

PATENT SPECIFICATION

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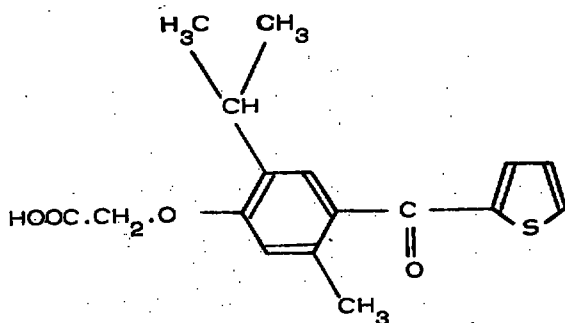


(54) [2-ISOPROPYL-4-(2'-THENOYL)-5-METHYL] PHENOXY ACETIC ACID

(71) We, SOCIETE D'ETUDES DE PRODUITS CHIMIQUES, a French company, of 4 Rue Thedule Ribot, 75017 Paris, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a new phenoxy acetic acid derivative, to alkali metal salts thereof, to a method for its preparation and to therapeutic compositions containing it or its alkali metal salts.

The new derivative of the invention is [2-isopropyl - 4 - (2' - thenoyl) - 5 - methyl]-phenoxy acetic acid, which has the formula:



The new compound has the general formula $C_{17}H_{18}O_4S$ and has a molecular weight of 318. It is a white crystalline product melting at 147—148°C (Tottoli), and is insoluble in water, but soluble in ethanol, chloroform, dimethylsulphoxide and transcutanol.

The compound is particularly interesting for its therapeutic activities in the field of choleresis. It may be used as such *per os* or in the form of its soluble salts with alkali metals for intravenous administration. The invention accordingly provides a compound according to the invention in admixture with one or more pharmacologically acceptable diluents or carriers.

A toxicity study undertaken on this compound has given *per os* LD 50 figures of about 0.8 g/kg for female mice and 2.35 g/kg for female rats. Sodium and potassium salts are a little less toxic.

Complete comparative pharmacological studies (on rats) have shown that the compound of the invention has a very favourable activity, for choleresis as compared with sodium dehydrocholate which was used as reference compound.

The technique used was that described in *J. Pharmacologie, Paris*, 1971, 2, 2, 175—182 on anaesthetised female rats. In this experimentation there were determined, 1, 2, 3 and 4 hours after *per os* administration, the percentage of variation of bile flow (A), the percentage of variation of amount of protein in the bile flow (B) and the percentage of variation of cholesterol amount (C). In each case the variation was assessed as a comparison of the results on treated and non-treated rats.

A control batch, of 10 rats, was anaesthetised, and subsequent time measurements were taken from 15 minutes after anaesthesia. 1, 2, 3 and 4 hours later there were measured the bile flows, the amounts of protein and cholesterol. The average figures obtained were retained as a basis for comparison.

Similar measurements were made for 4 batches each of 6 rats treated *per os* by 4 different doses of the compound of the invention (free acid form) and, in each case, the percentage of variation was calculated with respect to the corresponding values of non-treated animals. The doses used were 25 and 50 mg/kg, which preliminary tests had shown to be favourable, and one lower and one higher dose to provide a broader indication of activity.

Similar measurements were then made for 3 batches each of 6 rats treated by 3 different doses of sodium dehydrocholate. The doses used were the generally accepted dose of 100

mg/kg, together with one lower and one higher dose for comparison. The results obtained are shown in the accompanying Table.

TABLE

Product	Dose mg/kg	1 hour			2 hours			3 hours			4 hours		
		A	B	C	A	B	C	A	B	C	A	B	C
Product of the invention (free acid)	12.5	+42	+59	-17	+16	+2	+8	+10	-13	-3	+10	+13	+3
	25.0	+52	+58	+35	+26	+40	+27	+13	+7	+10	+6	+16	+10
	50.0	+62	+77	-1	+49	+50.5	+24	+30	+36	+18	+21	+26	-1
	75.0	+87	+103	-	+75	+78	-	+60	+56	-	+44	+47	-
Sodium dehydrocholate	50.0	+33	+24	+14	+16	+10	+7.5	+11	+5	+9.5	+7	-2	+4
	100.0	+77	+50	+10	+18	+20	-2	+7	+5.5	+4	+6	+36	+8
	150.0	+144	+98	-	+48	+32	-	+23	+11	-	+2	+11	-

5 The compound according to the invention does not induce the liberation of cholesterol at a high rate; this is nevertheless an advantage as demonstrated by the publication FEUILLETS DE BIOLOGIE, 1977—Vol. XVIII—No. 97—pages 65 to 70.

10 Turning now to the form of administration; for the oral route, tablets and gelatine capsules are preferred. Each unit may comprise from 0.05 to 0.25 g. of active ingredient, acid form.

15 For intravenous administration, the preferred

form is an alkali metal salt of the compound with a dosage of 0.25 to 0.50 g. of active ingredient per phial.

20 The usual posology in human administration comprises 0.05 to 0.25 g. *per diem* for the oral route and 0.25 to 0.50 g. *per diem* for the intravenous route.

25 The invention accordingly provides a therapeutic composition comprising the compound according to the invention or an alkali metal salt of the same in admixture with one or

more pharmacologically acceptable diluents or carriers.

The new compound may be prepared according to the invention by reacting 2-isopropyl - 4 - (α - thenoyl) - 5 - methylphenol with ethyl monobromoacetate under reflux in a ketonic solvent. From the resulting ethyl ester, the compound of the invention may be directly obtained by hydrolysis.

2 - isopropyl - 4 - (α - thenoyl) - 5 - methylphenol may be obtained by reacting thymol and thenoyl chloride in the presence of aluminium chloride in acetylene tetrachloride.

The invention is illustrated by the following example:

Example:

Into a one-litre reactor, fitted with stirring, warming and cooling means there were poured: 31.44 g. (0.12 mole) of 2 - isopropyl - 4 - (α - thenoyl) - 5 - methylphenol, 400 ml of methyl ethyl ketone, 33 ml. of ethyl bromoacetate, 24 g. (0.19 mole) of potassium carbonate, and some potassium iodide crystals.

The mixture was then stirred and refluxed for four hours. Then it was evaporated to dryness, extracted with 400 ml of diethyl ether, washed with water, once more evaporated to dryness and recrystallized from hexane.

There were thus obtained 38.4 g. of the ethyl ester of the compound of the invention (yield: 85%).

38.4 g. (0.106 mole) of this ester, 22 g. (0.55 mole) of pure sodium hydroxide and 600 ml of ethanol were added to a one-litre reactor fitted with stirring and warming means, and then refluxed for three hours, evaporated to about 400 ml, cooled and mixed under stirring with 34 ml of acetic acid (a 10% excess).

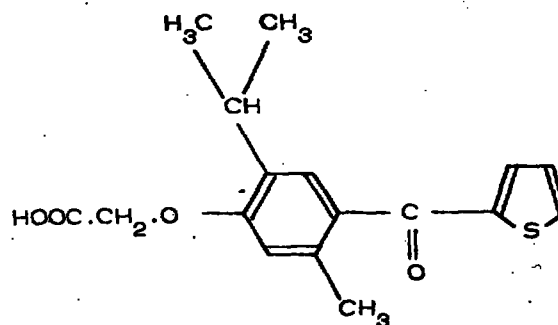
After 30 minutes of stirring, the mixture was filtered and the precipitate was washed and recrystallized from benzene.

There were thus obtained 28.6 g (yield: 85%) of the product, [2 - isopropyl - 4 - (2' - thenoyl) - 5 - methyl] - phenoxy acetic acid, the structure of which was confirmed by analysis and U.V. spectrum.

Corresponding alkali metal salts were obtained from the acid by the usual routes.

WHAT WE CLAIM IS:—

1. [2 - isopropyl - 4 - (2' - thenoyl) - 5 - methyl] - phenoxy acetic acid, which has the formula:



or an alkali metal salt thereof.

2. A process for the preparation of a compound according to claim 1, comprising reacting 2 - isopropyl - 4 - (α - thenoyl) - 5 - methylphenol with ethyl monobromoacetate under reflux in a ketonic solvent, and subsequently hydrolysing the compound thus obtained.

3. A therapeutic composition comprising a compound according to claim 1 in admixture with one or more pharmacologically acceptable diluents or carriers.

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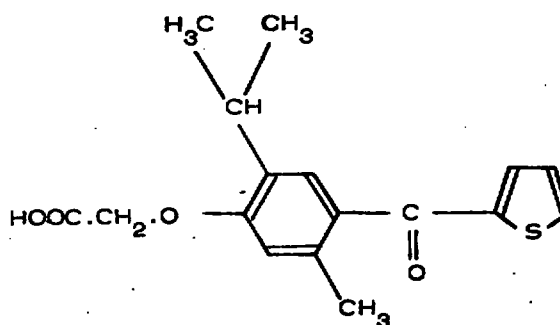
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