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PATENT SPECIFICATION

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International Classification:—A61k, C07c.

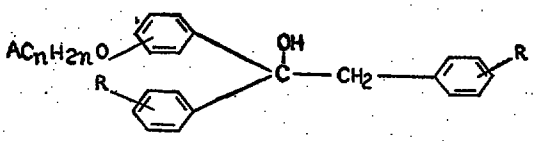
COMPLETE SPECIFICATION

Substituted Triphenylethanols and their production

We, THE WM. S. MERRELL COMPANY, a corporation organised under the laws of the State of Delaware, United States of America, of Lockland Station, Cincinnati 15, Ohio, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Our invention relates to substituted triphenylethanols which are distinguished, in general, by their anti-estrogenic activity in the endocrine system and anti-inflammatory activity.

The substituted triphenylethanols provided by the present invention have the following formula:



wherein the $-OC_nH_{2n}A$ group is attached in the meta or para position to the benzene ring, n is an integer from 2 to 4, A is an alkylamino group of which the alkyl portion contains 1 to 4 carbon atoms or a dialkylamino group of which each alkyl portion contains 1 to 4 carbon atoms or an N-piperidyl, an N-morpholinyl, or an N-pyrrolidinyl group, and the atoms or groups R, which may be the same or different, are hydrogen, halogen, methyl or methoxy, with the proviso that, where one R is hydrogen, the other R must be a halogen atom or a methyl or methoxy group.

Useful estrogen antagonists must be sufficiently active, non-toxic and free from side reactions. While estriol, for example, has been shown to have estrogen antagonist activity, it is also estrogenic; and thus its use is somewhat complicated. Other available estrogen antagonists have such undesirable activity as androgenic or progestational action. The compounds of this invention, however, are non-estrogenic and have a high degree of activity as estrogen antagonists. They are active both orally and parenterally and so can be administered by either route although the oral route is preferred in most instances. As estrogen antagonists the compounds are useful in the treatment of hyperestrogenism and disorders related to this condition, e.g., endometriosis, functional bleeding, and similar conditions.

As anti-inflammatory agents the new compounds are useful in alleviating the symptoms of such collagen diseases as arthritis and rheumatism and in the topical treatment of inflammation.

The new compounds can be used orally in doses ranging between 25 mg. and 5—10 grams daily, depending on the condition under treatment. Parenterally lower doses are used, i.e., about 25 to 500 mg. For topical use the compounds can be incorporated into creams, ointments or lotions in concentrations of up to 10 per cent. In aerosol sprays the concentration can be on the order of about 0.05 to 1 per cent.

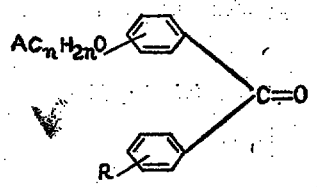
These substituted triphenylethanols dehydrate rather easily in the presence of acids and may be used as a base. They do not appear to be affected by gastric acid following oral administration but can be better protected against such acid by being incorporated in enteric-coated tablets or by the use of buffers such as aluminium hydroxide, calcium carbonate, and magnesium trisilicate when liquid preparations for oral use are desired. Some of these substituted triphenylethanols can be isolated as water-soluble salts of organic acids such as citric acid. Such salts may be useful for special purposes.

These new substituted triphenylethanols are prepared in accordance with the invention by:

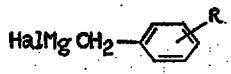
(a) where A is the indicated dialkylamino

[*Price 3s. 6d.*]

or heterocyclic group, reacting a benzophenone having the general formula:

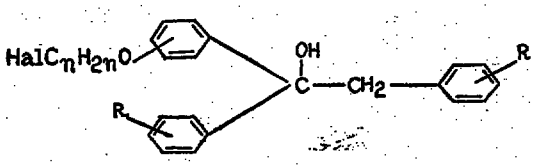


wherein n and R have the same meaning as above and A is the indicated dialkylamino or heterocyclic group, with a benzylmagnesium halide having the general formula:



where R has the same meaning as above and Hal is a halogen; or

(b) where A is the indicated dialkylamino or alkylamino group, reacting a triphenylethanol having the general formula:



wherein n and R have the same meaning as above and Hal is a halogen, with

(i) a lithium dialkylamide in which each alkyl group contains 1 to 4 carbon atoms, or

(ii) an alkylamine in which the alkyl group contains 1 to 4 carbon atoms.

The benzylmagnesium halide is advantageously the bromide or chloride; and the substituted benzophenone is obtained by reacting an alkali metal salt of the corresponding hydroxybenzophenone with the corresponding dialkylaminoalkyl halide, advantageously the bromide or chloride, or the corresponding haloalkylheterocyclic such as chloroethyl piperidine.

The preparation of these new substituted triphenylethanols will be illustrated by the following examples:

EXAMPLE 1

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

One litre of a 0.45—N ethereal solution of *p*-methoxybenzylmagnesium chloride is added in 30 minutes to a stirred solution of 104 gm. (0.35 mole) of 4-(β-diethylamino)ethoxybenzophenone in 400 ml. of dry ether. After stirring an additional hour, the mixture is decomposed by pouring onto one litre of a cold 10 per cent ammonium chloride solution; the ether solution is washed with water, and the ether is replaced with hot isopropanol containing a trace of ammonia. 1-[*p*-(β-Diethylamino)-ethoxyphenyl] - 1-phenyl-2-*p*-methoxyphenylethanol separates as white crystals melting at 104—106° C. The compound has oral anti-estrogenic activity and anti-inflammatory activity.

The 4-(β-diethylamino)ethoxybenzophenone is prepared as follows: a mixture of 200 gm. of 4-hydroxybenzophenone, 55 gm. of powdered sodium methoxide and 400 ml. of ethanol is stirred for 30 minutes. A solution of 150 gm. of β-diethylaminoethyl chloride in 300 ml. of toluene is added, and the mixture is refluxed four hours. The solvent is removed; the residue is taken up in ether and extracted with a 5 per cent NaOH solution and twice with water; the ether is removed; and the residue is distilled. The product is obtained as an oil boiling at 200—204° C. at 0.7 mm.

EXAMPLE 2.

1-[*m*-(β-Diethylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

When the procedure of Example 1 is followed, using 3-hydroxybenzophenone in place of 4-hydroxybenzophenone, 1-[*m*-β-diethylamino)ethoxyphenyl] - 1-phenyl-2-*p*-methoxyphenylethanol is obtained as an oil whose dihydrogen citrate salt melts at 91—3° C. The compound is uterotrophic, has slightly less antiestrogenic activity than the ether compounds and has antiinflammatory activity.

The 3-(β-diethylaminoethoxy)benzophenone obtained from the 3-hydroxybenzophenone boiled at 173° C. at 0.35 mm.

EXAMPLE 3.

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-phenyl-2-*p*-chlorophenylethanol.

When *p*-chlorobenzylmagnesium chloride replaces *p*-methoxybenzylmagnesium chloride of Example 1 in the procedure of Example 1, 1 - [*p* - (β - diethylamino)ethoxyphenyl] - 1-phenyl-2-*p*-chlorophenylethanol is obtained, melting at 116—7° C. The compound has anti-estrogenic and anti-inflammatory activities.

EXAMPLE 4.

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-phenyl-2-*p*-tolylethanol.

Using the procedure of Example 1 but replacing the Grignard reagent of Example 1 with *p*-methylbenzylmagnesium chloride, 1-[*p*-(β - diethylamino)ethoxyphenyl] - 1 - phenyl-2-*p*-tolylethanol is obtained, melting at 91—2° C. The compound has anti-estrogenic activity.

EXAMPLE 5.

1-[*p*-(β-Diethylamino)ethoxyphenol]-1-*p*-chlorophenyl-2-*p*-methoxyphenylethanol.

When the 4-hydroxybenzophenone is replaced with 4-hydroxy-4¹-chlorobenzophenone in Example 1, 4-(β-diethylamino)ethoxy-4¹-chlorobenzophenone is obtained, melting at 79—80° C. (from ethanol). This ketone, when

treated with *p*-methoxybenzylmagnesium chloride, gives 1-[*p*-(β-diethylamino)ethoxyphenyl]-1-*p*-chlorophenyl-2-*p*-methoxyphenylethanol melting at 125° C. This compound has anti-inflammatory activity.

EXAMPLE 6.

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-*p*-tolyl-2-phenylethanol.

When 4-hydroxy-4¹-methylbenzophenone replaces 4-hydroxybenzophenone in Example 1, 4-(β-diethylamino)ethoxy-4¹-methylbenzophenone is obtained, boiling at about 232° C. at 0.6 mm. This ketone, when treated with benzylmagnesium chloride, gives 1-[*p*-(β-diethylamino)ethoxyphenyl]-1-*p*-tolyl-2-phenylethanol. The product has a melting point of 106.5—108.5° C.

EXAMPLE 7.

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-*p*-tolyl-2-*p*-methoxyphenylethanol.

When the basic ether ketone of Example 6 is treated with *p*-methoxybenzylmagnesium chloride according to the method of Example 1, 1-[*p*-(β-diethylamino)ethoxyphenyl]-1-*p*-tolyl-2-*p*-methoxyphenylethanol is obtained. The product has a melting point of 99—101° C.

EXAMPLE 8.

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-*p*-tolyl-2-*p*-chlorophenylethanol.

Replacing the Grignard reagent of Example 6 with *p*-chlorobenzylmagnesium chloride in the procedure of Example 6 gives 1-[*p*-(β-diethylamino)ethoxyphenyl]-1-*p*-tolyl-2-*p*-chlorophenylethanol. The product has a melting point of 102—104° C.

EXAMPLE 9.

1-[*p*-(β-Dimethylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

Following the procedure of Example 1, using β-dimethylaminoethyl chloride instead of β-diethylaminoethyl chloride, 4-(β-dimethylamino)ethoxybenzophenone is obtained, boiling at 176—180° C. at 0.3 mm. Treatment of this ketone with the Grignard reagent of Example 1 as in the procedure of Example 1 gives 1-[*p*-(β-dimethylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol melting at 122—3° C. The compound has anti-estrogenic and anti-inflammatory activities.

EXAMPLE 10.

1-[*p*-(β-Di-*n*-butylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

When β-di-*n*-butylaminoethyl chloride replaces β-diethylaminoethyl chloride in Example 1, 4-(β-di-*n*-butylamino)ethoxybenzophenone boiling at 209° C. at 0.3 mm. is obtained. Treatment of this ketone as described in Example 1 gives 1-[*p*-(β-di-*n*-butylamino)-ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol melting at 63—4° C. The compound has anti-estrogenic activity.

EXAMPLE 11.

1-[*p*-(β-piperidino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

Using N-β-chloroethylpiperidine in place of β-diethylaminoethyl chloride in Example 1, 4-(β-piperidino)ethoxybenzophenone is obtained, boiling at 225—6° C. at 1.5 mm., melting at 64—5° C. When treated with *p*-methoxybenzylmagnesium chloride as in Example 1, 1-[*p*-(β-piperidino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol is obtained, melting at 123—5° C. (from methanol). The compound has anti-estrogenic and anti-inflammatory activities.

When N-β-chloroethylpyrrolidine or N-β-chloroethylmorpholine replaces the N-β-chloroethylpiperidine in the above reaction, then there are obtained, respectively, 1-[*p*-(β-1-pyrrolidinyl)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol and 1-[*p*-β-morpholino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

EXAMPLE 12.

1-[*p*-(β-Dimethylamino)isopropoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

When 1-dimethylamino-2-chloropropane is substituted for the β-diethylaminoethyl chloride in Example 1, 4-(β-dimethylamino)-isopropoxybenzophenone is obtained, boiling at 193° C. at 1.2 mm. Treatment with the Grignard reagent as in Example 1 gives 1-[*p*-(β-dimethylamino)isopropoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol, an oil which forms an oxalate salt melting at 155—161° C.

EXAMPLE 13.

1-[*p*-(δ-Diethylamino)butoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

A mixture of 100 gm. of 4-hydroxybenzophenone and 27 gm. of powdered sodium methoxide in 400 ml. of ethanol is stirred for thirty minutes, 250 gm. of 1,4-dichlorobutane is added, and the mixture is refluxed for 17 hours. The solvent is removed; the residue is taken up in ether and washed with a 5 per cent sodium hydroxide solution and twice with water; and the product is distilled, giving 4-(δ-chlorobutoxy)benzophenone, 204° C. at 0.3 mm.

When this ketone is treated with *p*-methoxybenzylmagnesium chloride as in Example 1, 1-[*p*-(δ-chlorobutoxy)phenyl]-1-phenyl-2-*p*-methoxyphenylethanol is obtained, m.p. 110—112° C.

An ethereal solution of butyllithium is treated with an ethereal solution of diethylamine so as to obtain an equivalent of lithium diethylamide. A solution of 0.4 equivalent of the 1-[*p*-(δ-chlorobutoxy)phenyl]-1-phenyl-2-*p*-methoxyphenylethanol in benzene is added, and the mixture is refluxed 16 hours. After decomposing with a 10% ammonium chloride solution and removing the solvent, the residue is allowed to react with a solution of citric acid in ethanol. The white crystals so obtained are recrystallized from butanone to give 1-[*p*-(δ-diethylamino)butoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol as the dihydrogen

citrate salt, m.p. 87—89° C.

EXAMPLE 14.

1-[*p*-(β-Methylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

When ethylene chlorobromide replaces 1,4-dichlorobutane in the procedure of Example 13, 4-(β-chloroethoxy)benzophenone is obtained, melting at 78° C. (from ether). Treatment of this ketone as in Example 13 with *p*-methoxybenzylmagnesium chloride gives 1-[*p*-(β-chloroethoxy)phenyl]-1-phenyl-2-*p*-methoxyphenylethanol melting at 103° C. (from methanol). A mixture of 45 gm. of this product, 21 gm. of methylamine and 240 ml. of absolute ethanol is heated in a pressure bottle at 56° C. for three days. Cooled, the desired product, 1-[*p*-(β-methylamino)-ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol, separates, melting at 156° C. An additional quantity may be obtained by removing the solvent, washing the residue with water, 10 per cent sodium hydroxide, and then water and repeatedly washing with methylene chloride followed by a crystallization from a mixture of chloroform and ethanol.

EXAMPLE 15

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-*p*-chlorophenyl-2-phenylethanol.

When the 4-hydroxybenzophenone is replaced with 4-hydroxy-4¹-chlorobenzophenone in Example 1, 4-(β-diethylaminoethoxy-4¹-chlorobenzophenone is obtained, melting at 79—80° C. (from ethanol). This ketone, when treated with benzylmagnesium chloride, gives 1-[*p*-(β-diethylamino)ethoxyphenyl]-1-*p*-chlorophenyl-2-phenylethanol melting at 121—2° C. This compound has anti-inflammatory activity.

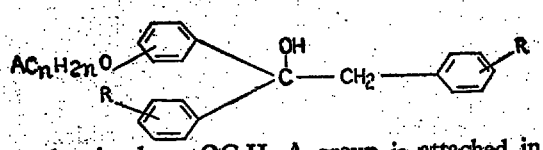
EXAMPLE 16

1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-*p*-chlorophenyl-2-*p*-chlorophenylethanol.

By replacing the Grignard reagent of Example 15 with *p*-chlorobenzylmagnesium chloride and by using the procedure of Example 15, 1-[*p*-(β-diethylamino)ethoxyphenyl]-1-*p*-chlorophenyl-2-*p*-chlorophenylethanol is obtained, m.p. 128—130° C. This compound has anti-inflammatory activity.

WHAT WE CLAIM IS:—

1. Substituted triphenylethanols having the following formula:

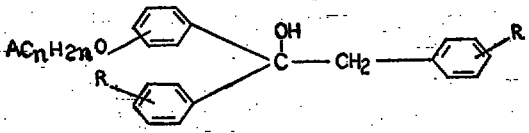


wherein the $-OC_nH_{2n}A$ group is attached in the meta or para position to the benzene ring, n is an integer from 2 to 4, A is an alkylamino group of which the alkyl portion contains 1 to 4 carbon atoms or a dialkylamino group of which each alkyl portion contains 1 to 4 carbon atoms or an N-piperidyl, an N-morpholinyl, or an N-pyrrolidinyl group, and the atoms or groups R, which may be the same or different, are hydrogen, halogen, methyl or methoxy, with the proviso that, where one R is hydrogen, the other R must be a halogen atom or a methyl or methoxy group.

2. 1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

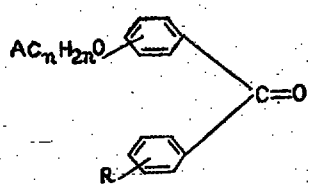
3. Substituted triphenylethanols as claimed in Claim 1 substantially as hereinbefore described with reference to, and as illustrated in, Examples 1 to 16.

4. A method of preparing substituted triphenylethanols having the general formula:

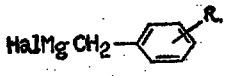


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(a) where A is the indicated dialkylamino or heterocyclic group, reacting a benzophenone having the general formula:

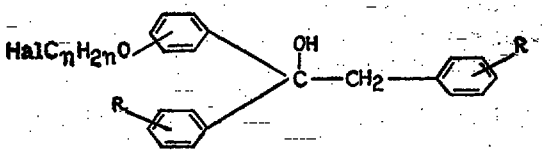


wherein n and R have the same meaning as above and A is the indicated dialkylamino or heterocyclic group, with a benzylmagnesium halide having the general formula:



wherein R has the same meaning as above and Hal is a halogen; or

(b) where A is the indicated dialkylamino or alkylamino group, reacting a triphenylethanol having the general formula:



citrate salt, m.p. 87—89° C.

EXAMPLE 14.

1-[*p*-(β-Methylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

When ethylene chlorobromide replaces 1,4-dichlorobutane in the procedure of Example 13, 4-(β-chloroethoxy)benzophenone is obtained, melting at 78° C. (from ether). Treatment of this ketone as in Example 13 with *p*-methoxybenzylmagnesium chloride gives 1-[*p*-(β-chloroethoxy)phenyl]-1-phenyl-2-*p*-methoxyphenylethanol melting at 103° C. (from methanol). A mixture of 45 gm. of this product, 21 gm. of methylamine and 240 ml. of absolute ethanol is heated in a pressure bottle at 56° C. for three days. Cooled, the desired product, 1-[*p*-(β-methylamino)-ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol, separates, melting at 156° C. An additional quantity may be obtained by removing the solvent, washing the residue with water, 10 per cent sodium hydroxide, and then water and repeatedly washing with methylene chloride followed by a crystallization from a mixture of chloroform and ethanol.

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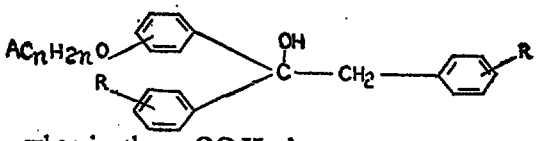
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WHAT WE CLAIM IS:—

1. Substituted triphenylethanols having the following formula:

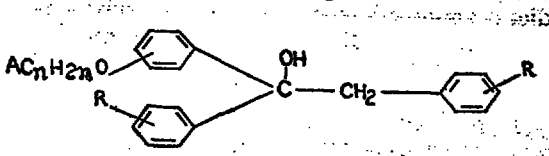


wherein the $-OC_nH_{2n}A$ group is attached in the meta or para position to the benzene ring, n is an integer from 2 to 4, A is an alkylamino group of which the alkyl portion contains 1 to 4 carbon atoms or a dialkylamino group of which each alkyl portion contains 1 to 4 carbon atoms or an N-piperidyl, an N-morpholinyl, or an N-pyrrolidinyl group, and the atoms or groups R, which may be the same or different, are hydrogen, halogen, methyl or methoxy, with the proviso that, where one R is hydrogen, the other R must be a halogen atom or a methyl or methoxy group.

2. 1-[*p*-(β-Diethylamino)ethoxyphenyl]-1-phenyl-2-*p*-methoxyphenylethanol.

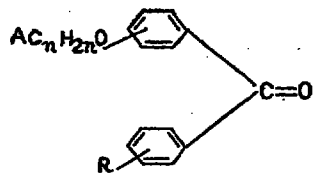
3. Substituted triphenylethanols as claimed in Claim 1 substantially as hereinbefore described with reference to, and as illustrated in, Examples 1 to 16.

4. A method of preparing substituted triphenylethanols having the general formula:

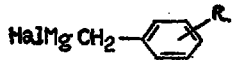


wherein the $-OC_nH_{2n}A$ group is attached in the meta or para position to the benzene ring, n is an integer from 2 to 4, A is an alkylamino group of which the alkyl portion contains 1 to 4 carbon atoms or a dialkylamino group of which each alkyl portion contains 1 to 4 carbon atoms or an N-piperidyl, an N-morpholinyl, or an N-pyrrolidinyl group, and the atoms or groups R, which may be the same or different, are hydrogen, halogen, methyl or methoxy, with the proviso that, where one R is hydrogen, the other R must be a halogen atom or a methyl or methoxy group, which comprises

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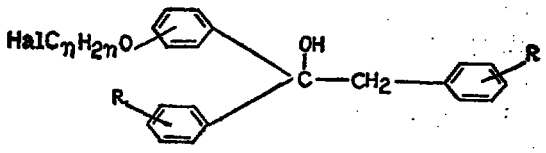


wherein n and R have the same meaning as above and A is the indicated dialkylamino or heterocyclic group, with a benzylmagnesium halide having the general formula:



wherein R has the same meaning as above and Hal is a halogen; or

(b) where A is the indicated dialkylamino or alkylamino group, reacting a triphenylethanol having the general formula:



wherein n and R having the same meaning as above and Hal is a halogen with

(i) a lithium dialkylamide in which each alkyl group contains 1 to 4 carbon atoms, or

(ii) an alkylamine in which the alkyl group contains 1 to 4 carbon atoms.

5. A method of preparing substituted triphenylethanols as claimed in Claim 1 substantially as hereinbefore described with reference to, and as illustrated in, Examples 1 to 16.

6. Substituted triphenylethanols whenever prepared by the method according to Claim 4 or 5.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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

* C L M S *