $—CHR_4—$ group in which R_4 represents a hydrogen atom or an alkyl group having not more than 4 carbon atoms, or an aryl group and R_3 represents a hydrogen atom or a nitro group, which comprises reacting the corresponding amines of the type:



with chloral cyanhydrin, or with chloral and an alkali metal cyanide, or with chloral hydrate and an alkali metal cyanide, in the presence of an acid-binding agent.

2. A process according to claim 1 in which the cyanide is employed in quantity less than one molecular equivalent of the reacting amine.

3. A process according to claim 1 in which chloral cyanhydrin is employed and the acid-binding agent is an inorganic base or a tertiary organic base or an excess of the said amine.

4. A process according to claim 1 in which chloral or chloral hydrate and a cyanide are employed and the acid-binding agent is calcium carbonate, magnesium oxide or sodium carbonate, or is in the form of an excess of the alkali metal cyanide.

5. A process according to claim 1 in which chloral cyanhydrin is directly employed and in which the reaction is effected in an organic solvent medium at a temperature between 0° and 25°C.

6. A process according to claim 5 in which the organic solvent consists of dioxan.

7. A process according to claim 5 or 6 in which the acid-binding agent is triethylamine.

8. A process according to claim 1 or to any one of claims 5, 6 and 7 in which chloral cyanhydrin is first reacted with an acid-binding agent and the reaction product then reacted with the said amine.

9. A process according to claim 1 in which chloral or chloral hydrate and a cyanide are employed and the reaction is effected in aqueous medium at a temperature of 60° to 100°C.

10. A process according to any one of the preceding claims in which the reacting amine is DL-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

11. A process according to any one of claims 1 to 9 in which the reacting amine is D-threo 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

12. A process according to any one of claims 1 to 9 in which the reacting amine is DL-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

13. A process according to any one of claims 1 to 9 in which the reacting amine is L-erythro 2-amino-1-*p*-nitrophenylpropane 1:3-diol.

14. A process for the preparation of N-dichloracetyl derivatives as claimed in claim 1 and substantially as described in any of the foregoing Examples.

15. A process for the preparation of 2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diols substantially as described in any one of Examples III to XI and Examples XV to XXII and Example XXV.

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

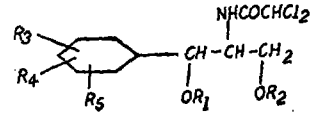
PROVISIONAL SPECIFICATION

No. 12622 A.D. 1950

Improvements in or relating to Dichloracetamides

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, Detroit, State of Michigan, United States of America, do hereby declare this invention to be described in the following statement:—

This present invention relates to the preparation of derivatives of organic amino alcohols and is particularly concerned with the preparation of N-dichloroacetyl derivatives of the general formula:



I

in which:

R_1 and R_2 are the same or different and each represent a hydrogen atom or an acyl, lower alkyl or aralkyl group or together constitute a divalent atom or group of atoms joining the two oxygen atoms such as —CO—, —SO_2—, or —CR_6R_7—, where R_6 and R_7, which may be the same or different, represent hydrogen atoms or lower alkyl, cycloalkyl, aryl or aralkyl groups:

R_3 and R_4 are the same or different and each represent a hydrogen or halogen atom or a lower alkyl or lower alkoxy radical; and

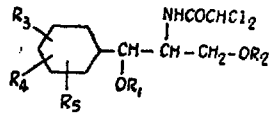
R_5 represents a hydrogen atom or a nitro group, preferably a nitro group in the 4-position.

Various processes have heretofore been employed for the preparation of certain of these compounds; thus, for example, the acid chloride, anhydride, or esters of dichloroacetic acids are known to react with the appropriate amines to give compounds of type I in which R_1 and R_2 represent hydrogen atoms or aryl groups — at least one of R_1 and R_2 being hydrogen (see Specification No. 32506/48 as laid open to public inspection).

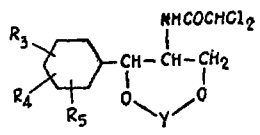
It has now unexpectedly been discovered, according to this present invention, that the N-dichloroacetyl derivatives of type I can be obtained from the corresponding amines by reaction with chloral or chloral hydrate in the presence of an alkali cyanide and an acid-binding agent.

In carrying this invention into effect, the acid-binding agents used may be organic or inorganic bases or an excess of the alkali metal cyanide catalyst. The reaction medium may be aqueous or non-aqueous and both pyridine and dioxan have been found to be suitable.

The products of this invention can be regarded as comprising the compounds of type II and those of type III:



II



III

in which R_1 and R_2 are separate radicals hereinbefore defined and Y represents the case where R_1 and R_2 in general formula I together constitute a divalent atom or group. These compounds, like the amines from which they are prepared, each contain two asymmeric carbon atoms and can exist in structural as well as optical isomeric forms. The term "structural" refers to the spatial relationship of the polar groups respectively attached to the two asymmetric carbon atoms. In conformity with the nomenclature adopted by M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Bartz, and L. M. Long and H. D. Troutman in the Journal of the American Chemical Society 1949, Volume *71*, pages 2458 to 2475, the structural isomeric forms are designated "erythro" and "threo" respectively.

Both the erythro and the threo forms can exist as racemates of optically active isomers when it follows that each compound can exist in six different forms and, accordingly, a given structural formula of conventional type as used herein, represents the 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.

By the use of this invention, the products of type II which (as is shown) are particularly useful as intermediates in the synthesis of organic compounds possessing antibiotic activity or which are themselves therapeutically valuable, such as *l*-ψ-1-*p*-nitrophenyl-2-dichloroacetamido-propane-1:3-diol (commonly known as Chloramphenicol), are conveniently prepared in excellent yield using the commercially readily available chloral (or chloral hydrate) thus avoiding the particularly inconvenient step of preparing a dichloroacetylating agent such as dichloroacetyl chloride or an ester of dichloroacetic acid. A further advantage is that the reaction time in the dichloroacetylating process may be significantly reduced.

The products represented by formula III are believed to be new compounds and certain of them have exhibited some chemotherapeutic activity. They may also be converted into compounds of type I by hydrolysis.

This invention is illustrated, but not limited, by the following examples:—

EXAMPLE I

To a stirred and refluxing mixture of *DL*-5-amino-4-phenyl-2-methyl 1:3-dioxan (19.3 g.) believed to be erythro, m.p. 73—75°C, precipitated calcium carbonate (12.0 g.) sodium cyanide (0.95 g.) and water (45 c.c.), a solution of chloral hydrate (23.4 g.) in water (10 c.c.) was added cautiously over ten minutes. The reaction mixture was stirred and refluxed for ten minutes further and then allowed to cool. Sufficient hydrochloric acid was added to the stirred reaction mixture to render it acid to Congo Red. The *DL*-5-dichloroacetamido - 4 - phenyl-2-methyl-1:3-dioxan (25.5 g.) 85% of theory was filtered off and dried at 100°C. The amide may be crystallised from methanol when it separates in colourless crystals m.p. 220—223°C.

EXAMPLE II

In place of 19.3 g. of *DL*-"erythro"-5-amino-4-phenyl-2-methyl 1:3-dioxan used in Example I, 21.2 g. of *DL*-threo-2-amino-1-*p*-nitrophenylpropane-1:3-diol were employed. The dichloroacetyl derivative, *DL*-threo-2-dichloroacetamido - 1 - *p*-nitrophenylpropane 1:3-diol was filtered off as in Example I and a further quantity obtained by extraction of the aqueous filtrate with ethyl acetate and

evaporation of the extract. The total yield was (28.1 g.) which is 87% of theory. Crystallisation from a mixture of ethyl acetate and petroleum ether gave an almost colourless product melting at 150°C.

EXAMPLE III

A mixture of *DL*-threo-2-amino-1-*p*-nitrophenylpropane 1:3-diol (2.12 g.) chloral hydrate (2.20 g.) dry pyridine (5 c.c.) and sodium cyanide (0.7 g.) was heated on the steam bath for some hours. The solution was poured on to water and the precipitated solid filtered off and dried at 100°C. After crystallisation from ethyl acetate-petroleum ether mixture, the so-obtained *DL*-threo-2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol melts at 150—151°C.

The reaction medium pyridine, used in this Example can be replaced by dioxan with a similar result.

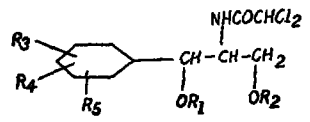
For the Applicants,
J. A. KEMP & CO.,
Chartered Patent Agents,
Bank Chambers,
329, High Holborn, London, W.C.1.

PROVISIONAL SPECIFICATION
No. 18308 A.D. 1950

Improvements in or relating to Dichloracetamides

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, Detroit, State of Michigan, United States of America, do hereby declare this invention to be described in the following statement:—

This present invention relates to the preparation of derivatives of organic amino alcohols and is particularly concerned with the preparation of N-dichloracetyl derivatives of the general formula:



I

in which:

R_1 and R_2 are the same or different and each represent a hydrogen atom or an acyl, lower alkyl or aralkyl group or together constitute a divalent atom or group of atoms joining the two oxygen atoms such as —CO—, —SO_2—, or —CR_6R_7— where R_6 and R_7, which may be the same or different, represent hydrogen atoms or lower alkyl, cycloalkyl, aryl or aralkyl groups:

R_3 and R_4 are the same or are different and each represent a hydrogen or halogen atom or a lower alkyl or lower alkoxy radical; and

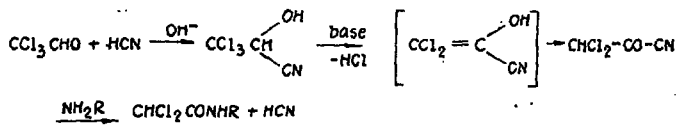
R_5 represents a hydrogen atom or a nitro group, preferably a nitro group in the 4-position.

Various processes have heretofore been employed for the preparation of certain of these compounds; thus, for example, the acid chloride, anhydride, or esters of dichloracetic acid are known to react with the appropriate amines to give compounds of type I in which R_1 and R_2 represent hydrogen atoms or acyl groups—at least one of R_1 and R_2 being hydrogen (see Specification No. 32506/48 as laid open to public inspection).

It has now unexpectedly been discovered, according to this present invention, that the N-dichloracetyl derivatives of type I can be obtained from the corresponding amines by reaction with chloral cyanhydrin in the presence of an acid-binding agent.

In carrying this invention into effect, the acid-binding agents used may be inorganic or tertiary organic bases or an excess of the amine of type I. Strong tertiary bases such as triethylamine are preferred. The reaction medium may be aqueous or non-aqueous and both pyridine and dioxan have been found to be suitable.

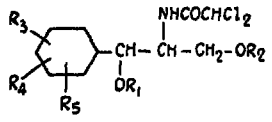
In the specification of co-pending Application No. 12622/50 there is described a process in which the amines of type I are reacted with chloral or chloral hydrate in the presence of an alkali cyanide and an acid-binding agent. It is believed that further experimental investigation will show that this process is an embodiment of the present invention in the sense that the reaction may well involve the intermediate formation *in situ* of chloral cyanhydrin and that, furthermore, both the aforesaid process and that hereinbefore described essentially involve the formation of dichloracetyl cyanide which then reacts with the amine of type I to give the required product. The over-all reaction may be postulated as follows:



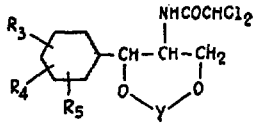
The present invention, therefore, includes within its scope the process of reacting amines of type I with dichloracetyl cyanide or precursors therefor in the presence of an acid-binding agent.

The products of this invention can be

regarded as comprising the compounds of type II and those of type III:



II



III

in which R_1 and R_2 are separate radicals hereinbefore defined and Y represents the case where R_1 and R_2 in general formula I together constitute a divalent atom or group. These compounds, like the amines from which they are prepared, each contain two asymmetric carbon atoms and can exist in structural as well as optical isomeric forms. The term "structural" refers to the spatial relationship of the polar groups respectively attached to the two asymmetric carbon atoms. In conformity with the nomenclature adopted by M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Bartz, and L. M. Long and H. D. Troutman in the Journal of the American Chemical Society 1949, Volume *71*, pages 2458 to 2475, the structural isomeric forms are designated "erythro" and "threo" respectively.

Both the erythro and threo forms can exist as racemates of optically active isomers whence is follows that each compound can exist in six different forms and, accordingly, a given structural formula of the conventional type as used herein, represents the 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.

By the use of this invention, the products of type II which (as is shown) are particularly useful as intermediates in the synthesis of organic compounds possessing antibiotic activity or which are themselves therapeutically valuable, such as D(-)threo-2-dichloracetamido - 1 - *p* - nitrophenyl propane 1:3-diol (commonly known as Chloramphenicol) are conveniently prepared in excellent yields. A further advantage is that the reaction proceeds at normal temperatures.

The products represented by formula III are believed to be new compounds and certain of them have exhibited some chemotherapeutic activity. They may be converted into compounds of type I by hydrolysis.

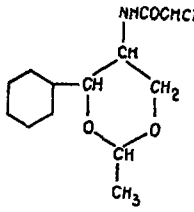
This invention is illustrated, but not limited, by the following examples:—

EXAMPLE I

DL-threo-2-amino- 1 -p-nitrophenylpropane 1:3-diol (4.24 g.) was dissolved in pure hot dioxan (25 c.c.) and the solution allowed to crystallise in an ice-water bath. When the temperature had reached 10°C solid chloral cyanhydrin (4.5 g.) was added, followed, after standing for five minutes, by the addition over a period of about 5 minutes of a solution of triethylamine (5.5 c.c.) in dioxan (12 c.c.). The last addition caused an exothermic reaction to take place and the temperature was maintained below 30°C. by cooling in an ice-water bath. The pale brown suspension was allowed to stand overnight at normal temperatures and then poured onto ice (100 g.) and water (200 g.). After standing for four hours, the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid. The dichloracetyl derivative was filtered off and washed with water. The aqueous filtrate was extracted with ethyl acetate and, after concentration to small volume, a little petroleum ether added which caused a further quantity of the dichloracetyl derivative to separate. The yield (6.40 g.) of DL-threo-2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol (commonly known as racemic Chloramphenicol) was 99% of theory and it melted at 149—151°C. It was obtained as an almost colourless crystalline solid.

EXAMPLE II

Chloral cyanhydrin (10.9 g.) was dissolved in dioxan (20 c.c.) and cooled in an ice-water bath while 5-amino-4-phenyl-2-methyl-1:3-dioxan (9.65 g.) (believed to be erythro m.p. 73—75°C) was added over five minutes. To the cooled solution was added slowly triethylamine (10 g.). The almost solid suspension was allowed to stand at normal temperature for 14 hours and then poured on to ice and water. After standing for some time, the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid and the solid was filtered off. The yield of erythro DL-5-dichloracetamido - 4 - phenyl-2-methyl-1:3-dioxan was 90% of theory. After purification the melting point was 220—224°C. The product is believed to have the formula:



EXAMPLE III

Chloral cyanhydrin (10.9 g.) was dissolved in dioxan (20 c.c.) and cooled in an ice-water bath while 5-amino-4-phenyl-2-methyl-1:3-dioxan (9.65 g.) (believed to be threo b.p. 85—87°C/0.04 mm.; picrate m.p. 223°C) was added over five minutes. To the cooled solution was added slowly triethylamine (10 g.) and the suspension was then allowed to stand at normal temperature for ten hours. The suspension was poured on to ice and water and after allowing to stand for a few hours, the suspension was made acid to Congo Red by the addition of concentrated hydrochloric acid. The dichloracetyl derivative was filtered off and washed with water. The yield (15.18 g.) of DL-threo-5-dichloracetamido - 4 - phenyl-2-

methyl-1:3-dioxan was 100%. The purified product melted at 131—131.5°C. This product is also represented by the same structural formula as shown in Example II, although, of course, they are different chemical compounds.

EXAMPLE IV

Chloral cyanhydrin (4.3 g.) was added to dry pyridine (15 c.c.) and immediately afterwards DL-threo-2-amino-1 - *p* - nitrophenylpropane 1:3-diol (4.2 g.) was added to the cooled solution. The internal temperature rose to 40°C and the mixture was heated on a steam bath for 15 minutes. The light brown solution was poured on to water and ice and, after standing for one hour, acidified with concentrated hydrochloric acid. The DL-threo-2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was filtered off and crystallised from a mixture of ethyl acetate and petroleum ether. The product was identical with that of Example I.

EXAMPLE V

DL-threo-2-amino- 1 -*p*-nitrophenylpropane 1:3-diol hydrochloride (2.49 g.) was dissolved in water (15 c.c.). Chloral cyanhydrin (2.5 g.) was dissolved in this solution and, after cooling to 0°C, triethylamine (3.0 g.) was added drop by drop over five minutes with shaking between each addition. An oil was deposited which solidified after shaking for half an hour. The suspension was allowed to stand for four hours and then made acid to Congo Red by the addition of concentrated hydrochloric acid. The DL-threo-2-dichloracetamido-1-*p*-nitrophenylpropane 1:3-diol was filtered off, washed with water and dried. The yield (3.15 g.) was 97% of theory. The product is the same as that of Example I.

EXAMPLE VI

5-Amino - 4 - phenyl-2-methyl-1:3-dioxan (1.93 g.) (believed to be erythro, m.p. 73—75°C) was dissolved in 2*N* hydrochloric acid (5 c.c.) and water (10 c.c.). The solution was cooled to 0°C and chloral cyanhydrin (2.25 g.) added. To this stirred and cooled solution was added 2*N* sodium hydroxide over half an hour. The suspension was allowed to stand overnight when the crystalline solid was filtered off, washed with water and dried. The yield (2.0 g.) of erythro 5-dichloracetamido-4-phenyl-2-methyl-1:3-dioxan was 66% of theory.

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

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

"Ribbon accompanying seal or fastener was cut or removed during data conversion for the purposes of scanning in the document. Date: - 3 AUG 2000