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PATENT SPECIFICATION

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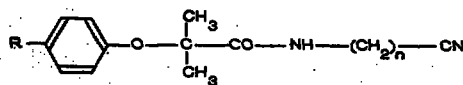


(54) ISOBUTYRAMIDES, THEIR PREPARATION AND THERAPEUTIC COMPOSITIONS CONTAINING THEM

(71) We, SOCIETE D'ETUDES DE PRODUITS CHIMIQUES, a French company of 4 Rue Theodule Ribot Paris 75017 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:—

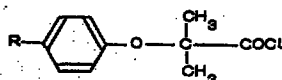
The invention relates to new isobutyramides, to methods for their preparation and to therapeutic compositions containing them.

The invention provides novel isobutyramides having the general formula 1.



wherein R represents a halogen atom and n is an integer from 2 to 6, and acid addition salts of those isobutyramides.

The new compounds may be prepared according to the invention by reacting stoichiometric amounts of the corresponding acid chloride of the general formula

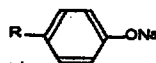


and the appropriate aminoalkyl nitrile derivative of the general formula

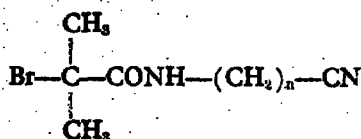


(in which formulae R and n are as above defined) in a mixture of polar and non-polar solvents.

The above compounds may alternatively be prepared according to the invention by the action of the corresponding substituted sodium phenate of the general formula



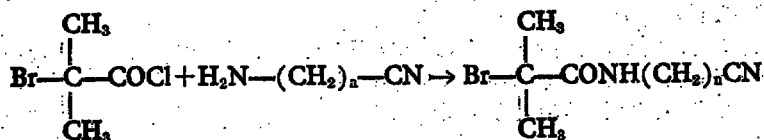
in solution in a non-polar solvent on the appropriate N-cyanoalkyl- α -bromo-isobutyramide of the general formula



in which R and n are as above defined.

The N-cyanoalkyl- α -bromo-isobutyramide may be readily obtained by the re-

action of α - bromo - isobutyryl chloride on the appropriate aminoalkyl nitrile according to the reaction scheme:



Preferably the synthesis commences with the appropriate substituted phenol which is converted *in situ* into the sodium phenate by reaction with sodium in solution in ethanol. The ethanol is then replaced by toluene by the addition of an excess of toluene and subsequent distillation of the azeotrope.

To the solution in toluene is added the N-cyanoalkyl α -bromo-isobutyramide and the reaction mixture is preferably refluxed for from 6 to 15 hours.

The new compounds and their acid addition salts are of interest in the therapeutic field and show a hypolipemic, hypotriglyceridemic and hypocholesterolemic activity. The invention accordingly provides therapeutic compositions containing one or more of the above compounds I or acid addition salts thereof in admixture with a therapeutically acceptable diluent or carrier.

The compounds of the invention may be presented in any suitable form for use in human therapy. For instance, a form for oral administration may be a gelatin capsule containing:

compound according to the invention	0.500 g
silicic acid	0.018 g
talc	0.042 g

The posology varies according to the patients but is typically between 0.5 and 4 g per day.

The invention is illustrated by the following Examples.

Example 1.

N-cyanoethyl-p-chlorophenoxyisobutyramide

In a 2.5 litre reactor fitted with cooling and stirring means there were poured 1 litre of dry dichloroethane, 74 g of triethylamine and 52 g (0.74 mol) of 3-aminopropionitrile. The mixture was stirred and there was then slowly added, over a period of 30 minutes, a solution of 172 g (0.74 mol) of p-chlorophenoxy-isobutyryl chloride in 0.5 litre of dry dichloroethane. The temperature was maintained below 10°C during the addition period and then the mixture was refluxed for 4 hours and evaporated to dryness. The product obtained was washed with a sodium carbonate solution, treated with water, extracted with chloroform, dried, treated with diethyl ether and crystallized from di-isopropyl ether.

There were thus obtained 128 g (yield 65%) of a white crystalline product melting at 70°C. The composition of the product was in complete agreement with the formula $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$ (molecular weight 266.7). This compound was insoluble in water but soluble in many organic solvents.

The p-chlorophenoxy-isobutyryl chloride was obtained by treating p-chlorophenoxy-isobutyric acid with SOCl_2 in anhydrous benzene.

Example 2.

N-cyanoethyl-p-fluorophenoxyisobutyramide

The procedure of Example 1 was repeated except that the p-chlorophenoxy-isobutyryl chloride was replaced by p-fluorophenoxy-isobutyryl chloride. There was thus obtained, with a yield of 71%, a white crystalline product melting at 75°C. The composition of the product was in agreement with the formula: $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{F}$; molecular weight 250.2.

Example 3.

N-cyanobutyl p-chlorophenoxy isobutyramide

The procedure of Example 1 was repeated except that the 3-aminopropionitrile was replaced by 5-aminopentanitrile. The yield was 81% of a white crystalline product melting at 88°C. Analysis of the product showed a good correspondence with the formula $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2\text{Cl}$.

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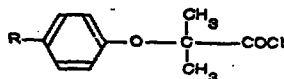
TABLE

	Reference Compound	Compound of Example 1
<u>Triglycerids</u>		
Initial	1.611 ($\pm$ 0.098)	1.59 ($\pm$ 0.155)
Final	1.137 ($\pm$ 0.085)	1.082 ($\pm$ 0.101)
Decrease	0.474 ($\pm$ 0.102)	0.507 ($\pm$ 0.088)
<u>Total cholesterol</u>		
Initial	3.31 ($\pm$ 0.121)	3.17 ($\pm$ 0.151)
Final	2.85 ($\pm$ 0.170)	2.70 ($\pm$ 0.169)
Decrease	0.46 ($\pm$ 0.107)	0.47 ($\pm$ 0.058)
<u>Total lipids</u>		
Initial	9.985 ($\pm$ 0.342)	9.94 ($\pm$ 0.454)
Final	8.755 ($\pm$ 0.491)	8.367 ($\pm$ 0.431)
Decrease	1.210 ($\pm$ 0.244)	1.572 ($\pm$ 0.198)

The activity of the compound of the invention appears similar on the total cholesterol rate but more favourable on the triglycerids and total lipids rates.

WHAT WE CLAIM IS:—

1. An isobutyramide of the general formula I or an acid addition salt thereof.
2. N-cyanoethyl-*p*-chlorophenoxyisobutyramide.
3. N-cyanoethyl-*p*-fluorophenoxyisobutyramide.
4. N-cyanobutyl-*p*-chlorophenoxy isobutyramide.
5. A process for the preparation of a compound according to claim 1, comprising reacting stoichiometric amounts of an acid chloride of the general formula

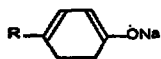


with an aminoalkyl nitrile derivative of the general formula



wherein R represents a halogen atom and *n* is an integer from 2 to 6, in a mixture of non-polar and polar solvents.

6. A process for the preparation of a compound according to claim 1, which comprises reacting, in a non-polar solvent, a substituted sodium phenate of the general formula



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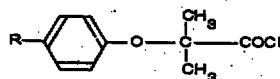
TABLE

	Reference Compound	Compound of Example 1
<u>Triglycerids</u>		
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The activity of the compound of the invention appears similar on the total cholesterol rate but more favourable on the triglycerids and total lipids rates.

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3. N-cyanoethyl-*p*-fluorophenoxyisobutyramide.
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5. A process for the preparation of a compound according to claim 1, comprising reacting stoichiometric amounts of an acid chloride of the general formula

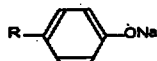


with an aminoalkyl nitrile derivative of the general formula



wherein R represents a halogen atom and *n* is an integer from 2 to 6, in a mixture of non-polar and polar solvents.

6. A process for the preparation of a compound according to claim 1, which comprises reacting, in a non-polar solvent, a substituted sodium phenate of the general formula



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Example 4.

N-cyanoethyl-p-chlorophenoxyisobutyramide

Into a 25 litre reactor fitted with cooling and stirring means there were poured 3 litres of ethanol, 60 g of sodium and 250 g of *p*-chlorophenol (1.944 mol). After stirring for 1 hour there were added 3 litres of toluene, and the ethanol/toluene azeotrope was removed by distillation. 2 more litres of toluene were added and also 425 g of N-cyanoethyl- α -bromo-isobutyramide, (1.944 mol).

The mixture was refluxed for 10 hours, and 2 litres of toluene were then removed by distillation. The resulting mixture was treated with water which gave a precipitate which was separated, washed with water, neutralized with HCl, dried and crystallized from di-isopropyl ether.

There were thus obtained 348 g (yield 67%) of a white crystalline product melting at 71°C. The composition of the product corresponded to the formula $C_{13}H_{15}O_2N_2Cl$ (molecular weight 266.72). The compound was insoluble in water but soluble in most common organic solvents.

Example 5.

N-cyanoethyl-p-fluorophenoxyisobutyramide

The procedure of Example 4 was repeated except that the *p*-chlorophenol was replaced by *p*-fluorophenol, which after the sodium treatment was reacted with N-cyanoethyl- α -bromo-isobutyramide. There was thus obtained, with a yield of 67%, a white crystalline product melting at 75°C. Analysis showed a good correspondence with the formula $C_{13}H_{15}O_2N_2$ (molecular weight 250.2).

Example 6.

N-cyanobutyl-p-chlorophenoxyisobutyramide

The procedure of Example 4 was repeated except that the N-cyanoethyl- α -bromo-isobutyramide was replaced by N-cyanobutyl- α -bromo-isobutyramide. The yield was 87% of a white crystalline product melting at 88°C, analysis of which showed a good correspondence with the formula $C_{15}H_{19}N_2O_2Cl$.

Example 7.

The product of Examples 1 to 3 were submitted to toxicological, pharmacological and clinical studies which are summarized below.

TOXICITY

The acute toxicity was determined *per os* on mice and rats, by the usual techniques. The LD 50 values are respectively 1 g/kg for mice and over 2.4 g/kg for rats for the compound of Example 1.

For the compounds of Examples 2 and 3, the LD 50 was 1.2 g/kg for both on mice, and over 2.5 g/kg for both on rats.

The subacute toxicity of the compound of Example 1 was researched on rats at the doses of 40, 80 and 160 mg/kg (*per os*) and no difference was noticed between treated and control animals.

PHARMACOLOGY

Triton test.

Experimental hyperlipemia and hypercholesterolemia were induced in male rats by an intraperitoneal injection of triton (dose : 5 ml/kg). These rats were treated immediately *per os*, either with the product of Example 1 or with a reference compound, which was 2-(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester or nicotinic acid (three batches each of 10 animals) at the same doses. The best hypocholesterolemic activities were found for the compound of Example 1 and the first-mentioned reference compound, whereas the best hypotriglyceridemic activities were found for the second reference compound and the compound of Example 1.

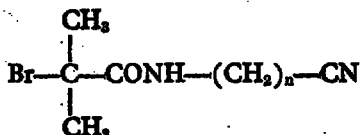
CLINICAL TRIALS

20 patients were treated comparatively, successively by 2-(4-chlorophenoxy)-2-methyl propanoic acid ethyl ester as reference compound (30 days, 2 g/day) and after 15 days without treatment, by the compound of Example 1 (30 days, 2 g/day). The average figures in g/l for initial values, final values and decrease for triglycerids, total cholesterol and total lipids are listed in the following Table.



* C L M S *

with an N-cyanoalkyl- α -bromoisobutyramide of the general formula



in which R represents a halogen atom and n is an integer from 2 to 6.

7. A process according to claim 6, wherein the sodium phenate is prepared *in situ* by the action of sodium on the corresponding substituted phenol.

8. A process according to claim 6 or claim 7, wherein the non-polar solvent is toluene.

9. A process according to any of claims 6 to 8, wherein the reaction is carried out under reflux for from 6 to 15 hours.

10. A process for the preparation of a compound according to claim 1, substantially as disclosed in any of Examples 1 to 6 herein.

11. A therapeutic composition containing one or more compounds according to claim 1 in admixture with a therapeutically acceptable diluent or carrier.

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