

1474377

PATENT SPECIFICATION

(11) 1474377

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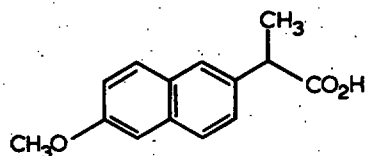


(54) NAPHTHALENE DERIVATIVES

(71) We, BEECHAM GROUP LIMITED, a British Company of Beecham House, Great West Road, Brentford, Middlesex, England, 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 present invention relates to pharmaceutical compositions useful for the treatment of inflammatory disorders, to certain novel naphthalene derivatives for inclusion in such composition and to processes for the preparation of such compounds.

Certain naphthalene derivatives are known to possess useful anti-inflammatory activity and to be suitable for use in the treatment of various rheumatic and arthritic conditions. One particularly effective naphthalene derivative that has found clinical use in the United Kingdom is Naproxen which has the formula (I):



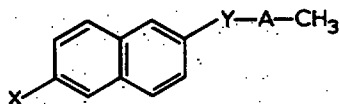
(I)

In common with other anti-inflammatory agents, the compound of the formula (I) can be formulated in conventional manner especially for oral administration. Certain suitable types of formulations include those described in British Patent Specifications Nos. 1,211,134, 1,271,132 and 1,291,386.

Unfortunately, the compound of formula (I) can cause severe irritation of the gastro-intestinal tract in some subjects at doses not greatly in excess of the therapeutic dose.

It has now been discovered that other naphthalene derivatives have good anti-inflammatory activity while having an improved therapeutic ratio as based on gastro-intestinal irritancy.

Accordingly, the present invention provides pharmaceutical compositions which comprise a compound of the formula (II):



(II)

wherein X is a chlorine or bromine atom or a methoxyl, methylthio or alkyl group of 1—4 carbon atoms; Y is a —CHR₁—CH₂— or —CR₁=CH— group where R₁ is a hydrogen atom or a methyl group and A is a CHOH or CO group, and a pharmaceutically acceptable carrier.

Suitably X is a methoxyl, methylthio or methyl group.

Most suitably X is a methoxyl or methylthio group.

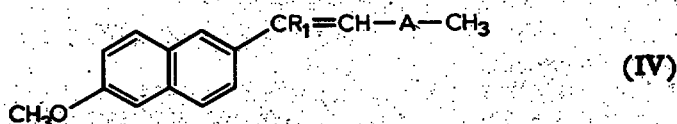
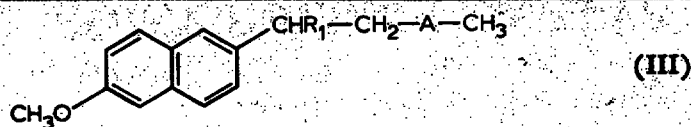
Particularly suitable compounds of the formula (I) include those of the formulae (III) and (IV):

SEE CORRECTION SLIP ATTACHED

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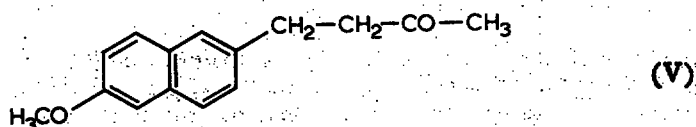


wherein R_1 and A as defined in relation to formula (II).

Most suitably R_1 is a hydrogen atom.

Most suitably A is a CO group.

Thus a particularly suitable compound of the formula (III) is that of the formula (V):

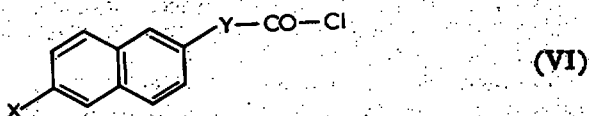


The compositions of this invention may be in any conventional form but in general, orally administrable compositions, for example unit dosage forms such as tablets or capsules, are preferred. Such dosage forms will normally contain from 20 mg to 1000 mg and more usually from 100 mg to 600 mg. Such dosage forms may be taken one or more times a day (preferably 2 to 4 times a day) so that the daily dose is normally between 300 mg and 3000 mg and more usually from 500 mg to 2000 mg, for example 600 mg to 1600 mg.

The present invention also provides compounds of the formula (II) as hereinbefore described excepting 4-(6'-methoxy-2'-naphthyl)-butan-2-one.

Suitable novel compounds of the formula (I) include those wherein A is CHOH group, those wherein Y is a $-\text{CH}(\text{CH}_3)\text{CH}_2-$ group, those wherein Y is a $-\text{CR}=\text{CH}-$ group, and those wherein X is other than a methoxyl group.

The present invention provides a process for the preparation of the novel compounds of the invention which process comprises the methylation of a compound of the formula (VI):

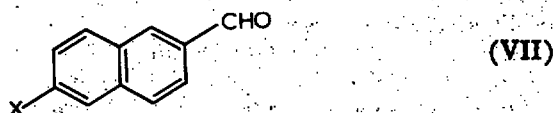


wherein X and Y are as defined in relation to formula (II) except that Y is not $-\text{CH}_2-\text{CH}_2-$ when X is methoxyl; by reaction with methyl lithium and thereafter if desired reducing the CO group to a CHOH group.

This reaction is normally carried out in an inert, aprotic solvent at a depressed temperature and preferably under an inert atmosphere. The reaction may be carried out at below -40°C in dry diethyl ether.

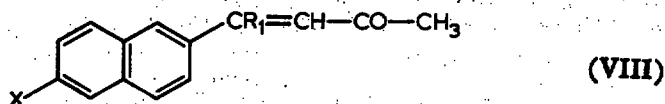
The reduction of the CO group to the CHOH group may take place using conventional methods of reduction such as hydrogenation in the presence of a transition metal catalyst or by the use of a hydride such as NaBH_4 or LiAlH_4 .

The present invention also provides a process for the preparation of the novel compounds of the formula (II) as hereinbefore described wherein Y is $\text{CH}=\text{CH}$ which process comprises the base-catalysed reaction of acetone with a corresponding compound of the formula (VII):



and thereafter reducing the CO group to a CHOH group if desired.

This invention also provides a process for the preparation of the novel compounds of the formula (II) wherein Y is a $-\text{CHR}_1-\text{CH}_2-$ group which process comprises the reduction of a compound of the formula (VIII):



wherein X and R_1 are as defined in relation to formula (II) except that R_1 is not hydrogen when X is methoxyl.

Such a reduction may be effected by hydrogenation using a conventional transition metal catalyst such as palladium on charcoal. Such reactions are normally carried out in an inert organic solvent at ambient temperature using an atmospheric or slightly super-atmospheric pressure of hydrogen.

The intermediates of the formula (VI) may be prepared by the reaction of thionyl chloride with the corresponding acid.

The following Examples illustrate the preparations of the compounds of the formula (II).

Example 1.

4-(6'-Methoxy-2'-naphthyl)-pentan-2-one

(a) Ethyl 3-(6'-methoxy-2'-naphthyl)-2-butenate

Sodium hydride (10.8 g., 60% dispersion in mineral oil) was washed three times with cyclohexane and blown dry in a stream of nitrogen. Dry 1,2-dimethoxyethane (150 ml) was added and the slurry was stirred at room temperature. Triethyl phosphonoacetate (54 g.) was added dropwise and the mixture stirred at room temperature for 1 hour under nitrogen. A solution of 2-acetyl-6-methoxynaphthalene (30 g.) in 1,2-dimethoxyethane (300 ml) was run in and the solution refluxed overnight under nitrogen.

The reaction mixture was diluted with water, acidified and extracted with ether. The ethereal layer was washed with sodium carbonate solution and with water, dried over anhydrous magnesium sulphate and evaporated to give ethyl 3-(6'-methoxy-2'-naphthyl)-2-butenate as a yellow solid in quantitative yield. The product was shown by NMR to be predominantly the trans isomer.

(b) Ethyl 3-(6'-methoxy-2'-naphthyl)-butyrate

Ethyl 3-(6'-methoxy-2'-naphthyl)-2-butenate (24 g.) was taken up in ethyl acetate (100 ml) and 10% Pd/C (2.4 g.) added. The mixture was hydrogenated at room temperature and 50 psi pressure for two hours.

The catalyst was removed by filtration and the filtrate evaporated to give ethyl 3-(6'-methoxy-2'-naphthyl)-butyrate as a colourless solid in quantitative yield.

(c) 3-(6'-Methoxy-2'-naphthyl)-butyric acid

Ethyl 3-(6'-methoxy-2'-naphthyl)-butyrate (14.4 g.) was taken up in methanol (300 ml) and 10% sodium hydroxide solution (150 ml) and the mixture was refluxed for 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The aqueous layer was acidified and extracted with ethyl acetate. The acid extract was washed with water, dried over anhydrous magnesium sulphate and evaporated to give 3-(6'-methoxy-2'-naphthyl)-butyric acid as a white solid (11.9 g., 92%), mp. 126—129°.

(d) 4-(6'-Methoxy-2'-naphthyl)-pentan-2-one

Thionyl chloride (8.15 ml) was added dropwise to a solution of 3-(6'-methoxy-2'-naphthyl)-butyric acid (19.0 g) in dry benzene (200 ml) and the mixture was gently refluxed overnight. The solvent was evaporated to give the crude acid chloride as a brown oil.

Methyl lithium (253 ml., 2.18 M in ether) was diluted to 2 litres with dry ether, cooled to 0°C and stirred under nitrogen. Cuprous iodide (48.6 g) was added and stirring continued for 10 minutes. The mixture was cooled to -70°C and a solution of the crude acid chloride in ether (250 ml) was run in. The mixture was stirred under nitrogen at -70°C for 15 minutes. Methanol (350 ml) was added to quench the reaction and the mixture was diluted with water and acidified. Kieselguhr was added to

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aid filtration and the reaction mixture was filtered through a pad of Kieselguhr. The ether layer was washed with sodium carbonate solution and with water, dried over anhydrous magnesium sulphate and evaporated to give a brown oil. The product was purified by short column chromatography to give 4-(6'-methoxy-2'-naphthyl)-pentan-2-one as a pale yellow oil, which solidified slowly on standing. Yield 10.7 g, 57%.

Example 2.

Trans-4-(6'-Methoxy-2'-naphthyl)-pent-3-ene-2-one

(a) Trans-3-(6'-methoxy-2'-naphthyl)-2-butenic acid

Ethyl trans-3-(6'-methoxy-2'-naphthyl)-2-butenate (27.4 g) was taken up in methanol (600 ml) and 10% sodium hydroxide solution (300 ml) and the mixture refluxed for 2 hours. The sodium salt of the required acid product crystallised out and was filtered off. The filtrate was extracted with ethyl acetate and the aqueous layer was separated.

The sodium salt of the acid was suspended in the aqueous layer and the mixture was acidified. Ethyl acetate was added and the mixture warmed until all the solid had dissolved. The ethyl acetate layer was separated, washed with water, dried over anhydrous magnesium sulphate and evaporated to give a pale yellow solid (20.7 g). The product was recrystallised from ethyl acetate to give trans-3-(6'-methoxy-2'-naphthyl)-2-butenic acid as a colourless solid (15.9 g, 67.8%), mp. 195–204°.

(b) Trans-4-(6'-methoxy-2'-naphthyl)-pent-3-ene-2-one

Thionyl chloride (8.15 ml) was added dropwise to a solution of trans-3-(6'-methoxy-2'-naphthyl)-2-butenic acid (14.0 g) in dry benzene (140 ml) and the mixture was gently refluxed for 4 hours. The solvent was evaporated to give the crude acid chloride as a brown oil.

Methyl lithium (173.3 ml, 2.1 M in ether) was diluted to 1200 ml. with dry ether, cooled to 0°C and stirred under nitrogen. Cuprous iodide (34.75 g) was added and stirring continued for 10 minutes. The mixture was cooled to –70°C and a solution of the crude acid chloride in ether (150 ml) was run in. The mixture was stirred under nitrogen at –70° for 15 minutes. Methanol (150 ml) was added to quench the reaction and the mixture was diluted with water and acidified. Kieselguhr was added to aid filtration and the reaction mixture was filtered through a pad of Kieselguhr. The ether layer was washed with sodium carbonate solution and with water, dried over anhydrous magnesium sulphate and evaporated to give a yellow solid. The product was purified by short column chromatography and recrystallisation from 60–80° petrol to give trans-4-(6'-methoxy-2'-naphthyl)-pent-3-ene-2-one as a pale yellow solid (11.5 g, 82.8%), mp. 98–101°C.

Example 3.

4-(6'-Methoxy-2'-naphthyl)-pentan-2-ol

To a solution of 4-(6'-methoxy-2'-naphthyl)-pentan-2-one (2 g) in methanol (100 ml), cooled in ice, was added sodium borohydride (1 g). The solution was stirred for 1 hour, acidified with dil. HCl and extracted with ether (100 ml × 3). The water-washed ether extracts were dried (anh. Na₂SO₄) and evaporated, giving a clear colourless oil (1.3 g).

Example 4.

4-(6'-Methoxy-2'-naphthyl)-3-buten-2-one

6-Methoxy-2-naphthaldehyde (30 g) was stirred in acetone (500 ml) with sodium hydroxide (10 mls of 10% aqueous solution) for 3 hours. The solution was acidified and extracted with ether. The ether solution was dried (MgSO₄) and evaporated under reduced pressure to yield a solid (30 g). This impure material was purified on a silica gel column using benzene as eluant to give 4-(6'-methoxy-2'-naphthyl)-3-buten-2-one (15 g), m.p. 120°C.

Example 5.

4-(6'-Methoxy-2'-naphthyl)-butan-2-one

4-(6'-Methoxy-2'-naphthyl)-3-buten-2-one (32 g) in ethyl acetate (500 ml) was shaken at room temperature over 10% Pd/C (3 g) under atmospheric pressure hydrogen until no further uptake of hydrogen occurred to yield 4-(6'-methoxy-2'-naphthyl)-butan-2-one (22.5 g), m.p. 78.5°C.

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Example 6.

Pharmacological Data

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Using a conventional Allen-Doisy Test, the Oestrogenic activity of certain compounds of the invention was ascertained. The results are shown in Table 1. The anti-inflammatory activity of certain compounds of the invention was ascertained by using a standard Rat Paw Carrageenin Test. These results are also shown in Table 1.

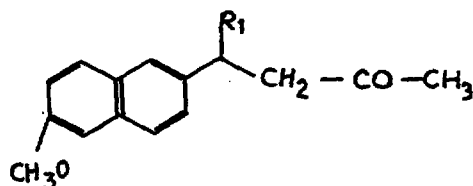
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These results show that compounds of this invention have a good level of activity at a dosage where excessive oestrogenicity is not to be expected. Further, it is believed that an absence of branching at the α -carbon atom reduces greatly any oestrogenicity which might be present while not effecting the anti-inflammatory activity of the compounds to any great extent.

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It has further been observed that compounds of the formula:



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wherein R_1 is H or CH_3 , do not excessively irritate the rat stomach at a dose of 300 mg/kg/day orally after 3 days while at the end of 1½ days oral treatment with the compound of formula (I), very severe gastric irritation was noted at the same dose level.

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TABLE I

Compound	Oestrogenicity Allan-Doisy Test	Anti-Inflammatory Rat Carrageenan
4-(6'-methoxy-2'-naphthyl)- pent-3-en-2-one	100 mg/kg sub. cut. Inactive (mouse)	100 mg/kg orally, Active
4-(6'-methoxy-2'-naphthyl)- pentan-2-one	300 mg/kg orally, Active (rat)	300 mg/kg orally, Active
4-(6'-methoxy-2'-naphthyl)- butan-2-one	200 mg/kg orally, Inactive (rat)	50 mg/kg orally, Slightly Active 100 mg/kg orally, Active 1 hr. after dosing*
4-(6'-methoxy-2'-naphthyl)-3- butene-2-one	300 mg/kg orally, Inactive (rat)	300 mg/kg orally, Active

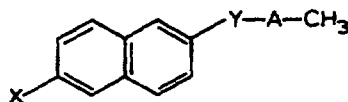
* Aspirin (300 mg/kg) gives equivalent activity 2 hours after dosing.

WHAT WE CLAIM IS:—

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1. A pharmaceutical composition which comprises a compound of the formula (II):

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(II)

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wherein X is a chlorine or bromine atom or a methoxyl, methylthio or alkyl group of 1—4 carbon atoms; Y is a $—CHR_1—CH_2—$ or $—CR_1=CH—$ group wherein R_1 is a hydrogen atom or a methyl group; and A is a CHOH or CO group and a pharmaceutically acceptable carrier.

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2. A composition as claimed in claim 1 wherein X is a methoxyl, methylthio or methyl group.

3. A composition as claimed in claim 1 wherein X is a methoxyl or methylthio group.

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4. A composition as claimed in any of claims 1—3 which contains a compound of the formula (III) or (IV):

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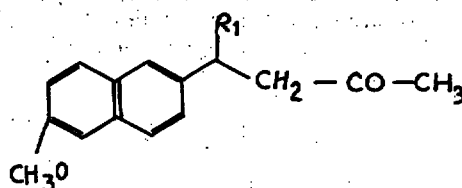
Example 6.

Pharmacological Data

Using a conventional Allen-Doisy Test, the Oestrogenic activity of certain compounds of the invention was ascertained. The results are shown in Table 1. The anti-inflammatory activity of certain compounds of the invention was ascertained by using a standard Rat Paw Carrageenin Test. These results are also shown in Table 1.

These results show that compounds of this invention have a good level of activity at a dosage where excessive oestrogenicity is not to be expected. Further, it is believed that an absence of branching at the α -carbon atom reduces greatly any oestrogenicity which might be present while not effecting the anti-inflammatory activity of the compounds to any great extent.

It has further been observed that compounds of the formula:



wherein R_1 is H or CH_3 do not excessively irritate the rat stomach at a dose of 300 mg/kg/day orally after 3 days while at the end of 1½ days oral treatment with the compound of formula (I), very severe gastric irritation was noted at the same dose level.

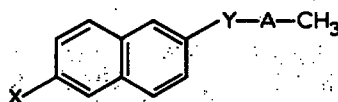
TABLE I

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4-(6'-methoxy-2'-naphthyl)- pent-3-en-2-one	100 mg/kg sub. cut. Inactive (mouse)	100 mg/kg orally, Active
4-(6'-methoxy-2'-naphthyl)- pentan-2-one	300 mg/kg orally, Active (rat)	300 mg/kg orally, Active
4-(6'-methoxy-2'-naphthyl)- butan-2-one	200 mg/kg orally, Inactive (rat)	50 mg/kg orally, Slightly Active 100 mg/kg orally, Active 1 hr. after dosing*
4-(6'-methoxy-2'-naphthyl)-3- butene-2-one	300 mg/kg orally, Inactive (rat)	300 mg/kg orally, Active

* Aspirin (300 mg/kg) gives equivalent activity 2 hours after dosing.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition which comprises a compound of the formula (II):



(II)

wherein X is a chlorine or bromine atom or a methoxyl, methylthio or alkyl group of 1-4 carbon atoms; Y is a $-CHR_1-CH_2-$ or $-CR_1=CH-$ group wherein R_1 is a hydrogen atom or a methyl group; and A is a CHOH or CO group and a pharmaceutically acceptable carrier.

2. A composition as claimed in claim 1 wherein X is a methoxyl, methylthio or methyl group.

3. A composition as claimed in claim 1 wherein X is a methoxyl or methylthio group.

4. A composition as claimed in any of claims 1-3 which contains a compound of the formula (III) or (IV):

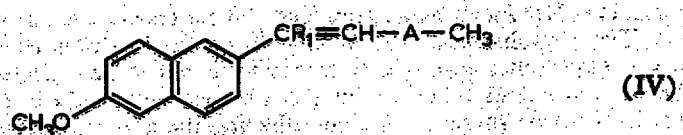
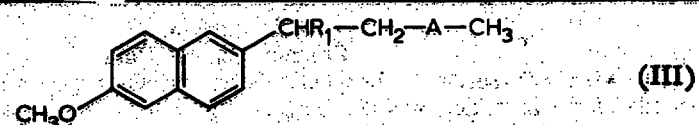


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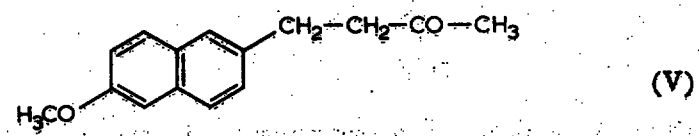
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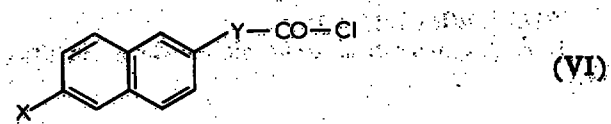


wherein R₁ is a hydrogen atom or a methyl group and A is a CO or CHOH group.

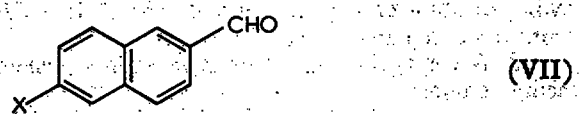
- 5 5. A composition according to claim 4 wherein R₁ is a hydrogen atom.
 6. A composition according to either of claims 4 or 5 wherein A is a CO group.
 7. A pharmaceutical composition which comprises a compound of the formula (V):



- 10 and a pharmaceutically acceptable carrier.
 8. A composition as claimed in any of claims 1—7 adapted for oral administration.
 9. A composition as claimed in claim 8 in the form of a unit dose composition containing from 20 mg to 1000 mg of a compound of the formula (II).
 10. A composition as claimed in claim 9 containing from 100 mg to 600 mg of a compound of the formula (II).
 15 11. The compounds of the formula (II) as defined in claim 1 except 4-(6'-methoxy-2'-naphthyl)-butan-2-one.
 12. The compounds according to claim 11 wherein A is a CHOH group.
 13. The compounds according to claim 11 wherein Y is a —CH(CH₃)CH₂— group.
 20 14. The compounds according to claim 11 wherein Y is a —CR₁=CH— group.
 15. The compounds according to claim 11 where X is other than a methoxyl group.
 16. 4-(6'-methoxy-2'-naphthyl)-pentan-2-one.
 17. 4-(6'-methoxy-2'-naphthyl)-pent-3-ene-2-one.
 25 18. 4-(6'-methoxy-2'-naphthyl)-pentan-2-ol.
 19. 4-(6'-methoxy-2'-naphthyl)-but-3-ene-2-one.
 20. A process for the preparation of the compounds of the formula (II) as claimed in claim 11 which comprises the methylation of a compound of the formula (VI):



- 30 wherein X and Y are as defined in claim 1 by reaction with methyl lithium and thereafter if desired reducing the CO group to a CHOH group.
 22. A process for the preparation of the compounds of the formula (II) as claimed in claim 11 wherein Y is a —CH=CH— group which process comprises the base catalysed reaction of acetone with a compound of the formula (VII):



and thereafter if desired reducing the CO group to a CHOH group.



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Agent for the Applicants.

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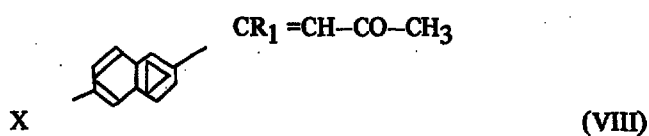
PATENTS ACT 1949
SPECIFICATION NO. 1474377

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The following corrections were allowed under Section 76 on 12 September 1977.

Page 6, line 31, *after* group. *Start New Paragraph insert*

21. A process for the preparation of the compounds of the formula (II) wherein Y is a $-\text{CHR}_1-\text{CH}_2-$ group which process comprises the reduction of a compound of the formula (VIII):



wherein X and R_1 are as defined in relation to formula (II) except that R_1 is not hydrogen when X is methoxyl.