



**PATENT INFORMATION**

Pursuant to 21 USC Section 355 (b)(1) of the Federal Food, Drug and Cosmetic Act, Allergan, Inc. is reference two existing patents for nedocromil sodium. Both patents list FISIONS as the assignee. Rhône – Poulenc Rorer subsequently has acquired the rights to these patents from FISIONS.

US Patent No. 4,474,787, issued October 1, 1984, expires October 2, 2006.

This patent refers to a broad genus of compounds, including the acidic form of the active nedocromil. Allergan, Inc. has acquired a license to this patent for ophthalmic use only, in the United States and Canada.

US Patent No. 4,760,072, issued July 26, 1988, expires July 26, 2005.

This patent applies to a solid nedocromil sodium preparation containing bound water. We are referencing this patent because of Allergan's future intention to purchase this solid form from Rhône – Poulenc Rorer Pharmaceuticals.

*A copy of both of the above referenced patents and the grant clause from Allergan's license are appended to this section.*

I, the undersigned, hereby declare that Patent Nos. 4,474,787 and 4,760,072 cover the formulation and method of use of nedocromil sodium. The subject of this application for which approval is being sought is covered by these patents.

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Allergan, Inc.

3/30/99

Date

EXHIBIT B

Patents

U.S. Patent No.

4,760,072

4,474,787

Table 2: Volumes of urine collected

Subject number	Urine volume (ml) on:	
	Day 1	Day 7
21		
27		
61		
76		
95		
144		
28		
56		
99		
105		
129		
141		

APPEARS THIS WAY  
ON ORIGINAL

Table 1 Concentrations of nedocromil sodium in the urine samples

Urine collection period	Concentration of nedocromil sodium (ng cm <sup>-3</sup> )											
	1% formulation						2% formulation					
	Subject number											
	21	27	61	76	95	144	28	56	99	105	129	141
Pre-dose												
Day 1												
Day 7												

# United States Patent [19]

Cairns et al.

[11] Patent Number: 4,474,787

[45] Date of Patent: Oct. 2, 1984

[54] 7,6  
DIOXO-4H,6H-PYRANO(3,2-g)QUINOLINE  
DICARBOXYLIC ACIDS AND  
ANTI-ALLERGIC USE THEREOF

[75] Inventors: Hugh Cairns; David Cox, both of  
Loughborough, England

[73] Assignee: Fisons Limited, England

[21] Appl. No.: 344,982

[22] Filed: Feb. 2, 1982

### Related U.S. Application Data

[63] Continuation of Ser. No. 946,492, Sep. 28, 1978, abandoned, which is a continuation-in-part of Ser. No. 897,416, Apr. 18, 1978, abandoned.

### [30] Foreign Application Priority Data

May 4, 1977 [GB] United Kingdom ..... 18597/77  
Nov. 4, 1977 [GB] United Kingdom ..... 48565/77  
Apr. 25, 1978 [GB] United Kingdom ..... 16168/78

[51] Int. Cl.<sup>3</sup> ..... A61K 31/47; C07D 491/04

[52] U.S. Cl. .... 424/258; 546/89;  
546/92

[58] Field of Search ..... 546/89, 92; 424/258

### [56] References Cited

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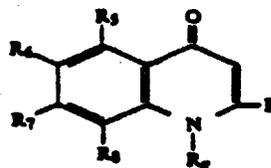
#### FOREIGN PATENT DOCUMENTS

073427 3/1975 Japan ..... 546/89

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Assistant Examiner—D. B. Springer  
Attorney, Agent, or Firm—Marshall, O'Toole, Gerstein,  
Murray & Bicknell

### [57] ABSTRACT

There are described compounds of formula I



in which an adjacent pair of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> form a chain —COCH=CE—O—, and the remainder of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>, which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or —NR<sub>1</sub>R<sub>2</sub> in which R<sub>1</sub> and R<sub>2</sub>, which are the same or different, are each hydrogen or alkyl.

R<sub>9</sub> is hydrogen, alkyl, alkenyl or phenyl-alkyl, and E is —COOH, a 5-tetrazolyl group or an (N-tetrazol-5-yl) carboxamido group,

and pharmaceutically acceptable derivatives thereof.

There are also described processes for making the compounds and pharmaceutical, e.g. anti-allergic, compositions containing the compounds.

11 Claims, No Drawings

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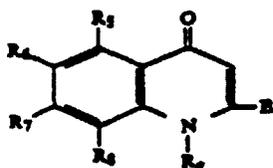
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7,6-DIOXO-4H,6H-PYRANO[3,2-G]QUINOLINE  
DICARBOXYLIC ACIDS AND ANTI-ALLERGIC  
USE THEREOF

This is a continuation of application Ser. No. 946,492, filed Sept. 28, 1978 abandoned which is a CIP of Ser. No. 897,416 filed Apr. 18, 1978 abandoned.

This invention relates to new pyranoquinolinone derivatives, compositions containing them and methods for their preparation.

According to our invention we provide compounds of formula I,



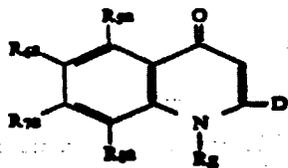
in which an adjacent pair of  $R_3$ ,  $R_4$ ,  $R_7$  and  $R_8$  form a chain  $-\text{COCH}=\text{CE}-\text{O}-$ , and the remainder of  $R_3$ ,  $R_4$ ,  $R_7$  and  $R_8$ , which may be the same or different, each represent hydrogen, hydroxy, alkyl, halogen, alkenyl, alkoxy, or  $-\text{NR}_1\text{R}_2$  in which  $R_1$  and  $R_2$ , which are the same or different, are each hydrogen or alkyl,

$R_9$  is hydrogen, alkyl, alkenyl or phenyl-alkyl, and  $E$  is  $-\text{COOH}$ , a 5-tetrazolyl group or an (N-tetrazol-5-yl)carboxamido group,

and pharmaceutically acceptable derivatives thereof.

According to our invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable derivative thereof, which comprises,

(a) producing a compound of formula I in which  $E$  is  $-\text{COOH}$  by selectively hydrolyzing or oxidizing a compound of formula II,

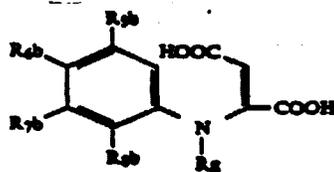


in which  $R_9$  is as defined above,

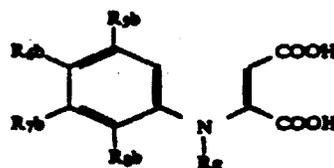
$R_{9a}$ ,  $R_{9b}$ ,  $R_{9c}$  and  $R_{9d}$  have the same significances as  $R_3$ ,  $R_4$ ,  $R_7$  and  $R_8$  above, save that an adjacent pair of  $R_{9a}$ ,  $R_{9b}$ ,  $R_{9c}$  and  $R_{9d}$  may represent a chain of formula  $-\text{COCH}=\text{C}(\text{D}_1)\text{O}-$ , and one or both of  $D$  and  $D_1$  represents a group hydrolyzable or oxidizable to a  $-\text{COOH}$  group, and the other may represent a  $-\text{COOH}$  group,

(b) producing a compound of formula I in which  $E$  is  $-\text{COOH}$  by cyclizing a compound of formula III or IV,

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III



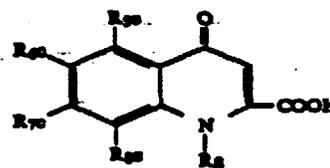
IV

or an ester of either thereof,

in which  $R_9$  is as defined above,

$R_{5b}$ ,  $R_{6b}$ ,  $R_{7b}$  and  $R_{8b}$  have the same significances as  $R_3$ ,  $R_4$ ,  $R_7$  and  $R_8$  above, save that an adjacent pair of  $R_{5b}$ ,  $R_{6b}$ ,  $R_{7b}$  and  $R_{8b}$  may represent the pair of groups  $-\text{H}$  and  $-\text{O}-\text{C}(\text{COOH})=\text{CH}-\text{COOH}$ ,

(c) producing a compound of formula I in which  $E$  is  $-\text{COOH}$  by cyclizing a compound of formula V,



V

or an ester thereof,

in which  $R_9$  is as defined above,

$R_{9c}$ ,  $R_{9d}$ ,  $R_{7c}$  and  $R_{8c}$  have the same significances as  $R_3$ ,  $R_4$ ,  $R_7$  and  $R_8$  above save that an adjacent pair of  $R_{9c}$ ,  $R_{9d}$ ,  $R_{7c}$  and  $R_{8c}$ , instead of forming a chain  $-\text{COCH}=\text{C}(\text{COOH})-\text{O}-$ , represent the pairs of groups:

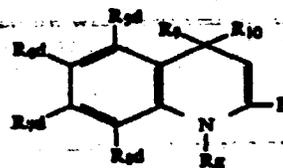
(I)  $-\text{COCH}_2\text{CO}-\text{COR}''$  or  $-\text{COCH}=\text{C}(\text{COOH})-\text{NL}_1\text{L}_2$ , or a suitable derivative thereof; and  $-\text{OM}$  or a halogen atom, or

(II)  $-\text{H}$  and  $-\text{O}-\text{C}(\text{COR}'')=\text{CH}-\text{COR}''$

$R''$  represents  $-\text{OM}$ , or a group which is hydrolyzable thereto,

$L_1$  and  $L_2$  which may be the same or different are each hydrogen, aryl or alkyl, or together form a saturated or unsaturated alkylene chain, and  $M$  represents hydrogen or an alkali metal, and if necessary or desired hydrolyzing the group  $-\text{COR}''$ , to a group  $-\text{COOM}$ ,

(d) conversion of a compound of formula VI,



VI

or an ester thereof,

in which  $R_9$  and  $E$  are as defined above,

$R_{9e}$ ,  $R_{9f}$ ,  $R_{9g}$  and  $R_{9h}$  have the same significances as  $R_3$ ,  $R_4$ ,  $R_7$  and  $R_8$  above save that an adjacent pair

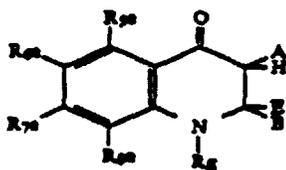
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of  $R_{5d}$ ,  $R_{6d}$ ,  $R_{7d}$  and  $R_{8d}$  may represent the chain  
 $—C(R_9R_{10})=CE—O—$ ,

at least one of the pairs of groups  $R_9$  and  $R_{10}$  together form a  $=S$  or together form an  $—S(CH_2)_nS—$  chain in which  $n$  is 2 or 3, and the other pair  $R_9$ ,  $R_{10}$  may represent  $=O$ ,

to a corresponding compound of formula I.

(e) selectively removing the groups A and B from a compound of formula VII,



VII

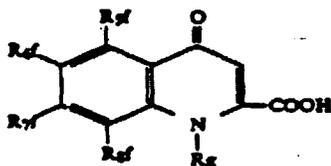
or an ester thereof,

in which  $R_9$  and E are as defined above,

$R_{5e}$ ,  $R_{6e}$ ,  $R_{7e}$  and  $R_{8e}$  have the same significances as  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  above save that an adjacent pair of  $R_{5e}$ ,  $R_{6e}$ ,  $R_{7e}$  and  $R_{8e}$  may represent a chain  
 $—COCHA—CBE—O—$ ,

in at least one of the pairs of groups A and B both A and B are hydrogen, or one of A and B is hydrogen and the other is halogen or hydroxy, and the other pair A, B may together form a double bond,

(f) producing a compound of formula I in which E is  $—COOH$  by cyclising a compound of formula VIII,



VIII

or an ester thereof,

in which  $R_9$  is as defined above,  $R_{5f}$ ,  $R_{6f}$ ,  $R_{7f}$  and  $R_{8f}$  have the same significances as  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  above save that an adjacent pair of  $R_{5f}$ ,  $R_{6f}$ ,  $R_{7f}$  and  $R_{8f}$ , instead of forming a chain  $—COCH=C(COOH)—O—$ , represent the pair of groups  
 $—COCH(SOR_{10})—CH(CH)—COOR''—$  and  $—OM$ ,

$R''$  and M are as defined above, and

$R_{10}$  represents an alkyl C 1 to 10 group,

(g) producing a compound of formula I in which E is a 5-tetrazolyl group by reacting a corresponding compound of formula I in which E is  $—CN$ , with an azide in a solvent which is inert under the reaction conditions, or

(h) producing a compound of formula I in which E is an (N-tetrazol-5-yl)carboxamido group by reacting a corresponding compound of formula I in which E is  $—COOH$ , or an acid halide, ester or mixed anhydride thereof,

with 5-aminotetrazole,

and if necessary or desired hydrolysing the ester of the compound of formula I and/or converting the compound of formula I to a pharmaceutically acceptable derivative thereof.

In process (a) the group D may be, for example an ester, acid halide, amide or a nitrile group, which may be hydrolysed to a  $—COOH$  group. The hydrolysis may be carried out using conventional techniques, for

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example under mildly basic conditions, e.g. using sodium carbonate, sodium hydroxide, sodium bicarbonate, or under acidic conditions, e.g. a mixture of aqueous dioxan and hydrochloric acid, or hydrogen bromide in acetic acid. The hydrolysis may be carried out at a temperature of from about 25° to 120° C. depending on the compounds used. Alternatively the group D may be an alkyl, e.g. a lower alkyl such as methyl, a hydroxymethyl, an aralkenyl, e.g. styryl, an acyl, e.g. a lower alkanoyl such as acetyl, or a formyl group. The oxidation may be carried out using conventional techniques which do not otherwise modify the molecule to such an extent that the yield of the desired product is uneconomical, for example an alkyl or a hydroxymethyl group may be oxidised using selenium dioxide, e.g. under reflux in aqueous dioxan; or chromic acid, e.g. under reflux in aqueous acetic acid. Aralkenyl groups may be oxidised using, for example neutral or alkaline potassium permanganate in aqueous ethanol, and acyl groups may be oxidised using, for example chromic acid or an aqueous hypochlorite, e.g. sodium hypochlorite. The formyl group may be oxidised using, for example chromic acid or silver oxide.

In process (b) the cyclisation may be carried out by treating the compound of formula III or IV, with a cyclising agent, for example a dehydrating agent such as chlorosulphonic, sulphuric or polyphosphoric acid. The reaction is preferably carried out under anhydrous conditions and may be carried out at a temperature of from about 25° to 150°, and preferably from 75° to 150° C. We have found that isomerisation of the maleic acid derivative of formula IV to the corresponding fumaric acid derivative of formula III takes place when polyphosphoric acid is used to cyclise these compounds to a compound of formula I, thus enabling a satisfactory yield of the compound of formula I to be obtained from a *prima facie* unsatisfactory mixture of compounds of formulae III and IV. Compounds of formula III may also be cyclised by subjecting the compound to an elevated temperature, e.g. of from 200° to 250° C., optionally in the presence of a high boiling solvent which is inert under the reaction conditions, e.g. diphenyl ether.

When one of the groups is  $—OM$  the cyclisation of process (c)(i) may be carried out by heating, or under basic or neutral conditions. It is however preferred to carry out the cyclisation in the presence of an acid, e.g. hydrochloric acid, and in a solvent which is inert under the reaction conditions, e.g. ethanol. The reaction may be carried out at from about 20° to 150° C. The group  $—COR''$  is preferably an ester group, e.g.  $R''$  may be a lower alkoxy group. When one of the groups is  $—COCH=C(COOH)—NL_1L_2$  the derivative of the  $—COOH$  group may be a group  $—CONL_1L_2$  in which  $L_1$  and  $L_2$  are as defined above. It is preferred that  $L_1$  and  $L_2$  are hydrogen, phenyl, alkyl C 1 to 6 or together form a 4 or 5 membered alkylene chain, e.g. together with the nitrogen atom form a piperidine ring. When one of the groups is halogen the cyclisation may be carried out in a solvent which is inert under the reaction conditions, preferably a high boiling polar solvent, e.g. pyridine, dimethylformamide or hexamethylphosphoramide. The reaction is preferably carried out with the aid of a strong base, for example an alkali metal hydride, e.g. sodium hydride. The reaction is preferably carried out at a temperature of from about 80° to 200° C., in the absence of free oxygen, e.g. under an inert atmosphere such as nitrogen.

The cyclisation of process (c)(ii) may be carried out by treating the compound of formula V with a cyclising agent, for example a dehydrating agent such as chlorosulphonic, polyphosphoric or sulphuric acid. The reaction is preferably carried out under anhydrous conditions and may be carried out at a temperature of from 0° to 100° C. Alternatively cyclisation may be achieved by converting the free carboxy groups of the compound of formula V to acyl halide groups and subjecting the resulting acyl halide to an intramolecular Friedel-Crafts reaction.

In processes (d), when R<sub>9</sub> and R<sub>10</sub> together form a chain —S—(CH<sub>2</sub>)<sub>n</sub>—S—, the conversion may comprise oxidative hydrolysis and may be carried out in an aqueous polar organic solvent, for example aqueous ethanol, acetone or tetrahydrofuran. The oxidative hydrolysis may be carried out in the presence of an oxidising agent, for example mercuric chloride, an N-halosuccinimide such as N-bromo- or N-chloro-succinimide, a per-acid such as periodic acid; or p-toluenesulphonchloramide or a salt thereof. When mercuric chloride is used the reaction may be carried out in the presence of a base, e.g. mercuric oxide, cadmium carbonate or calcium carbonate. N-halosuccinimides may be used alone or in the presence of a silver salt, e.g. silver perchlorate, or silver nitrate. The reaction may conveniently be carried out at a temperature of from about 15° to 100° C.

When R<sub>9</sub> and R<sub>10</sub> together form a =S group the conversion may comprise (oxidative) hydrolysis and may be carried out in the presence of a heavy metal compound, e.g. a compound of group Ib, IIb or IIIb of the Periodic Table of Mendeleef, as catalyst. Suitable compounds include mercury, thallium and silver compounds, e.g. mercury (II) acetate or chloride, thallium (III) trifluoroacetate, or silver oxide. The reaction may be carried out in the presence of water in an organic solvent system such as acetone-acetic acid, alkanols, tetrahydrofuran/methanol, or tetrahydrofuran. Alternatively the reaction may be carried out by alkylation followed by hydrolysis. In such cases the reaction may be effected by (i) an alkyl halide or sulphonate (e.g. methyl iodide), in a moist solvent, e.g. acetone, (ii) an alkylsulphosulphonate and water in sulphur dioxide, or (iii) a trialkyl oxonium fluoroborate followed by aqueous sodium hydroxide.

When both A and B are hydrogen process (e) is a dehydrogenation and may be carried out by oxidation using a mild oxidising agent, for example selenium dioxide, palladium black, chloranil, lead tetracetate or triphenyl methyl perchlorate. Alternatively the dehydrogenation of a compound of formula VII in which both A and B are hydrogen may be carried out indirectly by halogenation followed by dehydrohalogenation, e.g. by treatment with N-bromosuccinimide or pyridinium bromide perbromide to yield a compound of formula VII in which A is halogen and B is hydrogen, which is subsequently dehydrobrominated. When one of A and B is hydroxy the dehydration may be catalysed by an acid, e.g. sulphuric or oxalic acid; a base, e.g. potassium hydroxide; or a salt, e.g. potassium hydrogen sulphate; or N-bromosuccinimide. The reaction may be carried out in a solvent which is inert under the reaction conditions, e.g. a halogenated hydrocarbon, xylene, or glacial acetic acid. The reaction may be carried out at an elevated temperature, e.g. from 20° to 150° C.

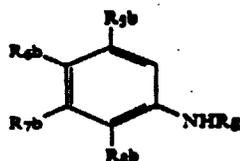
The cyclisation of process (f) may be carried out in a solvent which is inert under the reaction conditions, e.g. diethyl ether or benzene. The reaction may also, if de-

sired, be carried out in the presence of a Lewis acid, e.g. boron trifluoride. The reaction is preferably carried out at a temperature of from 10° to 120° C. in presence of an organic base, e.g. piperidine.

Suitable solvents which are inert under the reaction conditions of process (g) include those in which both the reagents are soluble, e.g. N,N-dimethylformamide. Other solvents which may be mentioned include dimethylsulphoxide, tetrahydrofuran, diethyl glycol and ethyl methyl glycol. The reaction is preferably carried out at a temperature of from about 20° to 130° C. for from about 1 to 20 hours. The azide used in the reaction is preferably ammonium or an alkali metal azide, e.g. sodium or lithium azide, but other azides, e.g. aluminium azide or the azides of nitrogen containing bases, e.g. mono-, di-, tri-, and tetra- methyl- ammonium, anilinium, morpholinium and piperidinium azides, may also be used if desired. Where an azide other than that of an alkali metal is used this azide may be prepared in the reaction mixture by double decomposition. The reaction may, if desired, be carried out in the presence of an electron acceptor, e.g. aluminium chloride, boron trifluoride, ethyl sulphonic acid or benzene sulphuric acid. As an alternative to the reaction conditions set out above, the reaction may be carried out using hydrazoic acid (hydrogen azide) at a temperature of from about 20° to 150° C. in a suitable solvent, under greater than atmospheric pressure. When an azide other than hydrazoic acid is used, e.g. sodium azide, the product of the reaction will be the corresponding tetrazole salt. This salt may readily be converted to the free acid by treatment with strong acid, e.g. hydrochloric acid.

In process (h) the anhydride is preferably a mixed anhydride of such a type that it will cleave preferentially, to give the desired chromone carboxamidotetrazole, as the major product when reacted with the 5-aminotetrazole. Examples of suitable acids from which the mixed anhydride may be derived are sulphonic acids e.g. benzene sulphonic acid, sterically hindered carboxylic acids, e.g. pivalic, isovaleric, diethylacetic or triphenylacetic acid, and alkoxy formic acids, e.g. a lower alkoxy formic acid such as ethoxy or isobutoxy formic acid. When an acid halide is used it may conveniently be an acid chloride. The reaction is preferably carried out under anhydrous conditions in a solvent which will not react with either the 5-aminotetrazole or the mixed anhydride or acid halide, e.g. pyridine or dimethylformamide. However when the reaction is carried out in a non-basic solvent, e.g. dimethylformamide, an adequate proportion of an acid acceptor, e.g. triethylamine, should also preferably be present. The reaction is preferably carried out at a temperature of from about -15° to +20° C. When an ester is used we prefer to use a lower alkoxy ester and to carry out the reaction in a solvent which is inert under the reaction conditions, e.g. glacial acetic acid, at a temperature of from about 100° to 150° C. When a compound of formula I in which E is —COOH is used as starting material the reaction may be carried out by heating the compound of formula I and the 5-aminotetrazole in a solvent which is inert under the reaction conditions, e.g. dimethylacetamide, at a temperature of from 100° to 200° C. Alternatively the reaction may be carried out in the presence of a condensation agent, e.g. N,N'-carbonyl-diimidazole or dicyclohexyl carbodiimide, in an aprotic solvent, e.g. dimethylformamide, at a temperature of from about 10° to 40° C.

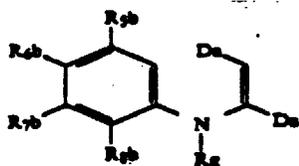
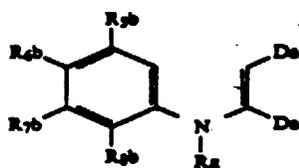
The starting materials for process (b) may be made by reacting a compound of formula IX,



in which Rg, R5b, R6b, R7b and R8b are as defined above, with a compound of formula X,



in which Da is an ester group, to produce a mixture of compounds of formulae XI and XII,



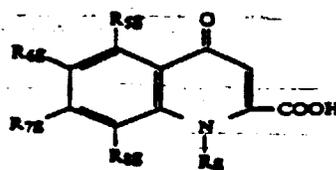
in which Rg, Da, R5b, R6b, R7b and R8b are as defined above.

The compounds of formula XI and XII may be hydrolysed to give compounds of formulae IV and III. Alternatively the groups Da in the compounds of formulae XI and XII may be converted using conventional techniques known per se, to other groups D and the resulting compounds cyclised, using the same conditions as for process (b) above, to yield a compound of formula II. As a further and preferred alternative the compounds of formula XI and XII may be cyclised, using the same conditions as for process (b) above, to give a compound of formula II in which D is an ester group, and the resulting compound of formula II is used itself in process (a), or the D group converted to another group D, e.g. an acid halide, amide or nitrile group, using techniques known per se.

The fumaric isomer of formula XII (or the corresponding compound in which Da has been converted to D) is the only isomer which can cyclise to give the required compounds of formula II. The proportion of the two isomers may be readily determined by nuclear magnetic resonance spectroscopy and we have found that, in general, the desired fumaric acid derivative is only a minor proportion of the mixture of isomers obtained from the reaction.

The compounds of formula V, in which an adjacent pair of R5c, R6c, R7c and R8c represent the groups  $-\text{COCH}_2\text{COCOR}''$  and  $-\text{OM}$  or halogen, may be made by reacting a compound of formula XIII,

IX



XIII

10

or an ester thereof, in which Rg is as defined above, and R5c, R6c, R7c and R8c have the same significances as R5, R6, R7 and R8 above, save that an adjacent pair of R5c, R6c, R7c and R8c, instead of forming a  $-\text{COCH}=\text{CH}(\text{COOH})-\text{O}-$  chain, represent the groups  $-\text{COCH}_2$  and  $-\text{OM}$  or halogen, in which M is as defined above, with a compound of formula XIV,

20



XIV

XI

in which R'' is as defined above, R' is a suitable leaving group, e.g. an alkoxy, halo, amino, alkylamino, substituted amino (e.g. an arylsulphonylamino group) or substituted alkylamino group, reactive with the carbanion of the  $-\text{COCH}_2$  group of the compound of formula XIII, and

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XII

each Z is a carbonyl oxygen atom, or one Z may represent two halogen atoms and the other a carbonyl oxygen atom,

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and if necessary hydrolysing the resulting compound to a compound of formula V. The preferred compounds of formula XIV are dialkyl oxalates, e.g. diethyl oxalate.

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Compounds of formula V bearing a  $-\text{COCH}=\text{C}(\text{COOH})-\text{NL}_1\text{L}_2$  group, or a derivative thereof, may be made from known compounds in one or more steps using processes known per se.

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The compounds of formula II may be made as described above or by a process analogous to process (c)(i).

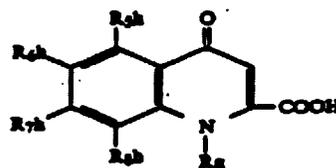
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Alternatively the compounds of formula II may, for example in the case of the acid halide, the amide and the nitrile, be made from compounds of formula I using conventional techniques, e.g. reaction of an ester of the compound of formula I with ammonia to produce the amide, followed by dehydration of the amide to form the nitrile.

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The compounds of formula V carrying substituents  $-\text{H}$  and  $-\text{O}-\text{C}(\text{COR}'')=\text{CH}-\text{COR}''$  may be made by reacting a compound of formula XV,

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XV

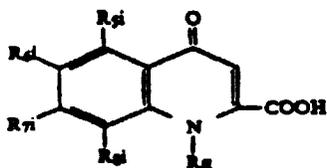
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or an ester thereof, in which Rg is as defined above, and R5h, R6h, R7h and R8h have the same significances as R5, R6, R7 and R8 above, save that an adjacent pair of R5h, R6h, R7h and R8h, instead of forming a  $-\text{COCH}=\text{C}(\text{COOH})-\text{O}-$  chain, represent the groups  $-\text{H}$  and  $-\text{OH}$ .

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with a dialkyl acetylene dicarboxylate, in conventional manner, followed if necessary by hydrolysis of the reaction product.

Compounds of formula VIII may be made by reacting a compound of formula XVI,



XVI

or an ester thereof,

in which R<sub>8</sub> is as defined above,

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> have the same significances as R<sub>3</sub>, R<sub>4</sub>, R<sub>7</sub> and R<sub>8</sub> above, save that an adjacent pair of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>, instead of forming a chain —COCH=C(COOH)—O—, represent the pair of 20 groups —OH and —COO—Alkyl,

with a methyl alkyl sulphoxide anion, e.g. the anion of dimethyl sulphoxide,

and reacting the resulting o-hydroxy-2-alkylsulphinyll compound with glyoxalic acid or an ester thereof. 25

The compounds of formula I in which E is —CN may be made by dehydrating the corresponding pyranoquinolinone amide using, for example, phosphorus oxychloride, as dehydrating agent. The reaction is preferably carried out using at least one molar equivalent of dehydrating agent per mole of the pyranoquinolinone amide. Where the dehydrating agent reacts with one of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> or R<sub>8</sub> (e.g. a substituent comprising an —CH group) sufficient dehydrating agent should be used to satisfy the side reaction as well as the main reaction. The reaction may, if desired, be carried out in the presence of an acid binding agent, e.g. triethylamine. The reaction may be carried out in the presence of a solvent, e.g. N,N-dimethylformamide, dimethyl sulphoxide, pyridine, benzene or hexamethyl phosphoramide, or an excess of the dehydrating agent may be used as the reaction medium. The reaction may be carried out at a temperature of from about 0° to 200° C. depending on the dehydrating agent used. When phosphorus oxychloride is used a temperature of from 0° to 100° C. is preferred.

The chromone amide starting materials may be made by reacting a corresponding pyranoquinolinone ester with ammonia, using techniques conventional in the production of amides from esters, e.g. using an alcohol as solvent at a temperature of 0° to 120° C.

Compounds of formulas VI, VII, IX, XIII, XIV, XV and XVI are either known or may be made from known compounds using conventional techniques known per se.

The processes as described above may produce the compound of formula I or a derivative thereof. It is also within the scope of this invention to treat any derivative so produced to liberate the free compound of formula I, or to convert one derivative into another.

The compounds of formula I and the intermediates therefore may be isolated from their reaction mixtures using conventional techniques.

Pharmaceutically acceptable derivatives of the compounds of formula I include pharmaceutically acceptable salts, and when E is a —COOH group, esters and amides of the 2-carboxylic acid group. Suitable salts include ammonium, alkali metal (e.g. sodium, potassium

and lithium) and alkaline earth metal (e.g. calcium or magnesium) salts, and salts with suitable organic bases, e.g. salts with hydroxylamine, lower alkylamines such as methylamine or ethylamine, with substituted lower alkylamines, e.g. hydroxy substituted alkylamines such as tris(hydroxymethyl)methylamine, or with simple monocyclic nitrogen heterocyclic compounds, e.g. piperidine or morpholine. Suitable esters include simple lower alkyl esters, e.g. the ethyl ester, esters derived from alcohols containing basic groups, e.g. di-lower alkyl amino substituted alkanols such as the β-(diethylamino)-ethyl ester, and acyloxy alkyl esters, e.g. a lower acyloxy-lower alkyl ester such as the pivaloyloxymethyl ester, or a bis-ester derived from a di-hydroxy compound, e.g. a di(hydroxy-lower alkyl)ether, e.g. the bis-2-oxapropan-1,3-diyl ester. The pharmaceutically acceptable acid addition salts of the basic esters, and also of those compounds in which one of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> is a group —NR<sub>1</sub>R<sub>2</sub>, e.g. the hydrochloride, the hydrobromide, the oxalate, the maleate or the fumarate salts, may also be used. The esters may be made by conventional techniques, e.g. esterification or transesterification. The amides may be, for example, unsubstituted or mono- or di- C 1 to 6 alkyl amides and may be made by conventional techniques, e.g. reaction of an ester of the corresponding acid with ammonia or an appropriate amine.

The compounds of formula I and pharmaceutically acceptable derivatives thereof are useful because they possess pharmacological activity in animals; in particular they are useful because they inhibit the release and/or action of pharmacological mediators which result from the in vivo combination of certain types of antibody and specific antigen, e.g. the combination of reaginic antibody with specific antigen (see Example 27 of British Patent Specification No. 1,292,601). The new compounds have also been found to interfere with reflex pathways in experimental animals and man and in particular those reflexes associated with lung function. In man, both subjective and objective changes which result from the inhalation of specific antigen by sensitised subjects are inhibited by prior administration of the new compounds. Thus the new compounds are indicated for use in the treatment of reversible airway obstruction and/or to prevent the secretion of excess mucous. The new compounds are thus indicated for the treatment of allergic asthma, so-called 'intrinsic' asthma (in which no sensitivity to extrinsic antigen can be demonstrated), bronchitis, coughs and the nasal and bronchial obstructions associated with the common colds. The new compounds may also be of value in the treatment of other conditions in which antigen-antibody reactions or excess mucous secretion are responsible for, or are an adjunct to, disease, for example, hay fever; certain eye conditions, e.g. trachoma; alimentary allergy, e.g. urticaria and atopic eczema; and gastrointestinal conditions, for example gastrointestinal allergy, especially in children, e.g. milk allergy, or ulcerative colitis.

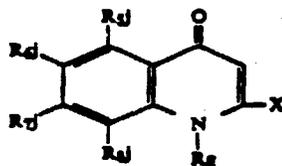
For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of from 0.001 to 50 mg per kg of animal body weight in the test set out in Example 27 of British Patent Specification No. 1,292,601. For man the indicated total daily dosage is in the range of from 0.01 mg to 1,000 mg

preferably from 0.01 mg to 200 mg and more preferably from 1 mg to 60 mg, which may be administered in divided doses from 1 to 6 times a day or in sustained release form. Thus unit dosage forms suitable for administration (by inhalation or oesophageally) comprise from 0.01 mg to 50 mg, preferably 0.01 mg to 20 mg and more preferably from 0.01 mg to 10 mg of the compound preferably admixed with a solid or liquid pharmaceutically acceptable diluent, carrier or adjuvant.

The compounds of formula I, and pharmaceutically acceptable derivatives thereof, have the advantage that they are more efficacious in certain pharmacological models, or are longer acting than compounds of similar structure to the compounds of formula I. Furthermore the compounds of formula I, and pharmaceutically acceptable derivatives thereof, are advantageous in that they are more efficacious in interfering with reflex pathways and in inhibiting the secretion of mucous than are compounds of similar structure to the compounds of formula I.

We prefer each of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>, when they contain carbon, to contain up to 8, and preferably up to 4 carbon atoms. Specifically we prefer R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> to be selected from hydrogen, methoxy, propyl, allyl, methyl, ethyl, chlorine, bromine and hydroxy. The —COCH=CE—O— chain may be bonded to the benzene ring in any sense and in any of the adjacent positions R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>. However, we prefer the chain to be bonded in the positions R<sub>6</sub> and R<sub>7</sub> the —O— part of the chain being in position R<sub>7</sub>. We also prefer the group E to be a —COOH group.

According to the invention there is also provided a process for the production of a pharmaceutically acceptable salt of a compound of formula I, which comprises treating a compound of formula Ic,



in which R<sub>8</sub> is as defined above,

R<sub>5j</sub>, R<sub>6j</sub>, R<sub>7j</sub> and R<sub>8j</sub> have the same significances as R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> above, save that an adjacent pair of R<sub>5j</sub>, R<sub>6j</sub>, R<sub>7j</sub> and R<sub>8j</sub> may form a chain —O—C(X)=CHCO—, and

X is a 5-tetrazolyl group, an (N-tetrazol-5-yl)carboxamido group, a carboxylic acid group (or an ester thereof, or another salt thereof), a nitrile group, an acid halide group or an amide group,

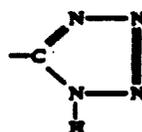
with a compound containing an available pharmaceutically acceptable cation and capable of converting the group X to a pharmaceutically acceptable salt of an E group.

Compounds capable of converting the group X to a pharmaceutically acceptable salt of an E group include compounds, e.g. bases and ion exchange resins, containing pharmaceutically acceptable cations, e.g. sodium, potassium, calcium, ammonium and appropriate nitrogen containing organic cations. In general we prefer to form the pharmaceutically acceptable salt by treating the free acid of formula I with an appropriate base, e.g. with an alkaline-earth or alkali metal hydroxide, carbonate or bicarbonate in aqueous solution or by a metathetical process with an appropriate salt. When a

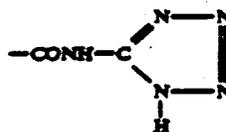
strongly basic compound is used care should be taken, e.g. by keeping the temperature sufficiently low, to ensure that the compound of formula I is not hydrolysed or otherwise degraded. The pharmaceutically acceptable salt may be recovered from the reaction mixture by, for example, solvent precipitation and/or removal of the solvent by evaporation, e.g. by freeze drying.

According to our invention we also provide a pharmaceutical composition comprising (preferably less than 80%, and more preferably less than 50% by weight) of a compound of formula I, or a pharmaceutically acceptable derivative thereof, in combination with a pharmaceutically acceptable adjuvant, diluent or carrier. Examples of suitable adjuvants, diluents or carriers are: for tablets capsules and dragées; microcrystalline cellulose, calcium phosphate, distomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin; for suppositories, natural or hardened oils or waxes; and for inhalation compositions, coarse lactose. The compound of formula I, or the pharmaceutically acceptable derivative thereof, preferably is in a form having a mass median diameter of from 0.01 to 10 microns. The compositions may also contain suitable preserving, stabilising and wetting agents, solubilizers, sweetening and colouring agents and flavourings. The compositions may, if desired, be formulated in sustained release form. We prefer compositions which are designed to be taken oesophageally and to release their contents in the gastrointestinal tract.

The 5-tetrazolyl and (N-tetrazol-5-yl)carboxamido groups are of formulae XVII and XVIII respectively,



XVII



XVIII

The groups of formulae XVII and XVIII may exist in tautomeric forms and such tautomeric forms are included within the definition of the compounds of formula I.

The invention is illustrated, but in no way limited by the following Examples.

#### EXAMPLE 1

##### 4,6-Dioxo-10-propyl-4H,6H-pyrazo[3,2-g]quinoline-2,8-dicarboxylic acid

##### (a) 4-Acetamido-2-allyloxyacetophenone

4-Acetamido-2-hydroxyacetophenone (19.3 g) allyl bromide (12.1 ml) and anhydrous potassium carbonate (21.5 g) were stirred in dry dimethylformamide (250 ml) at room temperature for 24 hours. The reaction mixture was poured into water and the product was extracted with ethyl acetate. The organic solution was then washed well with water dried over magnesium sulphate and evaporated to dryness. The sub-title product was obtained as buff coloured solid (20.5 g). The structure of

the product was confirmed by NMR and mass spectroscopy.

(b) 4-Acetamido-3-allyl-2-hydroxyacetophenone

The above allyl ether (18.4 g) was heated at 200°-210° C. for 4 hours. 17.1 g of the thermally rearranged sub-title product was obtained as a brown solid. Again the structure was confirmed by NMR and mass spectroscopy.

(c) 4-Acetamido-2-hydroxy-3-propyl acetophenone

The product of step (b) (17 g) was dissolved in glacial acetic acid and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through a kieselguhr filter and the filtrate was evaporated to leave 13.0 g of almost colourless solid. The mass and NMR spectra confirmed the structure of the product.

(d) Ethyl 7-acetamido-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A mixture of diethyl oxalate (19.3 g; 17.9 ml) and the above product of step (c) (12.4 g) in dry ethanol (100 ml) was added to a stirred solution of sodium ethoxide in ethanol (prepared by dissolving sodium (6.1 g) in dry ethanol (200 ml)). The reaction mixture was refluxed for 3 hours and then poured into dilute hydrochloric acid and chloroform. The chloroform layer was separated, washed with water and dried. The solvent was evaporated to leave a brown solid which was dissolved in ethanol (300 ml) containing concentrated hydrochloric acid (3 ml) and the whole was refluxed for 1 hour. The reaction mixture was poured into water and the product was extracted into ethyl acetate which was washed with water and dried. The solvent was evaporated to leave 10 g of a sticky solid which had mass and NMR spectra consistent with the expected product.

(e) Ethyl 7-amino-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate

A solution of the amide of step (d) (10 g) in ethanol (300 ml), containing concentrated hydrochloric acid (5 ml), was refluxed for 8 hours. The reaction mixture was diluted with water and extracted into ethyl acetate. The extract was washed with water, dried and the solvent was evaporated to leave a dark brown semisolid. This was chromatographed on a silica gel column, using ether as eluant to give 4.8 g of the required product whose structure was confirmed by mass and NMR spectral evidence; mp 84°-87° C.

(f) 8-Ethoxycarbonyl-2-methoxycarbonyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline

The amino benzopyran of step (e) (2.0 g) and dimethyl acetylene dicarboxylate (1.24 g; 1.01 ml) were refluxed in ethanol (30 ml) for 26 hours. The reaction mixture was cooled to 0° C. and the insoluble yellow-brown solid was collected by filtration and washed with a little ethanol and dried to give 2.0 g of a product which was a mixture of maleic and fumaric esters obtained by Michael addition of the amine to the acetylene.

This mixture of esters (2.0 g) was treated with polyphosphoric acid (30 ml) and heated on the steam bath with stirring for 20 minutes. The reaction mixture was then poured onto ice and stirred with ethyl acetate. The organic layer was separated, washed with water and dried. The solvent was evaporated to leave 1.6 g of a yellow orange solid. Recrystallisation of this solid from ethyl acetate gave the required product as fluffy orange needles mp 187°-188° C.

Analysis Found: C, 62.0%; H, 5.1%; N, 3.7%;  $C_{20}H_{19}NO_7$  Required: C 62.3%; H, 4.9%; N, 3.6%.

(g) 4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (2.5 g) was refluxed with sodium bicarbonate (1.64 g) in ethanol (100 ml) and water (50 ml) for 1½ hours. The whole was poured into water and acidified to precipitate a gelatinous solid. This was collected by filtration, refluxed with ethanol and the product was separated by centrifugation (1.4 g) mp 303°-304° C. dec. The structure of the product was confirmed by mass and NMR evidence.

(h) Disodium 4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The bis acid from step (g) (1.35 g) and sodium bicarbonate (0.661 g) in water (150 ml) were warmed and stirred until a clear solution was obtained. This solution was filtered and the filtrate was freeze dried to give 1.43 g of the required disodium salt.

Analysis Found: C, 46.1%; H, 4.0%; N, 2.9%;  $C_{17}H_{11}NO_7 \cdot Na_2$  12.5%  $H_2O$  required: C, 46.1%; H, 3.8%; N, 3.15%.

### EXAMPLE 2

4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(a) 4-(N-Acetyl-N-ethyl)amino-2-allyloxyacetophenone

4-(N-acetyl-N-ethyl)amino-2-hydroxyacetophenone (92.6 g), allyl bromide (51 mls) and anhydrous potassium carbonate (90.4 g) were stirred in dry dimethylformamide (500 mls) for 17 hours. The reaction mixture was poured into water and the product was extracted with ether. The organic solution was then washed well with water, dried over magnesium sulphate and evaporated to dryness. The product was obtained as an oil (102.5 g). The structure of the product was confirmed by NMR and mass spectroscopy.

(b) 4-(N-Acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone

The allyl ether product of step (a) (100.5 g) was refluxed in diethylaniline (300 mls) for 3 hours. The reaction mixture was cooled and poured into dilute hydrochloric acid and extracted into ether, which latter was washed with dilute hydrochloric acid, and then with water. The organic solution was extracted with 10% sodium hydroxide solution which was then acidified. The precipitated product was extracted with ether which was dried over magnesium sulphate. The resulting ethereal solution was evaporated to dryness to give a yellow-brown oil (78.7 g). This oil was a mixture of 4-(N-acetyl-N-ethyl)amino-3-allyl-2-hydroxyacetophenone and 6-(N-acetyl-N-ethyl)amino-3-allyl-2-hydroxyacetophenone.

This mixture was dissolved in ethanol (500 mls) and glacial acetic acid (20 mls) and hydrogenated in the presence of Adams catalyst until hydrogen uptake had ceased. The catalyst was filtered off through kieselguhr and the filtrate evaporated to leave 79.9 g of brown oil. This brown oil was a mixture and was separated by high pressure liquid chromatography using ether/petroleum ether (1:1) as solvent to give 44.2 g of the sub-title compound and 23.8 g of 6-(N-acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone.

(c) 4-N-Ethylamino-3-propyl-2-hydroxyacetophenone

4-(N-Acetyl-N-ethyl)amino-3-propyl-2-hydroxyacetophenone (44 g) was refluxed in 48% hydrogen bromide in glacial acetic acid (100 mls), glacial acetic acid (500 mls) and water (20 mls) for 6 hours. The reaction mixture was poured on to ice-water and extracted with ethyl acetate which was washed with water, sodium bicarbonate solution, then water again and dried over magnesium sulphate. The organic solvent was evaporated to dryness to leave the sub-title compound as a red oil (34 g). The structure was confirmed by NMR and mass spectroscopy.

(d) Methyl 6-acetyl-1-ethyl-7-hydroxy-4-oxo-8-propyl-4H-quinoline-2-carboxylate

The amine product of step (c) (17 g) and dimethylacetylenedicarboxylate (11.3 mls) were refluxed in ethanol (300 mls) for 17 hrs. The reaction mixture was cooled and evaporated to dryness to leave a deep red oil. This oil was chromatographed on a silica gel column using ether/petroleum ether (1:1) as eluant to give 19.1 g of dimethyl 1-(4-acetyl-3-hydroxy-2-propylphenyl)-N-ethylaminomaleate m.p. 83°-87° C.

The maleic ester (5 g) was heated and stirred in polyphosphoric acid (100 mls) on the steam bath for 10 minutes. The reaction mixture was cooled and poured on to a mixture of ice-water and ethyl acetate. The organic solution was separated, washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to leave a pale yellow solid. This product was purified by high pressure liquid chromatography to give 2.6 g of the sub title compound m.p. 121°-123° C.

Analysis Found: C: 65.5%; H: 6.6%; N: 4.2%;  $C_{15}H_{17}NO_7$ ; Required: C: 65.3%; H: 6.34%; N: 4.23%.

Methyl 6-acetyl-1-ethyl-5-hydroxy-4-oxo-4H-quinoline-2-carboxylate was obtained from the purification as a pale yellow solid (100 mgs).

(e) Diethyl 4,6-dioxo-1-ethyl-10-propyl-4H-6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The hydroxy ketone product of step (d) (1.0 g) and diethyl oxalate (3.3 mls) in dry dimethylformamide (25 mls) were added to ether washed 50% sodium hydride (0.581 g) in dry dimethylformamide (20 mls) and the reaction mixture stirred for 4 hours. The reaction mixture was then poured into water, acidified and extracted with ethyl acetate, which was then washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to give an oil which was dissolved in ethanol (100 mls) and concentrated hydrochloric acid (a few drops) added. The solution was refluxed for 1 hr, cooled, poured into water and extracted with ethyl acetate, which was washed with water and dried over magnesium sulphate. The solvent was evaporated to dryness to leave an oil which solidified on trituration with 40°-60° petroleum ether (1.2 g). The structure of the compound was confirmed by NMR.

(f) 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

The above bis ester (1.0 g) and sodium bicarbonate (0.787 g) in ethanol (85 mls) and water (32 mls) were refluxed for 4 hours. The reaction mixture was poured into water, acidified and the precipitate was collected by filtration and dried. The product was purified by trituration with boiling ethanol, then twice with boiling acetone. After each trituration the mixture was centrifuged and the supernatant liquid was removed by decantation. The residual solid was dried to give 0.347 g of

the required di-acid as a yellow powder m.p. 298°-300° C. dec.

Analysis: Found: C: 61.3%; H: 5.0%; N: 3.6%;  $C_{19}H_{17}NO_7$ ; Required: C: 61.5%; H: 4.6%; N: 3.79%.

(g) Disodium 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate

The above di-acid (4.098 g), suspended in water (100 mls) and was treated with sodium bicarbonate (1.82 g). The resulting solution was filtered and the filtrate was treated with acetone until complete precipitation of the product had occurred. The required di-sodium salt was filtered off and dried to give 3.39 g of a pale yellow powder.

Analysis: Found: C: 51.1%; H: 4.3%; N: 3.0%;  $C_{19}H_{15}MN_2O_7$ ; Required: C: 51.1%; H: 4.1%; N: 3.1% (6.9% water).

### EXAMPLE 3

The following compounds may also be made by the processes described above:

(i) 5-Ethyl-4,8-dioxo-10-propyl-4H,8H-pyrano[2,3-h]quinoline-2,6-dicarboxylic acid

(ii) 4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-dicarboxylic acid

(iii) 10-Bromo-4,6-dioxo-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid

(iv) 5-Hydroxy-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid ;P1

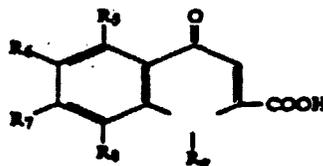
(v) 4,9-Dioxo-4H,9H-pyrano[2,3-g]quinoline-2,7-dicarboxylic acid

(vi) 4,10-Dioxo-4H,10H-pyrano[2,3-f]quinoline-2,8-di[N-(tetrazol-5-yl)]carboxamide

(vii) 10-Bromo-4,6-dioxo-2,8-di-(tetrazol-5-yl)-4H,6H-pyrano[3,2-g]quinoline.

We claim:

1. A compound having the formula



in which  $R_5$  and  $R_7$  form a chain  $-\text{COCH}=\text{C}(\text{COOH})-\text{O}-$ ,

$R_5$  and  $R_6$ , which may be the same or different, are sterically compatible substituents selected from hydrogen and alkyl having up to 8 carbon atoms, and

$R_8$  is hydrogen or alkyl having up to 8 carbon atoms, and pharmaceutically acceptable salts and ethyl esters thereof.

2. A compound according to claim 1, wherein each of  $R_5$ ,  $R_6$  and  $R_8$ , when they are alkyl, contain up to 4 carbon atoms.

3. A compound according to claim 1, wherein the  $-\text{COCH}=\text{C}(\text{COOH})-\text{O}-$  chain is bonded with the  $-\text{O}-$  end thereof in position  $R_7$ .

4. A compound according to claim 1, wherein  $R_5$  and  $R_6$  are selected from hydrogen and propyl.

5. A compound according to claim 1, wherein  $R_8$  is ethyl.

6. 4,6-Dioxo-1-ethyl-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylic acid or a pharmaceutically acceptable salt thereof.

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7. 4,6-Dioxo-10-propyl-4H,6H-pyrano[3,2-g]quino-  
line-2,8-dicarboxylic acid or a pharmaceutically accept-  
able salt thereof.

8. A pharmaceutical composition suitable for the 5  
treatment of a condition involving an antibody antigen  
reaction or a reflex pathway comprising an effective  
amount of a compound according to claim 1 in combi-  
nation with a pharmaceutically acceptable adjuvant, 10  
diluent or carrier.

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9. A composition according to claim 8 comprising  
less than 80% by weight of active ingredient.

10. A composition comprising from 0.01 mg to 50 mg  
of a compound according to claim 1, as active ingredi-  
ent, in unit dosage form.

11. A method of treatment of a condition involving  
an antibody antigen reaction or a reflex pathway, which  
comprises administering an effective amount of a com-  
pound according to claim 1 to an animal suffering from  
such a condition. . . . .

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# United States Patent (19)

Brown et al.

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[54] **SOLID NEDOCROMIL SODIUM, USEFUL FOR THE REMOVAL OF OBSTRUCTED AIR PATHWAYS**

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[58] **Field of Search** \_\_\_\_\_ 546/89, 92; 514/291

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## [57] ABSTRACT

There are described new forms of nedocromil sodium, methods of producing these new forms and pharmaceutical formulations, especially pressurized inhalation aerosol formulations, containing finely divided nedocromil sodium. The formulations are indicated for the treatment of reversible obstructive conditions of the airways.

15 Claims, 6 Drawing Sheets

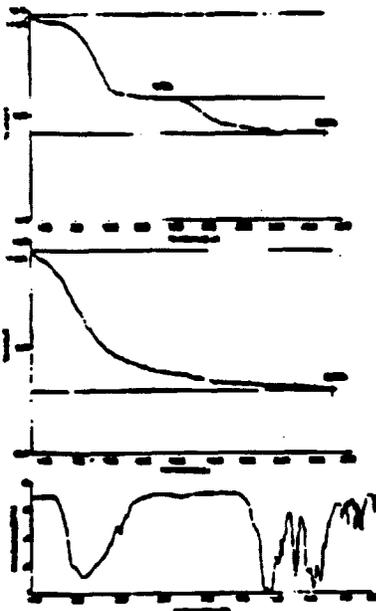


Fig.1

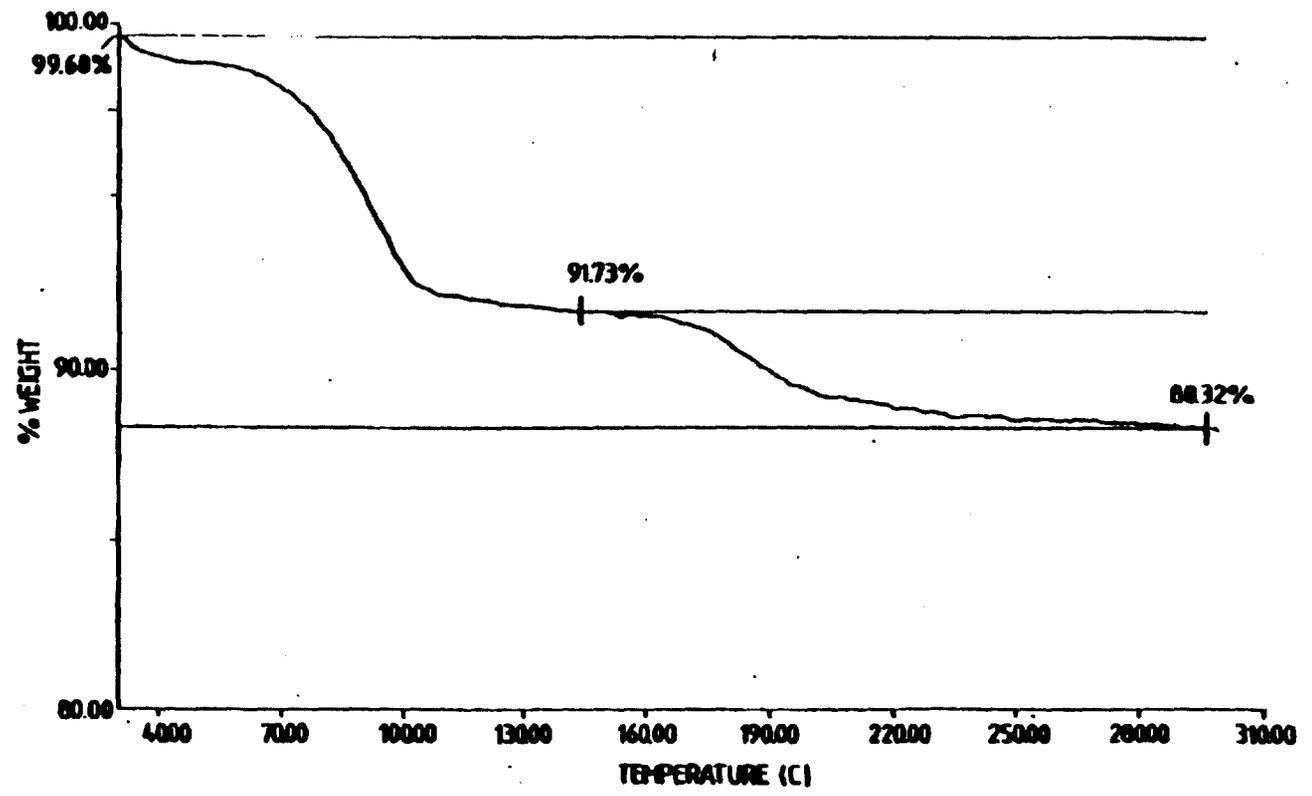


Fig. 2.

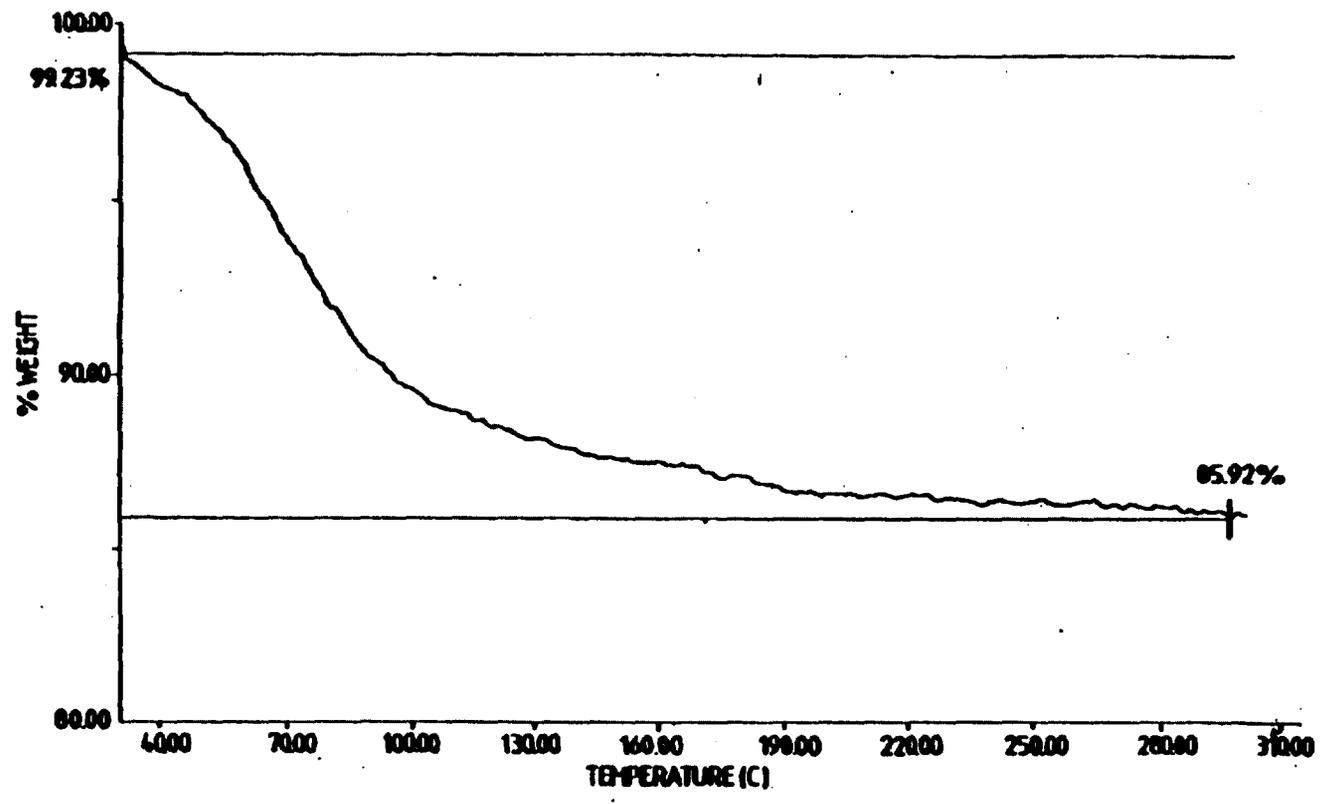


Fig.3.

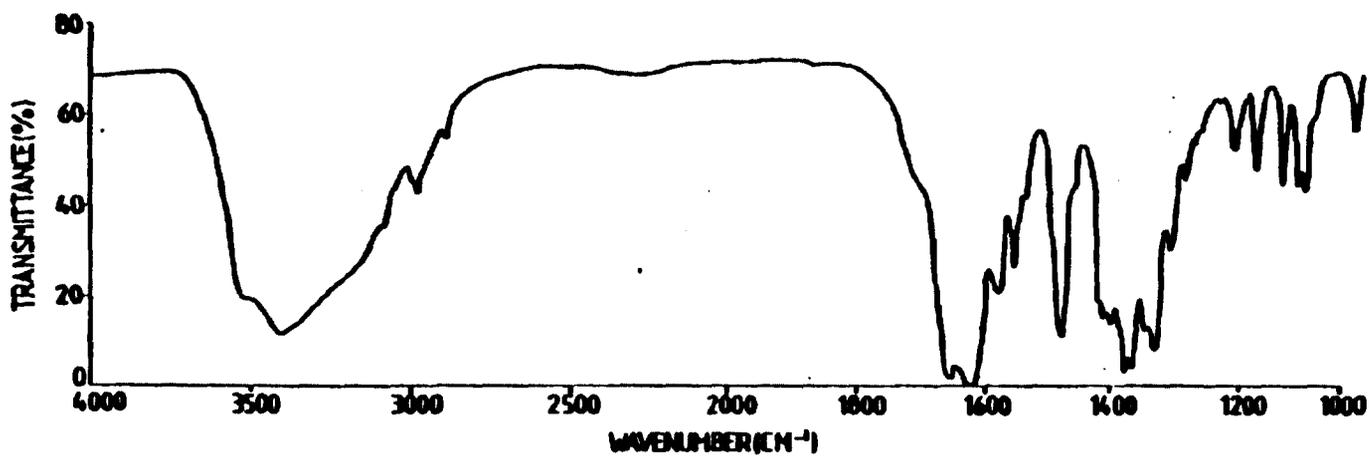


Fig. 4.

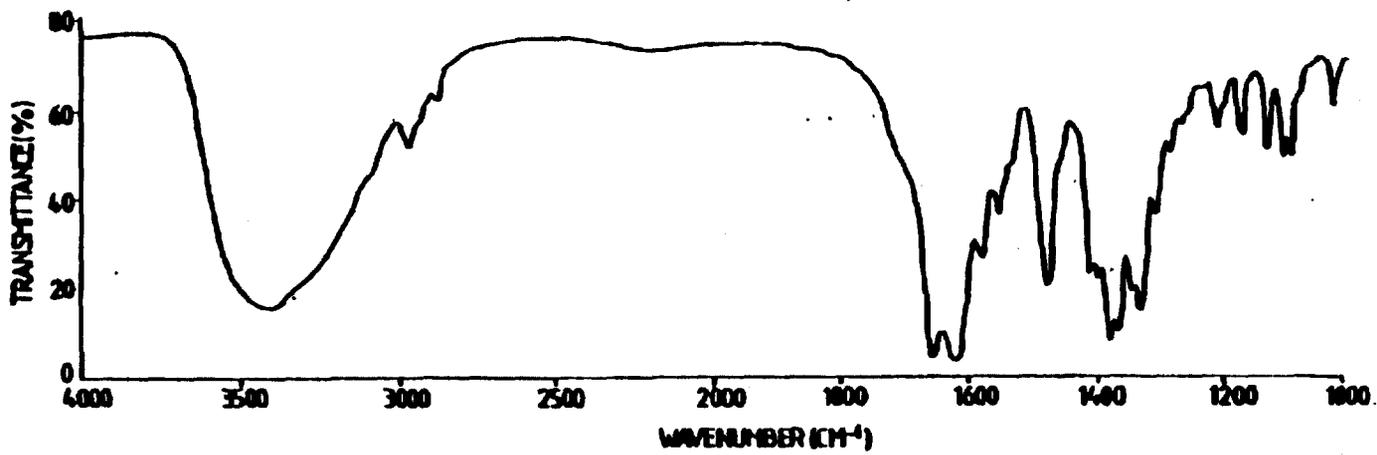


Fig. 5.

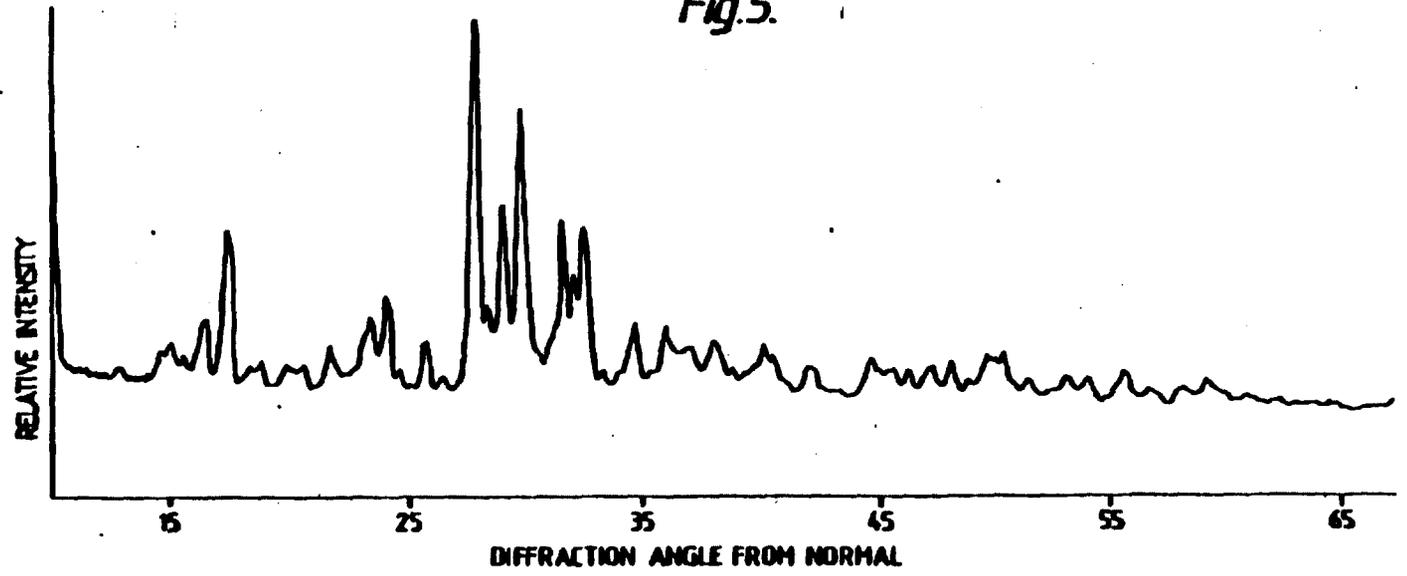
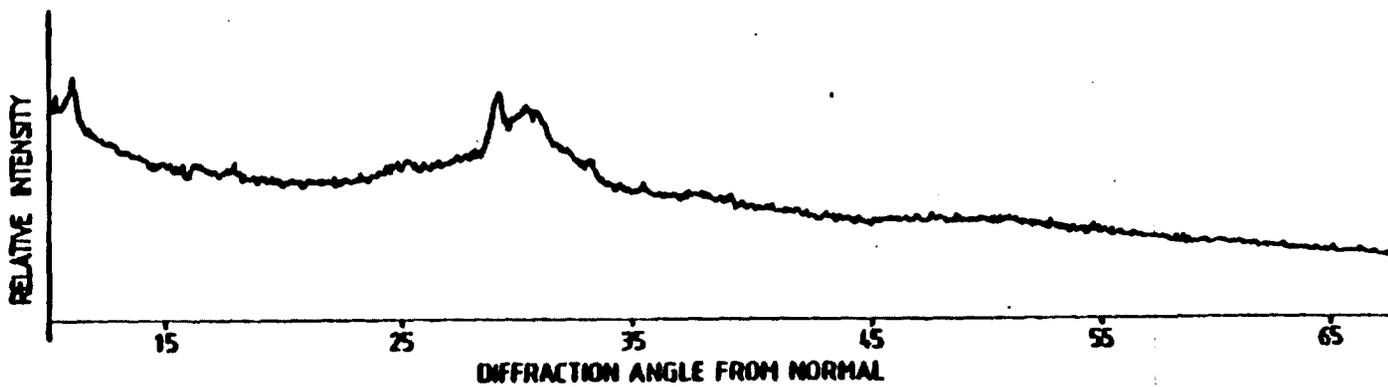


Fig. 6.



**SOLID NEDOCROMIL SODIUM, USEFUL FOR  
THE REMOVAL OF OBSTRUCTED AIR  
PATHWAYS**

This invention relates to a new form of drug and pharmaceutical formulations containing it.

In British Patent Specification No. 2,022,078 a large number of pyrazoquinolone derivatives are described as being useful *inter alia* as prophylactic inhalation anti-asthmatics when administered as unit dosages of from 0.01 to 10 mg in admixture with coarse lactose. This patent specification also discloses the disodium salt of 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrazo[3,2-g]quinoline-2,8-dicarboxylic acid, which salt is commonly known as nedocromil sodium or TILADE (TILADE is a registered trade mark).

It is further known to be desirable to make inhalation pharmaceuticals in the form of fine particles. These fine particles are conventionally made by grinding or milling larger sized particles of the pharmaceutical. Generally grinding and milling machines are extremely efficient and reduce the particle size of the material as far as they are capable in a single pass. Indeed the mass median diameter of product material can increase after a second pass through the grinder because some of the finest particles are lost to the system. We have also attempted to produce a material of very fine particle size by air classification of ground nedocromil sodium. However the product was of larger mean particle size than the starting material. We have thus found that with nedocromil sodium there is a very real difficulty in obtaining material which is of the optimum very fine particle size.

We have now found that nedocromil sodium is particularly suited to formulation as a pressurized aerosol formulation. We have also found new hydrated and fine particle forms of this compound.

According to the invention we provide a pharmaceutical formulation containing nedocromil sodium and a pharmaceutically acceptable liquefied gas aerosol propellant.

The nedocromil sodium is preferably finely divided, e.g. having a mass median diameter in the range 0.01 to 10 microns. We particularly prefer the nedocromil sodium to have a mass median diameter of less than 4 microns and especially of less than 3.0 microns and most preferably of less than 2.8 microns. We also prefer not more than 5% by weight of the particles to have a diameter of greater than 10 microns and more preferably not more than 90% by weight of the particles to have a diameter of less than 6 microns. The nedocromil sodium is also preferably in a hydrated form (contrary to conventional teaching in the aerosol art) containing from 3 to 8%, preferably 3 to 6%, w/w water. Nedocromil sodium containing less than 5%, preferably 3 to 4% and most preferably about 3.5% w/w of water is new and represents a further feature of this invention. This material can be made by drying material of higher water content for, for example, 8 to 15 hours at 80° to 150° C., preferably 100° to 120° C. and especially at 105° C.

We prefer the composition to contain from 0.5 to 12%, more preferably from 0.5 to 10%, and most preferably from 0.5 to 5%, e.g. about 1 to 3.5% by weight of finely divided nedocromil sodium.

We have also found that nedocromil sodium can exist in two different forms. Thus there is a more stable and

desired form A which is light yellow in colour. This form A of nedocromil sodium when in powder form containing 10% w/w of total water gives a yellow reading of below 2.0 and preferably of 0.8 to 1.8 using a Lovibond tintometer. Form A material has low readings, e.g. of less than 0.2 and preferably of zero, in the red and blue scales of the Lovibond tintometer.

Form A material also has bound water (i.e. between 3.0 and 4.0, e.g. about 3.5% w/w water) which cannot readily be removed by intensive drying at atmospheric pressure without destroying the compound. The presence of bound water is the most characteristic feature of form A material.

Form A material containing bound water can best be identified by thermogravimetric analysis in which the temperature of the material to be tested is increased at a constant rate and the change in weight of the sample is recorded against time. For material containing bound water the thermogravimetric trace is discontinuous and, for example, shows a plateau of substantially constant weight from about 100° to 160° C. when the temperature of a 5 mg sample is increased at 20° C. per minute.

Form A material can also be identified in that the powder X-ray diffraction pattern shows marked and separated peaks between 27° and 34° diffraction angle, typically peaks at 28.5°, 29.5°-30.5° (doublet) and 32°-33° (doublet). These peaks indicate that the material is crystalline.

Form A material also shows a shoulder in its infra-red spectrum at 3500  $\text{cm}^{-1}$  when the total (i.e. bound plus unbound) water content of the material under test is 10% w/w.

In addition to the form A material there is a less desired form B which is of darker yellow colour, i.e. gives a yellow reading of 2.0 or more at 10% w/w total water using a Lovibond tintometer. Form B material also has no bound water and gives an essentially continuous trace on thermogravimetric analysis. The powder X-ray diffraction pattern for form B material also shows no marked peaks and is indicative that the material is amorphous.

Form B material also shows no shoulder at 3500  $\text{cm}^{-1}$  in its infra-red spectrum when the total water content of the material is 10% w/w.

Both forms A and B of the material when examined under the microscope appear to be crystalline, but the powder X-ray diffraction patterns indicate otherwise.

Form B material is less preferred in that it can, but does not necessarily, change spontaneously (sometimes after a very considerable time) to form A and in so doing can coalesce to produce hard and intractable lumps of particle size larger than the original material. Such a change, if it were to take place when the nedocromil sodium was in a pharmaceutical formulation, e.g. an aerosol formulation, could prove highly deleterious.

We have also found a method of producing nedocromil sodium in either form A or form B, and particularly a sub-form of form A which is suitable for grinding to produce very fine material.

According to the invention we further provide a process for the preparation of solid nedocromil sodium, preferably in a sub-form of form A suitable for milling or grinding, which comprises mixing an aqueous solution of nedocromil sodium with a water miscible precipitating solvent for the nedocromil sodium the ratio of nedocromil sodium to water to precipitating solvent being in the range 1 part by weight of nedocromil sodium: from 2 to 5, preferably about 3, parts by volume

of water: from 10 to 25, preferably 16 to 20 and especially about 18 parts by volume of precipitating solvent.

Up to about 10, and preferably 3 to 8, e.g. 6, parts by volume of precipitating solvent per part by weight of nedocromil sodium may be present in the initial aqueous solution (prior to the mixing) and the remainder of the precipitating solvent may be used to precipitate the nedocromil sodium.

The precipitating solvent for the nedocromil sodium should be such that only a small amount of the nedocromil sodium will be dissolved in the final aqueous mixture containing the precipitating solvent. Suitable precipitating solvents include lower alkyl ketones, e.g. methyl ethyl ketone, and C2 to 6 alcohols, e.g. ethanol or most preferably propanol, especially isopropanol. Isopropanol is particularly advantageous in that it is a poor solvent for nedocromil sodium.

The aqueous solution preferably has a pH in the range 5.0 to 7.5.

The concentration of nedocromil sodium in the final mixture must be sufficiently low for the mixture to be adequately agitated, but should not be so low that the volumes involved and the losses of nedocromil sodium through solubility etc. become uneconomic.

We particularly prefer to use an aqueous solution of nedocromil sodium which is at a temperature of from 55° to 85° C., preferably about 65° to 75° C. and for the precipitating solvent to be at 25° C. or below before mixing.

The precipitating solvent is preferably mixed with, e.g. added to, the aqueous solution quickly, e.g. over a period of up to 20 minutes, and preferably over about 5 minutes. The mixing may also take place in a continuous process. Once the mixing has taken place the total mixture may be agitated, e.g. stirred, and preferably also cooled, to a temperature of from about 25° to 40° C., e.g. to about 25° C., for a further period, e.g. of about 1-3 hours, preferably 1.5 to 2.5 hours, to ensure that precipitation is as complete as possible. The use of lower temperatures, e.g. temperatures of the final mixture of below 25° C., lower proportions of solvent to water and longer stirring times tends to favour the production of viscous slurries which are difficult to handle and which contain form B of the nedocromil sodium. Thus we prefer to control the process so that the final mixture has a viscosity of less than 2,000, and more preferably less than 500 centipoise.

The nedocromil sodium may be separated from the aqueous solvent, e.g. by filtration, followed by washing with the precipitating solvent, and drying to constant weight, e.g. at 50° to 60°, for, for example, from 12 to 48 hours. The precipitating solvent, and any dissolved or entrained nedocromil sodium may, if desired, be recovered from the filtrate. Alternatively the filtrate may be recycled. Any form B material produced may also be recycled or may be converted to form A material by subjecting it to an atmosphere of high humidity, e.g. 90 to 95% humidity, and subsequently removing any excess water. The process may be carried out at ambient temperature, e.g. 15° to 30° C., over a period of, e.g. 5 to 24 hours. Any excess water may be removed by conventional drying techniques.

The dried product from the precipitation process can comprise crystalline needles of form A of nedocromil sodium having a breadth of from 1.5 to 3.5, and preferably 1.5 to 2.5, microns and a length to breadth ratio of up to 10:1. The nedocromil sodium in the form of the needles is new and forms a feature of this invention.

The new crystalline needles may be subjected to conventional grinding or milling techniques to provide nedocromil sodium of mass median diameter of less than 4 microns, e.g. of from 2 to 3 microns.

By mass median diameter we mean the diameter such that half the particulate mass is in particles of lesser diameter and half in particles of greater diameter. The mass median diameter is essentially a Stokes diameter and may be determined using a Joyce Lorbl sedimentation disc centrifuge either in a two layer or one start photometric mode (Bagness J and Orrway A. Proc Soc. Analyt. Chem. Part 4, Vol 9, 1972 pages 83-86).

The nedocromil sodium of mass median diameter less than 4 microns when formulated as aerosol units and when the units are examined using a single stage liquid impinger (modification of that described in J. Pharm. Pharmacol. 1973, 25, Suppl. 32P-36P) produces a greater dispersion than exactly analogous units containing nedocromil sodium of larger mass median diameter. The single stage liquid impinger samples the whole cloud delivered from the aerosol and separates it into two fractions by inertial impaction. The fraction of smaller particle size is less than 10 microns in aerodynamic diameter and represents material which is likely to penetrate into the deeper regions of the human airways.

By providing a greater proportion of fine particles of nedocromil sodium the invention enables a lower dosage of drug to be administered and/or for an equivalent amount of drug to produce a greater or longer lasting effect.

The precipitation process described above in addition to being capable of providing the nedocromil sodium in a form suitable for grinding also serves where necessary to remove water, and precipitating solvent, soluble impurities from the crude nedocromil sodium.

The fine nedocromil sodium is preferably dried thoroughly, e.g. to as close as possible to 3.5% w/w water, before it is incorporated into the liquefied propellant medium.

The liquefied propellant medium, and indeed the total formulation is preferably such that the nedocromil sodium does not dissolve therein to any substantial extent.

The liquefied propellant is preferably a gas at room temperature (20° C.) and atmospheric pressure i.e. it should have a boiling point below 20° C. at atmospheric pressure. The liquefied propellant should also be non-toxic. Among the suitable liquefied propellants which may be employed are dimethyl ether and alkanes containing up to five carbon atoms, e.g. butane or pentane, or a lower alkyl chloride, e.g. methyl, ethyl or propyl chlorides. The most suitable liquefied propellants are the fluorinated and fluorochlorinated lower alkanes such as are sold under the Registered Trade Mark 'Freon'. Mixtures of the above mentioned propellants may suitable be employed. Examples of these propellants are dichlorodifluoromethane ('Propellant 12'), 1,2-dichlorotetrafluoroethane ('Propellant 114') trichloromonofluoromethane ('Propellant 11'), dichloromonofluoromethane ('Propellant 21'), monochlorodifluoromethane ('Propellant 22'), trichlorotrifluoroethane ('Propellant 113'), and monochlorotrifluoroethane ('Propellant 13'). Propellants with improved vapour pressure characteristics may be obtained by using certain mixtures of these compounds, e.g. 'Propellant 11' with 'Propellant 12', or 'Propellant 12' with 'Propellant 114'. For example, 'Propellant 12', which has a vapour pressure of about 370 k Pa (absolute) at 20° C. and 'Pro-

pellant 114', with a vapour pressure of about 180 k Pa (absolute) at 20° C., may be mixed in various proportions to form a propellant having a desired intermediate vapour pressure. We prefer compositions which do not contain trichloromonofluoromethane.

It is desirable that the vapour pressure of the propellant employed be between 380 and 500, and preferably between 410 and 470 k Pa (absolute) at 20° C. Such a propellant mixture is usable safely with metal containers. Other mixtures of 'Propellant 12' with 'Propellant 114', or of 'Propellant 12' with 'Propellant 11', or of 'Propellant 12' with 'Propellant 11' and 'Propellant 114' with absolute vapour pressures at 20° C. in the range 230 to 380 k Pa are usable safely with specially reinforced glass containers.

The composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of the sodium salt.

The preferred solid anionic surface active agent is sodium dioctyl-sulphosuccinate.

The amount of the surface active agent required is related to the solids content of the suspension and to the particle size of the solids. In general it is only necessary to use 5-15%, and preferably 5-8%, of the solid anionic surface active agent by weight of the solids content of the suspension. We have found that, under certain conditions, use of a solid anionic surface active agent gives a better dispersion of medicament when the composition is released from a pressurised pack than does the use of a liquid non-ionic surface active agent.

When a liquid, non-ionic surface-active agent is employed it should have an hydrophile-lipophile balance (HLB) ratio of less than 10. The HLB ratio is an empirical number which provides a guide to the surface-active properties of a surface-active agent. The lower the HLB ratio, the more lipophilic is the agent, and conversely, the higher the HLB ratio, the more hydrophilic is the agent. The HLB ratio is well known and understood by the colloid chemist and its method of determination is described by W C Griffin in the *Journal of the Society of Cosmetic Chemists*, Vol 1, No 3, pages 311-326 (1949). Preferably the surface-active agent employed should have an HLB ratio of 1 to 5. It is possible to employ mixtures of surface-active agents, the mixture having an HLB ratio within the prescribed range.

Those surface-active agents which are soluble or dispersible in the propellant are effective. The more propellant-soluble surface-active agents are the most effective.

We prefer the liquid non-ionic surface-active agent to comprise from 0.1 to 2%, and more preferably from 0.2 to 1%, by weight of the total composition. Such compositions tend to be more physically stable on storage.

Among the liquid non-ionic surface-active agents which may be employed are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octoic, lauric, palmitic, stearic, linoleic, linolenic, elaeostearic and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arbutol, mannitol, sorbitol, the hexatriol anhydrides derived from sorbitol (the sorbitan esters sold under the Registered Trade Mark 'Span') and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides, may be employed.

The preferred liquid non-ionic surface-active agents are the esters of sorbitan, e.g. those sold under the Registered Trade Marks 'Arlacel C' (Sorbitan sesquioleate), 'Span 80' (Sorbitan monooleate) and 'Span 85' (Sorbitan trioleate). Specific examples of other liquid non-ionic surface-active agents which may be employed are sorbitan monolaurate, polyoxyethylene sorbitol tetraoleate, polyoxyethylene sorbitol pentaoleate, and polyoxypropylene mannitol dioleate. A solid non-ionic surface active agent which may be mentioned is lecithin, e.g. soya lecithin, a vegetable lecithin extracted from soya beans, but lecithin is not preferred.

We particularly prefer compositions containing a sorbitan or sorbitol ester, e.g. sorbitan trioleate, in a mixture of propellants 12 and 114. We prefer the ratio of propellant 12 to 114 to be in the range 2 to 1:1, and preferably about 1.5:1 by weight, i.e. we prefer an excess of propellant 12 over propellant 114.

As mentioned above contrary to the conventional teaching in the medicinal aerosol art, we prefer to use the nedocromil sodium in hydrated form. We also prefer the total water content of the formulation to be in the range of 500 to 3,500 ppm. The formulation when initially made preferably has a water content at the lower end of this range, but the water content tends to rise on storage.

Pressurised aerosol formulations of the nedocromil sodium are advantageous in that they are more convenient for the patient to use, and that lower dosages of nedocromil sodium can be used (thus avoiding any possible side-effects) when compared to so-called dry powder (e.g. lactose) formulations of the nedocromil sodium.

We prefer packages containing from about 8 to 30 ml of composition, e.g. a conventional aerosol pressure pack of 10 ml. The pack preferably has a valve adapted to deliver unit dosages of between 0.025 and 0.25 ml, and preferably 0.05 or 0.1 ml, of composition. We prefer the valve to deliver 1, 2 or 4 mg of nedocromil sodium and unit doses of these quantities of the drug are provided.

The compositions of the invention may be made by mixing the various components at a temperature and pressure at which the propellant is in the liquid phase and the nedocromil sodium is in the solid phase.

In producing the compositions and packages of the invention, a container equipped with a valve is filled with a propellant containing the finely-divided nedocromil sodium in suspension. A container may first be charged with a weighed amount of dry nedocromil sodium which has been ground to a predetermined particle size, or with a slurry of powder in the cooled liquid propellant. A container may also be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in that component of the propellant which boils above room temperature may be placed in the container, the valve sealed in place, and the balance of the propellant may be introduced by pressure filling through the valve nozzle. As a further alternative a bulk of the total composition may be made and portions of this bulk composition may be filled into the container through the valve. Throughout the preparation of the product care is desirably exercised to minimise the absorption of moisture. On operating the valve, the powder will be dispensed in a stream of propellant, which will vaporise providing an aerosol of dry powder.

The compositions of the invention may be used in the treatment of a number of allergic conditions in mammals, e.g. the inhalation treatment of reversible obstructive conditions of the airways, such as asthma or allergic rhinitis (hay fever). The treatment is preferably by oral or nasal inhalation and is preferably treatment of man.

The invention is illustrated, but in no way limited by the following Examples.

#### EXAMPLE 1

##### Method

The sorbitan ester is dispersed in up to half the propellant 12 at  $-40^{\circ}\text{C}$ . while stirring with a high dispersion mixer. The nedocromil sodium is added to the resulting dispersion and disperses in it very readily. The balance of the propellant 12 is then added at  $-50^{\circ}\text{C}$ , followed by the propellant 114 also cooled to  $-50^{\circ}\text{C}$ . The resulting mixtures are then filled into vials onto which valves, e.g. metering valves, are subsequently crimped.

Ingredients	
Nedocromil sodium (form A) containing 1.9% bound water, mean median diameter less than 1 micron	0.270
Sorbitan trioleate	0.081
Propellant 114	7.099
Propellant 12	10.059
	17.509

##### Stability

Batches of vials fitted with metering valves and containing the above formulations were stored at  $5^{\circ}\text{C}$ ,  $25^{\circ}\text{C}$  and  $37^{\circ}\text{C}$ , respectively for a period of 18 months. No change in (a) the amount of nedocromil sodium dispensed per shot, (b) the content of fine particles in the cloud or (c) the crystal size of the nedocromil sodium was observed over the period of observation.

#### EXAMPLE 2

Twenty grams of the nedocromil sodium were dissolved in 60 ml of deionised water and 180 ml of isopropyl alcohol by heating to reflux at  $81^{\circ}\text{C}$ . To this solution was then added a further 190 ml of isopropanol (temperature  $25^{\circ}\text{C}$ .) with agitation. The crystal slurry was then cooled in air, maintaining agitation, until a temperature of  $25^{\circ}\text{C}$ . had been reached. The crystals were then filtered on a Buchner filter, using a styrene filter cloth. The filter cake was washed with a displacement volume of isopropanol and filtered further. The cake was then dried in an oven, at atmospheric pressure and  $60^{\circ}\text{C}$ , to constant weight.

#### EXAMPLE 3

1 Kg of nedocromil sodium is dissolved in three litres of deionised water and six litres of isopropanol at  $30^{\circ}\text{C}$ , and the mixture is then heated to reflux (at  $81^{\circ}\text{C}$ .) with agitation to ensure dissolution. The resulting solution is cooled slightly to about  $75^{\circ}\text{C}$ . and then added to another 12.5 litres of isopropanol at a temperature of about  $-8^{\circ}\text{C}$ , as quickly as possible. This precipitates out most of the nedocromil sodium and produces a slurry. This slurry is then stirred and cooled to  $25^{\circ}\text{C}$ . over about an hour, to precipitate out further material. The temperature of the slurry is kept at  $25^{\circ}\text{C}$ . and the slurry

filtered as soon as possible to remove the mother liquor, and then dried to constant weight at  $60^{\circ}\text{C}$ .

#### EXAMPLE 4

Twenty grams of nedocromil sodium were mixed with 60 ml of deionised water and 180 ml isopropanol in a 700 ml reaction flask. The mixture was agitated with an anchor-type stirrer at 120 rpm, and heated to its boiling point at around  $80^{\circ}\text{C}$ . The flask was fitted with a water-cooled condenser to prevent escape of isopropanol vapour. The resulting solution was refluxed for about 10 minutes to ensure complete dissolution. The hot solution of nedocromil sodium was then cooled to  $75^{\circ}\text{C}$ . and then added in about 20 seconds to 190 ml of isopropanol at  $8^{\circ}\text{C}$ . The resulting slurry was stirred with the anchor agitator and cooled to  $25^{\circ}\text{C}$ . in the reaction flask. The time taken for cooling was about 45 minutes and throughout this time the crystal slurry remained as the pale yellow, free flowing form. The slurry was then filtered on a Buchner filter using styrene filter cloth, washed with about 50 ml isopropanol and dried in an oven at  $60^{\circ}\text{C}$ . to constant weight. The resulting dried material was Apex milled, and micronised in a fluid energy mill. The nedocromil sodium was then subjected to particle size analysis by the Joyce-Loebel disc centrifuge method.

In four laboratory precipitations using this method particles of mass mean diameter 2.1, 2.3, 2.8 and 2.8 microns were produced, and these gave aerosol dispersions of 26% and 23% from a 30 microthru valve using the formulation described in Example 1. The dispersion was measured with a single stage liquid impinger.

#### EXAMPLE 5

Twenty grams of crude nedocromil sodium were mixed with 60 ml of deionised water and 120 ml isopropanol in a 700 ml flask. The mixture was agitated with an anchor-type stirrer at 120 rpm, and heated to its boiling point. The solution was refluxed for about 10 minutes to ensure complete dissolution, and then cooled to  $75^{\circ}\text{C}$ . At this temperature the solution was added to a further 250 ml of isopropanol which was at a temperature of about  $-8^{\circ}\text{C}$ . The resulting slurry was stirred with an anchor agitator as in Example 4 and cooled to  $25^{\circ}\text{C}$  in air. At this temperature the slurry, which was pale yellow and free flowing, was filtered on the Buchner filter, washed and dried.

#### EXAMPLE 6

Twenty grams of crude nedocromil sodium were mixed with 60 ml of deionised water and 180 ml of isopropyl alcohol in a 700 ml reaction flask. The mixture was agitated with an anchor-type agitator at 120 rpm and heated to boiling point at about  $80^{\circ}\text{C}$ . The solution was refluxed for 10 minutes and then cooled to  $75^{\circ}\text{C}$ . To it was then added a further 140 ml isopropanol at  $15^{\circ}\text{C}$ . The resulting mixture had a temperature of  $66^{\circ}\text{C}$ . The resulting slurry was then agitated as in Example 4 and cooled in an ice/salt/isopropanol bath to  $22^{\circ}\text{C}$ . in 30 minutes. A thick, bright yellow slurry was produced which had a viscosity of about 20,000 centipoise. This slurry was filtered, washed and dried as in Example 4. The material was shown to contain no tightly bound water, i.e. in the form B.

Example 6 illustrates the production of the undesirable thick crystal slurry; i.e. using less isopropanol in the solvent mix and cooling quickly in an ice bath to

below 25° C. Examples 2 to 5 show methods of producing nedocromil sodium in form A.

EXAMPLE 7

(a) Two samples of about 5 mg of nedocromil sodium were submitted to thermogravimetric analysis at a scan rate of 20° C. per minute.

We claim:

1. Solid nedocromil sodium which is crystalline and which contains bound water as determined by thermogravimetric analysis.

2. Solid nedocromil sodium according to claim 1 containing between 3.0 and 4.0% w/w bound water.

3. Solid nedocromil sodium according to claim 1 containing 3.5% bound water.

4. Nedocromil sodium according to claim 2 in powder form and having a Lovibond yellow reading of below 2.0 when containing 10% w/w water.

5. Nedocromil sodium according to claim 4 having a Lovibond yellow reading of between 0.8 and 1.1.

6. Nedocromil sodium according to claim 1 wherein the powder X-ray diffraction pattern shows that the material is crystalline.

7. Nedocromil sodium according to claim 1 whose infra-red spectrum shows a shoulder at 3300 cm<sup>-1</sup> when its total water content is 10% w/w.

8. An inhalation formulation for treatment of a reversible obstructive condition of the airways comprising a pharmaceutically acceptable liquefied gas propel-

lant containing nedocromil sodium according to claim 1 having a mass median diameter of less than 4 microns in a proportion which is effective for treatment of said condition.

9. A formulation according to claim 8, wherein not more than 5% by weight of the particles has a diameter of greater than 10 microns and not less than 90% by weight of the particles has a diameter of less than 6 microns.

10. A formulation according to claim 8, containing from 0.5 to 10% by weight of finely divided nedocromil sodium.

11. A formulation according to claim 8 comprising a mixture of propellants 12 and 114, the proportion of propellant 12 to 114 being in the range 2 to 1:1 by weight.

12. A formulation according to claim 11 containing sorbitan trioleate.

13. Nedocromil sodium in accordance with claim 1 the form of needles having a breadth of 1.5 to 3.5 microns and a length to breadth ratio of up to 10:1.

14. Nedocromil sodium according to claim 13 having a breadth of 1.5 to 2.5 microns.

15. A method of treatment of a reversible obstructive condition of the airways in a mammal which comprises administering by inhalation an effective amount of solid nedocromil sodium according to claim 1 to a mammal suffering from said condition.

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EXCLUSIVITY SUMMARY for NDA # 21-009 SUPPL # NA  
Trade Name Alocril Generic Name Nedocromil Sodium 2%  
ophthalmic solution  
Applicant Name Allergan HFD-550  
Approval Date, if known \_\_\_\_\_

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / X / NO / \_\_\_ /

b) Is it an effectiveness supplement? YES / \_\_\_ / NO / X /

If yes, what type? (SE1, SE2, etc.) NA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / X / NO / \_\_\_ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:  
\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES / X / NO / \_\_\_ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES / \_\_\_ / NO / X /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / \_\_\_ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-660 Tilade Inhaler  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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YES /  / NO /  /

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /X/

If yes, explain: \_\_\_\_\_

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 1170/1, Study 1959, Study 1871, Study 1242

~~Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.~~

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Study 1242  
 Investigation #1 1170/1 YES /\_\_\_/ NO /X/  
 Investigation #2 1959 YES /\_\_\_/ NO /X/  
 Study 1871 NO X

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
 \_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Study 1242  
 Investigation #1 1170/1 YES /\_\_\_/ NO /X/  
 Investigation #2 1959 YES /\_\_\_/ NO /X/  
 Study 1871 NO X

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
 \_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 1242 Study 1959  
 Study 1170/1 Study 1871

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Study 1170/1	IND # <input type="checkbox"/>	YES / <input checked="" type="checkbox"/> /	NO / <input type="checkbox"/> /	Explain: _____
IND # 28,462	Study 1871	YES	<input checked="" type="checkbox"/>		
Investigation #2	Study 1959	IND # <input type="checkbox"/>	YES / <input checked="" type="checkbox"/> /	NO / <input type="checkbox"/> /	Explain: _____
IND <input type="checkbox"/>	Study 1242	YES	<input checked="" type="checkbox"/>		

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	YES / <input type="checkbox"/> / Explain _____	NO / <input type="checkbox"/> / Explain _____
Investigation #2	YES / <input type="checkbox"/> / Explain _____	NO / <input type="checkbox"/> / Explain _____



**CERTIFICATION FOR EXCLUSIVITY**

Pursuant to 21 CFR §314.108 the applicant, Allergan, Inc., is submitting information in support of a request for three-year exclusivity per Sections §505(b)(3)(D)(iv) of the Federal Food, Drug and Cosmetic Act for Nedocromil Sodium 2% Ophthalmic Solution, NDA 21-009.

The results of the five main controlled clinical studies demonstrate that Nedocromil Sodium 2% Ophthalmic Solution is both safe and efficacious for the prevention and treatment of seasonal allergic conjunctivitis. A sixth study, entitled CR1871, is used to support the safety of the drug product in children.

The clinical studies and data in this new drug application were sponsored by FISIONS Pharmaceuticals, currently Rhône – Poulenc Rorer Pharmaceuticals, and were conducted under IND [redacted]. An agreement between Allergan, Inc. and Rhône – Poulenc Rorer Pharmaceuticals granted us permission to use the following studies in this application for exclusivity.

In the applicant's opinion the following ocular studies are essential to the approval of the New Drug Application for Nedocromil Sodium Ophthalmic Solution.

**CR 1170/1 and CR 1170/2 - (Combined Studies)**

A Multicenter Double-Masked Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic Solution in the Treatment of Ragweed Seasonal Allergic Conjunctivitis.

**CR 1343 and CR 1344 - (Combined Studies)**

A Multicenter Double-Masked Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic Solution in the Treatment of Ragweed Seasonal Allergic Conjunctivitis.

**SD CR 1959**

A Multicenter Double-Masked Group Comparative Study of the Efficacy and Safety of 2% Nedocromil Sodium and Opticrom® vs. Placebo in the Treatment of Ragweed Seasonal Allergic Conjunctivitis.



**CERTIFICATION FOR EXCLUSIVITY**

Allergan, Inc., certifies, that to the best of its knowledge, the clinical investigations listed, herein, have not formed part of the basis of substantial evidence of effectiveness for a previously approved new drug application or supplement. Furthermore, no other drug product containing all of the same ingredients with the same conditions of approval has been previously approved. The scientific literature has been thoroughly searched and in the applicant's opinion there are no published studies or publicly available reports of clinical investigations (other than those sponsored by the applicant) to support approval of the new drug application for Nedocromil Sodium 2% Ophthalmic Solution. This formulation has been approved in twenty-six countries outside the United States and has been marketed in sixteen of these countries.

Peter Kresel, MS, MBA  
Sr. Vice President  
Global Regulatory Affairs  
Allergan, Inc.

3/30/99  
Date





**DEBARMENT CERTIFICATION**

Under the provisions of Section 306(k) of the Federal Food, Drug and Cosmetics Act, Allergan, Inc. has made a diligent effort to insure that no individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Act, as referenced above, has provided any services in connection with this application.

Allergan, Inc. did not conduct any preclinical or clinical studies associated with this application. These studies were conducted by the previous sponsor, FISONs, currently Rhône - Poulenc Rorer Pharmaceuticals.

Under confirmation from Rhône - Poulenc Rorer, Allergan, Inc. hereby certifies that no individual corporation, partnership or association debarred under Section 306(a) or 306(b) of the above referenced act, has provided any services in connection with this New Drug Application.

Peter Kresel, MS, MBA  
Sr. Vice President, Global Regulatory Affairs  
Allergan, Inc.

3/30/99  
(date)