

# PATENT SPECIFICATION

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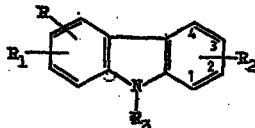
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## (54) CARBAZOLES

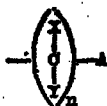
(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to carbazoles. More particularly, the invention is concerned with carbazoles, a process for the manufacture thereof and pharmaceutical preparations containing same.

The carbazoles provided by the present invention are compounds of the general formula



wherein R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy-(lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-(lower alkoxy), nitro, amino, mono-(lower alkyl)-amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group and R<sub>1</sub> represents a halogen atom or a hydroxy, cyano, lower alkyl, hydroxy-(lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-(lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R<sub>1</sub> together represent a lower alkylene-dioxy group, R<sub>2</sub> represents the grouping



in which A represents a cyano, hydroxy, lower alkoxy, amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy), di(lower alkyl)amino-(lower alkoxy) group or the grouping —C(O)—B wherein B represents a hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino, amino-(lower alkoxy), mono(lower alkyl)amino(lower alkoxy), di(lower alkyl)-amino-(lower alkoxy) group, Y and X each represent a hydrogen atom or a lower alkyl group and n stands for 1 to 7, and R<sub>3</sub> represents a hydrogen atom or a lower alkyl, acyl, halo-substituted acyl, carboxy-(lower alkyl), (lower alkoxy-carbonyl)-(lower alkyl), aralkyl or haloaralkyl group, or R<sub>1</sub> represents a hydro-

gen atom when R, X and R<sub>2</sub> each represent a hydrogen atom, Y represents a lower alkyl group and B represents a hydroxy or lower alkoxy group, and, when R or R<sub>1</sub> represents a carboxy and/or when B represents a hydroxy or carboxy group, salts thereof with bases and, when R or R<sub>1</sub> represents an amino or mono(lower alkyl)amino or di(lower alkyl)amino group and/or when B or A represents an amino-(lower alkoxy) or mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, addition salts thereof with acids.

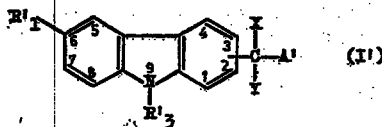
The compounds of formula I and pharmaceutically acceptable salts thereof with acids and bases are useful as anti-inflammatory, analgesic and anti-rheumatic agents.

The pharmaceutically unacceptable salts of the compounds of formula I can be converted into the compounds of formula I or into pharmaceutically acceptable salts thereof with bases or acids according to known methods.

As used in this description and in the accompanying claims, the term "lower alkyl" denotes a straight-chain or branched-chain hydrocarbon group containing 1-7 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, neopentyl, pentyl, heptyl and the like). The term "lower alkoxy" denotes an alkyl ether group in which the alkyl group is as defined earlier (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy and the like). The term "lower alkylthio" denotes an alkyl thioether group in which the alkyl group is as defined earlier (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio and the like). The term "halogen" denotes bromine, chlorine, fluorine and iodine with bromine and chlorine being preferred. The term "aryl" denotes the phenyl group or a phenyl group carrying one or more substituents selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro, amino, lower alkylamino and di(lower alkyl)amino. The term "aralkyl" denotes a straight-chain or branched-chain lower alkyl group in which one or more of the hydrogen atoms has been replaced by an aryl group. The term "acyl" denotes an alkanoyl group derived from an aliphatic carboxylic acid containing 1-7 carbon atoms (e.g. formyl, acetyl, propionyl and the like) or an aroyl group derived from an aromatic carboxylic acid (e.g. benzoyl and the like). The term "lower alkylene" denotes a straight-chain or branched-chain alkylene group containing 1-7 carbon atoms (e.g. methylene, ethylene, propylene, butylene, methylenemethylene and the like). The term "lower alkylenedioxy" preferably denotes methylenedioxy and the like. Examples of mono(lower alkyl)amino groups are methylamino, ethylamino and the like. Examples of di(lower alkyl)amino groups are dimethylamino, diethylamino and the like. Examples of amino-(lower alkoxy) groups are aminomethoxy, aminoethoxy and the like. Examples of mono-(lower alkyl)amino-(lower alkoxy) groups are methylaminomethoxy, ethylaminomethoxy and the like. Examples of di(lower alkyl)amino-(lower alkoxy) groups are dimethylaminomethoxy, diethylaminoethoxy and the like. Examples of di(lower alkyl)sulfamoyl groups are dimethylsulfamoyl, diethylsulfamoyl and the like.

Preferred compounds of formula I are those in which A represents a cyano, hydroxy or lower alkoxy group or the grouping  $-\text{C}(\text{O})-\text{B}$ , particularly those in which n stands for 1, A or B represents a hydroxy group, R represents a hydrogen atom and/or R<sub>1</sub> represents a halogen atom.

Other preferred carbazoles provided by the present invention are those compounds of the general formula



wherein A' represents a carboxy or hydroxymethyl group, R'1 represents a halogen atom or a lower alkyl or lower alkoxy group (preferably a halogen atom), R'3 represents a hydrogen atom or a lower alkyl group (preferably a hydrogen atom) and X and Y have the significance given earlier (the 2-acids being preferred), their enantiomers when X and Y are different, and salts of said compounds with bases.

Preferred compounds of formula I are:

racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid,  
(+) 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid,  
(-) 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid,  
2-(6-chloro-2-carbazolyl)-propanol,

(+) 2-(6-chloro-2-carbazolyl)-propanol,  
(-) 2-(6-chloro-2-carbazolyl)-propanol,  
6-chloro-carbazole-2-acetic acid and  
6-chloro-9-methyl-carbazole-1-acetic acid.

|    |                                                                        |    |
|----|------------------------------------------------------------------------|----|
| 5  | Examples of carbazoles provided by this invention are:                 | 5  |
|    | 6-chloro-carbazole-1-acetic acid,                                      |    |
|    | 6-chloro-carbazole-2-acetic acid ethyl ester,                          |    |
|    | 6-methyl-carbazole-3-acetic acid,                                      |    |
|    | 6-methoxy-carbazole-4-acetic acid,                                     |    |
| 10 | 6-chloro- $\alpha$ -methyl-carbazole-1-acetic acid,                    | 10 |
|    | 9-(4-chlorobenzyl)-6-methoxy-carbazole-2-acetic acid,                  |    |
|    | 6-nitro-carbazole-3-acetic acid,                                       |    |
|    | 7-chloro-carbazole-4-acetic acid,                                      |    |
| 15 | 6-chloro-carbazole-2-acetic acid,                                      | 15 |
|    | 6-chloro-carbazole-3-acetic acid ethyl ester,                          |    |
|    | 6-methyl-carbazole-4-acetic acid,                                      |    |
|    | 6-methoxy-carbazole-1-acetic acid,                                     |    |
|    | 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid,                    |    |
| 20 | 9-(4-chlorobenzyl)-6-methoxy-carbazole-3-acetic acid,                  | 20 |
|    | 6-nitro-carbazole-4-acetic acid,                                       |    |
|    | 7-chloro-carbazole-1-acetic acid,                                      |    |
|    | 6-chloro-carbazole-3-acetic acid,                                      |    |
|    | 6-chloro-carbazole-4-acetic acid ethyl ester,                          |    |
| 25 | 6-methyl-carbazole-1-acetic acid,                                      | 25 |
|    | 6-methoxy-carbazole-2-acetic acid,                                     |    |
|    | 6-chloro- $\alpha$ -methyl-carbazole-3-acetic acid,                    |    |
|    | 9-(4-chlorobenzyl)-6-methoxy-carbazole-4-acetic acid,                  |    |
|    | 6-nitro-carbazole-1-acetic acid,                                       |    |
| 30 | 7-chloro-carbazole-2-acetic acid,                                      | 30 |
|    | 6-chloro-carbazole-4-acetic acid,                                      |    |
|    | 6-chloro-carbazole-1-acetic acid ethyl ester,                          |    |
|    | 6-methyl-carbazole-2-acetic acid,                                      |    |
|    | 6-methoxy-carbazole-3-acetic acid,                                     |    |
| 35 | 6-chloro- $\alpha$ -methyl-carbazole-4-acetic acid,                    | 35 |
|    | 9-(4-chlorobenzyl)-6-methoxy-carbazole-1-acetic acid,                  |    |
|    | 6-nitro-carbazole-2-acetic acid,                                       |    |
|    | 7-chloro-carbazole-3-acetic acid,                                      |    |
|    | 7-methyl-carbazole-1-acetic acid,                                      |    |
| 40 | 8-chloro-carbazole-2-acetic acid,                                      | 40 |
|    | 6-fluoro-carbazole-3-acetic acid,                                      |    |
|    | 6-bromo-carbazole-4-acetic acid,                                       |    |
|    | 6,7-dichloro-carbazole-1-acetic acid,                                  |    |
|    | 5,6-dichloro-carbazole-2-acetic acid,                                  |    |
| 45 | 6-trifluoromethyl-carbazole-3-acetic acid,                             | 45 |
|    | 6-chloro-7-methyl-carbazole-4-acetic acid,                             |    |
|    | 6-chloro-5-methyl-carbazole-1-acetic acid,                             |    |
|    | 9-methyl-carbazole-2-acetic acid,                                      |    |
|    | 7,8-dichloro-carbazole-3-acetic acid,                                  |    |
| 50 | 6-sulfamoyl-carbazole-4-acetic acid,                                   | 50 |
|    | 6-difluoromethylsulfonyl-carbazole-1-acetic acid,                      |    |
|    | racemic 2-(6-chloro-2-carbazolyl)-propanol 2-dimethylaminoethyl ether, |    |
|    | 6-carbethoxy-carbazole-2-acetic acid,                                  |    |
|    | 5-chloro-6-sulfamyl-carbazole-3-acetic acid,                           |    |
| 55 | 6-chloro-9-(4-chlorobenzoyl)-carbazole-4-acetic acid ethyl ester,      | 55 |
|    | 9-benzoyl-6-chloro-carbazole-1-acetic acid,                            |    |
|    | 7-methyl-carbazole-2-acetic acid,                                      |    |
|    | 8-chloro-carbazole-3-acetic acid,                                      |    |
|    | 6-fluoro-carbazole-4-acetic acid,                                      |    |
| 60 | 6-bromo-carbazole-1-acetic acid,                                       | 60 |
|    | 6,7-dichloro-carbazole-2-acetic acid,                                  |    |
|    | 5,6-dichloro-carbazole-3-acetic acid,                                  |    |
|    | 6-trifluoromethyl-carbazole-4-acetic acid,                             |    |
|    | 6-chloro-7-methyl-carbazole-1-acetic acid,                             |    |

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|    | 6-chloro-5-methyl-carbazole-2-acetic acid,<br>9-methyl-carbazole-3-acetic acid,<br>7,8-dichloro-carbazole-4-acetic acid,<br>6-sulfamoyl-carbazole-1-acetic acid,<br>6-difluoromethylsulfonyl-carbazole-2-acetic acid,<br>6-carbethoxy-carbazole-3-acetic acid,<br>5-chloro-6-sulfamyl-carbazole-4-acetic acid,<br>6-chloro-9-(4-chlorobenzoyl)-carbazole-1-acetic acid ethyl ester,<br>9-benzoyl-6-chloro-carbazole-2-acetic acid,<br>7-methyl-carbazole-3-acetic acid,<br>8-chloro-carbazole-4-acetic acid,<br>6-fluoro-carbazole-1-acetic acid,<br>6-bromo-carbazole-2-acetic acid,<br>racemic 2-(6-chloro-2-carbazolyl)-propanol methyl ether,<br>6,7-dichloro-carbazole-3-acetic acid,<br>5,6-dichloro-carbazole-4-acetic acid,<br>6-trifluoromethyl-carbazole-1-acetic acid,<br>6-chloro-7-methyl-carbazole-2-acetic acid,<br>6-chloro-5-methyl-carbazole-3-acetic acid,<br>9-methyl-carbazole-4-acetic acid,<br>7,8-dichloro-carbazole-1-acetic acid,<br>6-sulfamoyl-carbazole-2-acetic acid,<br>6-difluoromethylsulfonyl-carbazole-3-acetic acid,<br>6-carbethoxy-carbazole-4-acetic acid,<br>5-chloro-6-sulfamyl-carbazole-1-acetic acid,<br>6-chloro-9-(4-chlorobenzoyl)-carbazole-2-acetic acid ethyl ester,<br>9-benzoyl-6-chloro-carbazole-3-acetic acid,<br>7-methyl-carbazole-4-acetic acid,<br>8-chloro-carbazole-1-acetic acid,<br>6-fluoro-carbazole-2-acetic acid,<br>6-bromo-carbazole-3-acetic acid,<br>6,7-dichloro-carbazole-4-acetic acid,<br>5,6-dichloro-carbazole-1-acetic acid,<br>6-trifluoromethyl-carbazole-2-acetic acid,<br>6-chloro-7-methyl-carbazole-3-acetic acid,<br>6-chloro-5-methyl-carbazole-4-acetic acid,<br>9-methyl-carbazole-1-acetic acid,<br>7,8-dichloro-carbazole-2-acetic acid,<br>6-sulfamoyl-carbazole-3-acetic acid,<br>6-difluoromethyl-sulfonyl-carbazole-4-acetic acid,<br>6-carbethoxy-carbazole-1-acetic acid,<br>5-chloro-6-sulfamoyl-carbazole-2-acetic acid,<br>6-chloro-9-(4-chlorobenzoyl)-carbazole-3-acetic acid ethyl ester,<br>9-benzoyl-6-chloro-carbazole-4-acetic acid,<br>6-dimethylsulfamoyl-carbazole-1-acetic acid,<br>6-methylthio-carbazole-2-acetic acid,<br>6-benzyloxy-carbazole-3-acetic acid,<br>6-cyano-carbazole-4-acetic acid,<br>6-carboxy-carbazole-1-acetic acid,<br>6-ethyl-carbazole-2-acetic acid,<br>6,7-methylenedioxy-carbazole-3-acetic acid,<br>6-acetyl-carbazole-4-acetic acid,<br>6-iodo-carbazole-1-acetic acid,<br>6-chloro-carbazole-2-acetic acid dimethylamino ethyl ester,<br>6,9-dimethyl-carbazole-3-acetic acid,<br>6-chloro-carbazole-4-acetic acid dimethylaminoethyl ester hydrochloride,<br>6-chloro-N,N-dimethyl-carbazole-1-acetamide,<br>6-methyl-carbazole-2-acetic acid ethyl ester,<br>6-hydroxy-carbazole-3-acetic acid,<br>6-dimethylsulfamoyl-carbazole-2-acetic acid,<br>6-methylthio-carbazole-3-acetic acid,<br>6-benzyloxy-carbazole-4-acetic acid,<br>6-cyano-carbazole-1-acetic acid,<br>6-carboxy-carbazole-2-acetic acid,<br>6-ethyl-carbazole-3-acetic acid, |    |
| 5  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 5  |
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| 45 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 45 |
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| 60 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 60 |
| 65 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 65 |

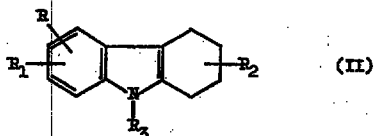
|    |                                                                              |    |
|----|------------------------------------------------------------------------------|----|
|    | 6,7-methylenedioxy-carbazole-4-acetic acid,                                  |    |
|    | 6-acetyl-carbazole-1-acetic acid,                                            |    |
|    | 6-iodo-carbazole-2-acetic acid,                                              |    |
| 5  | 6-chloro-carbazole-3-acetic acid dimethylamino ethyl ester,                  | 5  |
|    | 6,9-dimethyl-carbazole-4-acetic acid,                                        |    |
|    | 6-chloro-carbazole-1-acetic acid dimethylaminoethyl ester hydrochloride,     |    |
|    | 6-chloro-N,N-dimethyl-carbazole-2-acetamide,                                 |    |
|    | 6-methyl-carbazole-3-acetic acid ethyl ester,                                |    |
| 10 | 6-hydroxy-carbazole-4-acetic acid,                                           | 10 |
|    | 6-dimethylsulfamoyl-carbazole-3-acetic acid,                                 |    |
|    | 6-methylthio-carbazole-4-acetic acid,                                        |    |
|    | 6-benzyloxy-carbazole-1-acetic acid,                                         |    |
|    | 6-cyano-carbazole-2-acetic acid,                                             |    |
| 15 | 6-carboxy-carbazole-3-acetic acid,                                           | 15 |
|    | 6-ethyl-carbazole-4-acetic acid,                                             |    |
|    | 6,7-methylenedioxy-carbazole-1-acetic acid,                                  |    |
|    | 6-acetyl-carbazole-2-acetic acid,                                            |    |
|    | 6-iodo-carbazole-3-acetic acid,                                              |    |
| 20 | 6-chloro-carbazole-4-acetic acid dimethylamino ethyl ester,                  | 20 |
|    | 6,9-dimethyl-carbazole-1-acetic acid,                                        |    |
|    | 6-chloro-carbazole-2-acetic acid dimethylaminoethyl ester hydrochloride,     |    |
|    | 6-chloro-N,N-dimethyl-carbazole-3-acetamide,                                 |    |
|    | 6-methyl-carbazole-4-acetic acid ethyl ester,                                |    |
|    | 6-hydroxy-carbazole-1-acetic acid,                                           |    |
| 25 | 6-dimethylsulfamoyl-carbazole-4-acetic acid,                                 | 25 |
|    | 6-methylthio-carbazole-1-acetic acid,                                        |    |
|    | 6-benzyloxy-carbazole-2-acetic acid,                                         |    |
|    | 6-cyano-carbazole-3-acetic acid,                                             |    |
| 30 | 6-carboxy-carbazole-4-acetic acid,                                           | 30 |
|    | 6-ethyl-carbazole-1-acetic acid,                                             |    |
|    | 6,7-methylenedioxy-carbazole-2-acetic acid,                                  |    |
|    | 6-acetyl-carbazole-3-acetic acid,                                            |    |
|    | 6-iodo-carbazole-4-acetic acid,                                              |    |
| 35 | 6-chloro-carbazole-1-acetic acid dimethylamino ethyl ester,                  | 35 |
|    | 6,9-dimethyl-carbazole-2-acetic acid,                                        |    |
|    | 6-chloro-carbazole-3-acetic acid dimethylamino ethyl ester hydrochloride,    |    |
|    | 6-chloro-N,N-dimethyl-carbazole-4-acetamide,                                 |    |
|    | 6-methyl-carbazole-1-acetic acid ethyl ester,                                |    |
|    | 6-hydroxy-carbazole-2-acetic acid,                                           |    |
| 40 | 7-chloro-carbazole-2-acetic acid ethyl ester,                                | 40 |
|    | 8-chloro-carbazole-2-acetic acid ethyl ester,                                |    |
|    | 6-bromo-carbazole-2-acetic acid ethyl ester,                                 |    |
|    | 6-methyl-carbazole-2-acetic acid ethyl ester,                                |    |
|    | 7-chloro-carbazole-3-acetic acid ethyl ester,                                |    |
| 45 | 6-chloro-9-benzyl-carbazole-2-acetic acid ethyl ester,                       | 45 |
|    | 6-chloro-9-methyl-carbazole-2-acetic acid ethyl ester,                       |    |
|    | 6-chloro- $\alpha$ ,9-dimethyl-carbazole-2-acetic acid ethyl ester,          |    |
|    | 6-acetamido-carbazole-2-acetic acid ethyl ester,                             |    |
|    | 6-methyl-9-benzyl-carbazole-1-acetic acid ethyl ester,                       |    |
| 50 | 6-chloro-9-methyl-carbazole-1-acetic acid ethyl ester,                       | 50 |
|    | 6-chloro-carbazole-2-propionic acid ethyl ester,                             |    |
|    | 6-chloro- $\alpha$ , $\alpha$ -dimethyl-carbazole-2-acetic acid ethyl ester, |    |
|    | 6-chloro-carbazole-1-acetic acid ethyl ester,                                |    |
|    | 6-chloro-carbazole-4-acetic acid ethyl ester,                                |    |
| 55 | 6-trifluoromethyl-carbazole-2-acetic acid ethyl ester,                       | 55 |
|    | 7,8-dichloro-carbazole-2-acetic acid ethyl ester,                            |    |
|    | 5,6-dichloro-carbazole-2-acetic acid ethyl ester,                            |    |
|    | 6-methylthio-carbazole-2-acetic acid ethyl ester,                            |    |
|    | 6-carbethoxy-carbazole-2-acetic acid ethyl ester,                            |    |
| 60 | 6-fluoro-carbazole-2-acetic acid ethyl ester,                                | 60 |
|    | $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester,                        |    |
|    | $\alpha$ -methyl-carbozole-3-acetic acid ethyl ester,                        |    |
|    | 6-N,N-dimethylsulfamoyl-carbazole-2-acetic acid ethyl ester,                 |    |
|    | 6-cyano-carbazole-2-acetic acid ethyl ester,                                 |    |
| 65 | 6,7-dichloro-carbazole-2-acetic acid ethyl ester,                            | 65 |

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6-nitro-carbazole-2-acetic acid ethyl ester  
and the like.

According to the process provided by this invention, the carbazoles aforesaid  
(i.e. the compounds of formula I and salts thereof with bases or acids) are manu-  
factured by reacting a compound of the general formula



wherein R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the significance given earlier,  
with an aromatizing agent, for the manufacture of an ester of formula I in which  
R or R<sub>1</sub> represents a carbo-(lower alkoxy) group or B represents a lower alkoxy group  
esterifying an acid of formula I in which R or R<sub>1</sub> represents a carboxy group or B  
represents a hydroxy group, for the manufacture of an acid of formula I in which R  
or R<sub>1</sub> represents a carboxy group, R<sub>3</sub> represents a carboxy-(lower alkyl) group or B  
represents a hydroxy group hydrolysing an ester of formula I in which R or R<sub>1</sub> repre-  
sents a carbo-(lower alkoxy) group, R<sub>3</sub> represents a (lower alkoxycarbonyl)-(lower  
alkyl) group or B represents a lower alkoxy group, for the manufacture of a com-  
pound of formula I in which R<sub>1</sub> represents an amino group reacting a compound of  
formula I in which R<sub>1</sub> represents an acylamido group with an inorganic acid, if  
desired replacing a hydrogen atom denoted by R<sub>3</sub> in a compound of formula I by  
an acyl or (lower alkoxycarbonyl)-(lower alkyl) group, for the manufacture of a com-  
pound of formula I in which R or R<sub>1</sub> represents a di(lower alkyl)amino group alkylat-  
ing a compound of formula I in which R or R<sub>1</sub> represents an amino group, for the  
manufacture of a compound of formula I in which R, R<sub>1</sub> or A represents a hydroxy  
group hydrolysing an ether of formula I in which R, R<sub>1</sub> or A represents a lower alkoxy  
group, if desired converting a compound of formula I in which A represents a hydroxy  
group into a compound of formula I in which A represents a lower alkoxy, amino-  
(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower  
alkoxy) group, for the manufacture of an alcohol of formula I in which A represents  
a hydroxy group reducing an ester of formula I in which B represents a lower alkoxy  
group, if desired converting a hydroxy group denoted by B in an acid of formula I  
or in a salt of such an acid with a base into an amino-(lower alkoxy), mono(lower  
alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, for the  
manufacture of an optically active isomer of a compound of formula I resolving a  
racemate of formula I into its optically active isomers and isolating the desired isomer  
and for the manufacture of a salt of a compound of formula I in which R or R<sub>1</sub>  
represents a carboxy group and/or B represents a hydroxy or carboxy group or in  
which R or R<sub>1</sub> represents an amino, mono(lower alkyl)amino or di(lower alkyl)amino  
group and/or B or A represents an amino(lower alkoxy), mono(lower alkyl)amino-  
(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group reacting such a compound  
of formula I with a base or an acid.

A compound of formula II is converted into a compound of formula I using an  
aromatizing agent [e.g. 4-chloranil, 2-chloranil, 2,3-dichloro-5,6-dicyanobenzoquinone  
(DDQ), sulfur, palladium-on-carbon, or lead oxide] in the presence of a solvent [e.g.  
xylene, benzene, toluene, quinoline, dimethyl sulfoxide (DMSO), dimethylformamide  
(DMF)]. The aromatization is carried out at a temperature in the range of from about  
room temperature to about the reflux temperature of the reaction mixture, preferably  
at the reflux temperature of the reaction mixture. The compounds of formula I can  
be separated from the reaction mixture according to known procedures, including, for  
example, filtration and cyclization.

Alternatively, an acid of formula I (e.g. prepared from a corresponding acid of  
formula II in which R<sub>3</sub> represents a carboxy group) can be converted into a corres-  
ponding ester according to known procedures. For instance, (a) an acid of formula  
I can be reacted with an alkanol (e.g. methanol, ethanol, propanol or the like) in the  
presence of an acid catalyst (e.g. a hydrohalic acid such as hydrochloric acid, hydro-  
bromic acid or the like) at a temperature in the range of from about room temperature  
to the reflux temperature of the reaction mixture or (b) an alkali metal salt of an acid  
of formula I (e.g. the sodium salt) can be reacted with substituted or unsubstituted  
alkyl halide under known reaction conditions; for example, in an inert solvent (e.g.

benzene, toluene or dimethylformamide) at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture.

An acid of formula I in which  $R_3$  represents a hydrogen atom can be acylated at the indole nitrogen atom as follows: The acid is treated with 1,1-carbonyldiimidazole and a solvent such as tetrahydrofuran at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture. The resulting product is then treated with *tert*butyl alcohol in the presence of a catalytic amount of sodium *tert*butoxide. Then, the resulting *tert*butyl ester is treated with an organic acid halide or organic anhydride (e.g. an alkanolic acid halide such as an acetyl halide or an alkanolic anhydride such as acetic anhydride) under known conditions (e.g. at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture), whereby the corresponding N-acylated ester is obtained. Pyrolysis of this ester neat or in an inert high boiling solvent such as mineral oil at or about 160°C until the evolution of gas ceases gives the corresponding N-acylated acid.

A compound of formula I in which  $R_3$  represents a (lower alkoxy-carbonyl)-(lower alkyl) or acyl group can be obtained from a corresponding compound of formula I in which  $R_3$  represents a hydrogen atom according to known procedures; for example, by reaction with a (lower alkoxy-carbonyl)-(lower alkyl) halide (e.g. ethyl chloroacetate) in an inert organic solvent (e.g. dimethylformamide) in the presence of an alkali metal carbonate (e.g. potassium carbonate) or by reacting the alkali metal salt of the indole nitrogen atom, prepared in the usual manner (e.g. with sodium, sodium hydride or sodium amide in an inert solvent) with ethyl chloroacetate in dimethylformamide.

A compound of formula I in which  $R$  or  $R_1$  represents an amino group can be converted into a corresponding compound in which  $R$  or  $R_1$  represents a dialkylamino group according to known procedures; for example, using hydrogen at a pressure of from about 1 atmosphere to about several atmospheres and a catalyst such as Raney nickel together with an alkyl aldehyde such as formaldehyde at a temperature in the range of from about room temperature to about 100°C in a solvent (e.g. an alkanol such as methanol, ethanol or the like).

A compound of formula I in which  $R$ ,  $R_1$  or  $A$  represents an alkoxy group can be converted into a corresponding compound in which  $R$ ,  $R_1$  or  $A$  represents a hydroxy group according to known procedures. For example, a compound of formula I carrying an alkoxy group can be treated with a mineral acid (e.g. a hydrohalic acid such as hydrobromic acid or the like) in a solvent (e.g. an alkanol such as ethanol, propanol or the like) at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture. The conversion can also be carried out using a Lewis acid (e.g. aluminium tribromide, boron trifluoride or tin tetrachloride) in a solvent (e.g. benzene, toluene or dimethylformamide).

An alcohol of formula I (i.e. an alcohol prepared from a corresponding alcohol of formula II in which  $A$  represents a hydroxy group) can be converted into a corresponding compound of formula I in which  $A$  represents a lower alkoxy, amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group according to known procedures. For example, an alcohol of formula I in which  $A$  represents a hydroxy group is treated with an alkali metal such as sodium. The resulting compound is then treated with a halide of the formula  $RX$  in which  $X$  represents a halogen atom and  $R$  represents a lower alkyl, amino-(lower alkyl), mono(lower alkyl)amino-(lower alkyl) or di(lower alkyl)amino-(lower alkyl) group under known conditions.

A compound of formula I in which  $R$  or  $R_1$  represents a carbo-(lower alkoxy) group or  $B$  represents a lower alkoxy group can be de-esterified to a corresponding compound of formula I in which  $R$  or  $R_1$  represents a carboxy group or  $B$  represents a hydroxy group using an alkali hydroxide (e.g. sodium hydroxide, potassium hydroxide or the like) in the presence of a solvent (e.g. an alkanol such as methanol, ethanol or the like). The de-esterification can be carried out at a temperature in the range of from about room temperature to about the reflux temperature of the mixture, preferably at the reflux temperature of the mixture. The compound of formula I can be separated from the mixture according to known procedures.

An ester of formula I can be converted into a corresponding alcohol (e.g. a compound of formula I in which  $A$  represents a hydroxy group) according to known procedures. For example, an ester of formula I can be treated with a reagent such as lithium aluminium hydride at a temperature in the range of from about room temperature to the reflux temperature of the mixture. Thereafter, the corresponding alcohol which is formed can be separated using known procedures.

A compound of formula I in which  $R_1$  represents an acylamido group can be

converted into a corresponding compound of formula I in which  $R_1$  represents an amino group by treatment with an inorganic acid (e.g. a hydrohalic acid such as hydrochloric acid or the like) under known conditions.

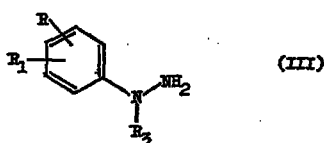
5 An acid of formula I (e.g. a compound of formula I in which B represents a hydroxy group) or a salt of such an acid with a base can be converted into a compound of formula I in which B represents an amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy group according to known procedures. For example, a salt of an acid of formula I is reacted with an amino-(lower alkyl) halide, a mono(lower alkyl)amino-(lower alkyl) halide or a di(lower alkyl)amino-(lower alkyl) halide (e.g. aminoethyl chloride, methylaminoethyl bromide, diethylaminomethyl chloride and the like) to yield the desired product. The temperature at which the reaction is carried out is not critical. The reaction is conveniently carried out at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture. Conveniently, the reaction can be carried out in a polar solvent (e.g. dimethylformamide or dimethyl sulfoxide). The molar ratio of reactant is not critical. The reactants are preferably used in a 1:1 molar ratio.

10 The compounds of formula I in which R or  $R_1$  represents a carboxy group and/or B represents a hydroxy or carboxy group form salts with bases (e.g. pharmaceutically acceptable bases). Examples of such bases are alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide and the like), alkaline earth metal hydroxides (e.g. calcium hydroxide, barium hydroxide and the like), sodium alkoxides (e.g. sodium ethoxide, potassium ethoxide and the like) and organic bases (e.g. piperidine, diethanolamine, N-methylglucamine and the like). Also included within this invention are the aluminium salts of the aforementioned compounds of formula I.

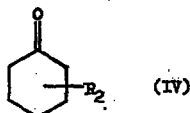
15 Since the compounds of the present invention in which X and Y in formula I are different possess an asymmetric carbon atom, they are ordinarily obtained as racemic mixtures. The resolution of such racemates into the optically active isomers can be carried out according to known procedures. Some racemic mixtures can be precipitated as eutectics and can thereafter be separated. Chemical resolution is, however, preferred. By this procedure, diastereomers are formed from the racemic mixture with an optically active resolving agent (e.g. an optically active base such as *d*- $\alpha$ -methylbenzylamine) which can be reacted with the carboxyl group. The diastereomers formed are separated by selective crystallization and converted into the corresponding optical isomer. Thus, the invention embraces the racemates of the compound of formula I as well as their optically active isomers.

20 The compounds of formula II used as starting materials in the foregoing process can be prepared as follows:

A hydrazine of the general formula



25 wherein R,  $R_1$  and  $R_2$  have the significance given earlier, is reacted with a cyclohexanone of the general formula



30 wherein  $R_2$  has the significance given earlier, to yield a compound of formula II.

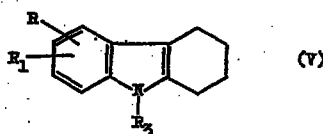
The hydrazines of formula III and the cyclohexanones of formula IV are known or can be prepared according to known procedures.

35 The reaction of a hydrazine of formula III with a cyclohexanone of formula IV to yield a corresponding 1,2,3,4-tetrahydrocarbazole of formula II is carried out at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture, preferably, at the reflux temperature of the reaction mixture. The reaction is carried out in the presence of a solvent (e.g. water, a lower alkanol such as methanol or ethanol, acetic acid, formic acid, hexane, dioxane, benzene, toluene or dimethylformamide) and an acidic condensing agent of the kind used in the Fischer indole synthesis (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, zinc

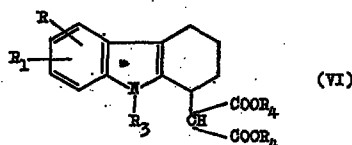
chloride, copper chloride, boron trifluoride, and various combinations thereof). The molar ratio of the reactants is not critical, but, preferably, the reactants are used in a 1:1 molar ratio. Alternatively, the reaction of a hydrazine of formula III with a cyclohexanone of formula IV can be carried out by thermal cyclization in the presence or absence of a solvent. Conveniently, this thermal cyclization is carried out at an elevated temperature (e.g. at a temperature in the range of from about 80°C to about 200°C). The resulting compound of formula II can be separated from the reaction mixture according to known procedures. If desired, however, the reaction mixture may be used directly without further separation in the process provided by this invention (i.e. the aromatisation to a compound of formula I).

The compounds of formula II in which R<sub>2</sub> represents a carboxymethyl group in the 1-position can also be prepared as follows:

A compound of the general formula

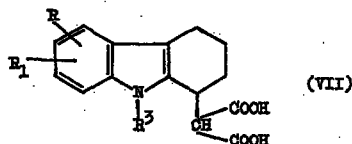


wherein R, R<sub>1</sub> and R<sub>3</sub> have the significance given earlier, is treated with a freshly prepared N-halo-succinimide and pyridine in the presence of an inert organic solvent (e.g. a hydrocarbon such as benzene or the like) and this mixture is treated with a dialkylmalonate in the presence of an alkaline carbonate (e.g. potassium carbonate) to yield a compound of the general formula



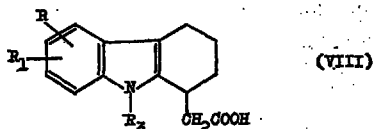
wherein R, R<sub>1</sub> and R<sub>3</sub> have the significance given earlier and R<sub>4</sub> represents a lower alkyl group.

A compound of formula VI is then treated with an alkali metal hydroxide (e.g. potassium hydroxide) in the presence of alkanol (e.g. ethanol or the like) at the reflux temperature of the mixture to yield a malonic acid of the general formula



wherein R, R<sub>1</sub> and R<sub>3</sub> have the significance given earlier.

Subsequently, a malonic acid of formula VII is heated alone or in the presence of an inert high boiling solvent (e.g. mineral oil) under an atmosphere of dry nitrogen to yield an acid of the general formula



wherein R, R<sub>1</sub> and R<sub>3</sub> have the significance given earlier.

Examples of compounds of formula II which can be used as starting materials in the foregoing process are:

- 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid,
- 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid,
- 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester,
- 6-methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid,
- 6-methoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid,
- 6-methoxy-1,2,3,4-tetrahydrocarbazole-4-acetic acid,
- 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,
- 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester,

|    |                                                                                                |    |
|----|------------------------------------------------------------------------------------------------|----|
|    | 9-(4-chlorobenzyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                        |    |
|    | 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                             |    |
|    | 6-nitro-1,2,3,4-tetrahydrocarbazole-1-acetic acid,                                             |    |
| 5  | 7-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                            | 5  |
|    | 7-chloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid,                                            |    |
|    | 7-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                            |    |
|    | 8-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid methyl ester,                               |    |
|    | 8-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                            |    |
| 10 | 6-fluoro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                          | 10 |
|    | 6-bromo-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                             |    |
|    | 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid,                                        |    |
|    | 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                        |    |
|    | 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                   |    |
| 15 | 6-methyl- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid,                          | 15 |
|    | 6-chloro-7-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                   |    |
|    | 6-chloro-5-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                   |    |
|    | 9-methyl- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                          |    |
|    | 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid,                                        |    |
| 20 | 1,2,3,4-tetrahydro-6-sulfamoyl-carbazole-4-acetic acid,                                        | 20 |
|    | 6-difluoromethylsulfonyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid,                            |    |
|    | 6-carbethoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                        |    |
|    | 5-chloro-1,2,3,4-tetrahydro-6-sulfamyl-carbazole-2-acetic acid,                                |    |
|    | 6-carbethoxy-1,2,3,4-tetrahydrocarbazole-1-acetic acid,                                        |    |
| 25 | 6-chloro-9-(4-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester,            | 25 |
|    | 9-benzoyl-6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                  |    |
|    | 6-dimethylsulfamoyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                 |    |
|    | 6-methylthio- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                      |    |
|    | 6-benzyloxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                         |    |
| 30 | 6-cyano-1,2,3,4-tetrahydrocarbazole-4-acetic acid,                                             | 30 |
|    | 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                           |    |
|    | 6-ethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                             |    |
|    | 6,7-methylenedioxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                  |    |
|    | 6-acetyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid,                                            |    |
| 35 | 6-iodo-1,2,3,4-tetrahydrocarbazole-2-acetic acid,                                              | 35 |
|    | 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid dimethylaminoethyl ester, |    |
|    | 6,9-dimethyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid,                                        |    |
|    | 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid dimethylaminoethyl ester hydrochloride,     |    |
| 40 | 6-chloro-N,N-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetamide,                                 | 40 |
|    | 6-methyl- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-4-acetic acid ethyl ester,              |    |
|    | 6-hydroxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid and the like.                              |    |

Examples of hydrazines of formula III hereinbefore are:

|    |                                                           |    |
|----|-----------------------------------------------------------|----|
| 45 | 4-chlorophenylhydrazine,                                  | 45 |
|    | 3-chlorophenylhydrazine,                                  |    |
|    | 2-chlorophenylhydrazine,                                  |    |
|    | 4-fluorophenylhydrazine,                                  |    |
|    | 4-bromophenylhydrazine,                                   |    |
| 50 | 3,4-dichlorophenylhydrazine,                              | 50 |
|    | 4-trifluoromethylphenylhydrazine,                         |    |
|    | 4-chloro-1-methylphenylhydrazine,                         |    |
|    | 2,3-dichlorophenylhydrazine,                              |    |
|    | 4-methylphenylhydrazine,                                  |    |
|    | 3-methylphenylhydrazine,                                  |    |
| 55 | 4-methoxyphenylhydrazine,                                 | 55 |
|    | N <sup>1</sup> -(4-chlorobenzyl)-4-chlorophenylhydrazine, |    |
|    | 4-nitrophenylhydrazine,                                   |    |
|    | 1-methyl-1-phenylhydrazine,                               |    |
|    | 4-sulfamidophenylhydrazine,                               |    |
| 60 | 4-difluoromethylsulfonyl-phenylhydrazine,                 | 60 |
|    | 4-carbethoxyphenylhydrazine,                              |    |
|    | 4-aminosulfonyl-3-chlorophenylhydrazine and the like.     |    |

Examples of cyclohexanones of formula IV hereinbefore are:

$\alpha$ -methyl-1-oxo-cyclohexane-acetic acid,  
 $\alpha$ -methyl-2-oxo-cyclohexane-acetic acid,  
 $\alpha$ -methyl-3-oxo-cyclohexane-acetic acid,  
 $\alpha$ -methyl-4-oxo-cyclohexane-acetic acid,  
1-oxo-cyclohexane-acetic acid,  
2-oxo-cyclohexane-acetic acid,  
3-oxo-cyclohexane-acetic acid,  
4-oxo-cyclohexane-acetic acid,  
 $\alpha$ -methyl-1-oxo-cyclohexane-acetic acid ethyl ester,  
 $\alpha$ -methyl-1-oxo-cyclohexane-acetic acid methyl ester,  
1-oxo-cyclohexane-acetic acid ethyl ester,  
1-oxo-cyclohexane-acetic acid methyl ester and the like.

The compounds of formula I and the salts thereof with pharmaceutically acceptable bases and acids possess anti-inflammatory, analgesic and anti-rheumatic activity and are therefore useful as anti-inflammatory, analgesic and anti-rheumatic agents. They also exhibit a significantly low incidence of ulcerogenic activity, which renders them highly desirable as anti-inflammatory, analgesic and anti-rheumatic agents. Their pharmacologically useful activities are demonstrated in warm-blooded animals using standard procedures.

For example, the anti-inflammatory activity is demonstrated in Albino rats of Hart Strain, weighing 125—155 g. The rats are given 10 ml of vehicle [Hilgar, A. G. and Hummel, D. J.: Endocrine Bioassay Data, No. 1, p. 15, August 1964 (Cancer Chemotherapy National Service Center, N.I.H.)] which contains the compound to be tested per kg of body weight. The rats are treated daily for 5 consecutive days. 3 hours after the first treatment, 0.05 ml of an 0.5 per cent suspension of heat-killed desiccated *Mycobacterium butyricum* in olive oil, which has been steam sterilized for 30 minutes, is injected into the right hind foot of each rat. The paw volume is measured immediately after the injection of the adjuvant and again 96 hours later. The difference is recorded as volume of oedema. The paw volume is measured by immersion of the paw into a column of mercury to an ink mark exactly at the level of the lateral malleolus. Per cent inhibition is calculated by dividing the average control oedema minus the average treatment oedema by the average control oedema times 100. The per cent inhibition is plotted against dose on semi-logarithmic probability paper and the dose required to produce a 30 per cent reduction in oedema is estimated therefrom and is expressed as  $ED_{30}$ .

When 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid, which has demonstrated an  $LD_{50}$  of, for example, 400 mg *p.o.* in mice, is used in the foregoing test at a dosage of 0.03 mg *p.o.*, an anti-inflammatory activity is observed ( $ED_{30}=0.17$ ).

The analgesic activity is demonstrated, for example, using the method which is a modification of that described by Eddy (1950), Wolfe and MacDonald (1944) and Eddy and Leimbach (1952). The method determines the reaction time of mice dropped on to a hot plate maintained at  $55^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . Six groups of male mice (5 mice per group) weighing between 20—30 g are used. The initial reaction time of these mice is determined once and the reaction time of each group is then averaged. The mice are then administered the vehicle and/or the compound to be tested by the oral, intraperitoneal or subcutaneous route. The average reaction time of each group is determined again at 30, 60 and 90 minutes after administration and is compared to controls. Reaction time is recorded as per cent changes from control. All groups are averaged before and after treatment. A combined reaction time average (recorded as per cent change of reaction time threshold from controls) for all three periods is plotted against dose on graph paper and a curve is drawn. The  $ED_{50}$  is read from this curve.

When 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid, which has demonstrated an  $LD_{50}$  of, for example, 400 mg *p.o.* in mice, is used in this test, analgesic activity is observed at an  $ED_{50}$  of 15.

The carbazoles of this invention have effects qualitatively similar to those of phenylbutazone and indomethacin which are known for their therapeutic uses and properties. Thus, they demonstrate a pattern of activity associated with anti-inflammatory agents of known efficacy and safety.

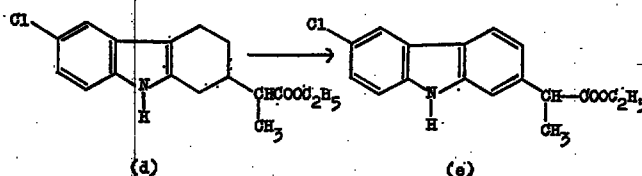
The carbazole derivatives of this invention can be incorporated into standard pharmaceutical dosage forms. For example, they are useful for oral or parenteral administration together with the usual pharmaceutical adjuvant material (e.g. organic

or inorganic inert carrier materials such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols and the like). The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, trochés, suppositories or capsules) or in a liquid form (e.g. as solutions, suspensions or emulsions). Pharmaceutical adjuvant materials can be added and these include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

The following Examples illustrate the process provided by the present invention:

#### Example 1

#### Preparation of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester



A mixture of 34.9 g of 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (mixture of diastereomers), 350 ml of xylene and 56.0 g of 4-chloranil is stirred and heated under an atmosphere of dry nitrogen. The reaction flask is wrapped in aluminium foil in order to keep out any extraneous light. After the reaction mixture has been stirred at reflux temperature for 6 hours, heating and stirring are stopped and the reaction mixture is left overnight at room temperature. The supernatant liquid is decanted through a filter. The residue is triturated with 100 ml of warm benzene and the supernatant liquid is decanted through a filter. This procedure is repeated a further 3 times. 300 ml of ether are added to the combined filtrates. The solution is extracted three times with 100 ml of cold 2-N sodium hydroxide each time, washed by extraction with water until neutral and dried over anhydrous magnesium sulfate. After filtration of the desiccant and evaporation of the solvent, a residue of 35.5 g remains. Crystallization from 50 ml of methanol gives 14.8 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester of melting point 106°—107.5°C (43.2%).

In an analogous manner, when the 1,2,3,4-tetrahydro-carbazole of formula (d) is replaced as hereinafter set forth, the corresponding carbazoles are obtained:

by replacing (d) by 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-chlorocarbazole-2-acetic acid ethyl ester of melting point 176°—178°C (methanol);

by replacing (d) by 7-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 7-chlorocarbazole-2-acetic acid ethyl ester of melting point 200°—202°C (methanol);

by replacing (d) by 8-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 8-chlorocarbazole-2-acetic acid ethyl ester of melting point 110°—113°C (methanol);

by replacing (d) by 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-acetamido-carbazole-2-acetic acid ethyl ester of melting point 208°—210°C (ethanol);

by replacing (d) by 6-methyl-9-benzyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester there is obtained 6-methyl-9-benzyl-carbazole-1-acetic acid ethyl ester of melting point 130°—131°C (methanol);

by replacing (d) by 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester there is obtained 6-chloro-9-ethyl-carbazole-1-acetic acid ethyl ester;

by replacing (d) by 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid ethyl ester there is obtained 6-chlorocarbazole-2-propionic acid ethyl ester of melting point 149°—150.5°C (methanol);

by replacing (d) by 6-chloro- $\alpha,\alpha$ -dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-chloro- $\alpha,\alpha$ -dimethyl-carbazole-2-acetic acid ethyl ester;

by replacing (d) by 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester there is obtained 6-chlorocarbazole-1-acetic acid ethyl ester of melting point 152.5°—154°C (methanol);

by replacing (d) by 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid ethyl ether

there is obtained 6-chlorocarbazole-4-acetic acid ethyl ester of melting point 154°—155°C (methanol);

by replacing (d) by 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-trifluoromethyl-carbazole-2-acetic acid ethyl ester of melting point 130°—131°C (carbon tetrachloride);

by replacing (d) by 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 7,8-dichloro-carbazole-2-acetic acid ethyl ester of melting point 154°—155°C (methanol);

by replacing (d) by 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 5,6-dichloro-carbazole-2-acetic acid ethyl ester of melting point 139°—140°C (methanol);

by replacing (d) by 6-methylthio-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-methylthio-carbazole-2-acetic acid ethyl ester;

by replacing (d) by 6-carbethoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-carbethoxy-carbazole-2-acetic acid ethyl ester of melting point 141°—143°C (methanol);

by replacing (d) by 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-fluoro-carbazole-2-acetic acid ethyl ester of melting point 178°—179°C (methanol);

by replacing (d) by  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained  $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester of melting point 104°—105°C (hexane);

by replacing (d) by  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid ethyl ester there is obtained  $\alpha$ -methyl-carbazole-3-acetic acid ethyl ester of melting point 97.5°—99°C (methanol);

by replacing (d) by 6-N,N-dimethylsulfamoyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-N,N-dimethylsulfamoyl-carbazole-2-acetic acid ethyl ester of melting point 146°—147°C (methanol);

by replacing (d) by 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-cyano-carbazole-2-acetic acid ethyl ester of melting point 157°—158°C (methanol);

by replacing (d) by 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6,7-dichloro-carbazole-2-acetic acid ethyl ester of melting point 186°—187.5°C (methanol); and

by replacing (d) by 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester there is obtained 6-nitro-carbazole-2-acetic acid ethyl ester of melting point 164°—165°C (methanol).

The ester of formula (d) used as the starting material can be obtained as follows:

#### A) Preparation of $\alpha$ -methyl-3-oxo-cyclohexane-malonic acid diethyl ester

2.2 g of sodium are dissolved in 300 ml of ethanol in a 1 litre 3-necked round-bottomed flask equipped with a nitrogen gas inlet, thermometer and dropping funnel. 182 g of diethylmethylmalonate are added with stirring and the stirring is continued for 1 hour. After this time, 92 g of 2-cyclohexene-1-one in 118 ml of ethanol are added slowly over the course of 1 hour. The stirring is continued for an additional 5 hours. The solution is then acidified with concentrated acetic acid and the excess ethanol is removed on a rotating evaporator under reduced pressure. The residue is dissolved in 1200 ml of ether and washed three times with 200 ml of water each time. The ether solution is dried over anhydrous sodium sulfate with stirring. After removal of the sodium sulfate, the ether is removed and a residue of 308.7 g of oil is obtained. This residue is distilled to yield 204.4 g (78.7%) of  $\alpha$ -methyl-3-oxo-cyclohexane-malonic acid diethyl ester as a clear oil of boiling point 149°—152°C/0.8 mm;  $n_D^{20}$  = 1.4660.

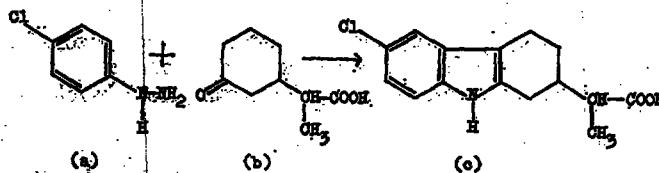
#### B) Preparation of $\alpha$ -methyl-3-oxo-cyclohexane-acetic acid

15.75 g of  $\alpha$ -methyl-3-oxo-cyclohexane-malonic acid diethyl ester, 235 ml of 6-N hydrochloric acid and 235 ml of dioxane are combined in a 1 litre flask equipped with a reflux condenser. The solution is heated to reflux with stirring and refluxed for 10 hours. After the solution has cooled down to room temperature, a 50% solution of sodium hydroxide (75 g of sodium hydroxide/75 g of water) is added until the solution is basic. The basic solution is then cooled with stirring in an ice bath before extracting it once with 500 ml of ether. The ether layer is discarded and the aqueous layer is made acidic with concentrated hydrochloric acid. The acidic solution is concentrated to dryness on a rotating evaporator and the salt remaining is triturated three

times with 350 ml of ether each time. The ether solution is dried over anhydrous sodium sulphate with stirring.

The drying agent is removed by filtration and the ether is concentrated to dryness on a rotating evaporator to yield 13.6 g of an oily residue. The residual oil is distilled to yield 5.4 g (54.9%) of  $\alpha$ -methyl-3-oxo-cyclohexane-acetic acid of boiling point  $164^{\circ}$ — $166^{\circ}$ C/0.7 mm;  $n_D^{20}$ =1.4794.

C) Preparation of 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid (diastereomers)



A mixture of 25 g of 4-chlorophenylhydrazine hydrochloride, 150 ml of 80% acetic acid (120 ml of glacial acetic plus 30 ml of water) and 23.8 g of  $\alpha$ -methyl-3-oxo-cyclohexane-acetic acid is stirred at ambient temperature under an atmosphere of nitrogen. After 1.5 hours, solution is complete and the reaction is heated to reflux. After 10 minutes at reflux, a heavy precipitate forms. After an additional 0.5 hour under reflux, the heat is removed and the reaction mixture is stirred while cooling to room temperature. The contents of the reaction flask are poured into 2 litres of water with stirring. The mixture is stirred for an additional 20 minutes and filtered. The filter cake is washed with water, allowed to dry and then completely dried in a vacuum oven ( $95^{\circ}$ C, over sodium hydroxide, water pump pressure) to yield 36.3 g (93%) of 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $193^{\circ}$ — $202^{\circ}$ C (mixture of diastereomers).

In an analogous manner, when the phenylhydrazine of formula (a) and/or the oxo-cyclohexane of formula (b) are replaced as hereinafter set forth, the corresponding 1,2,3,4-tetrahydrocarbazoles are obtained:

by replacing (b) by cyclohexane-3-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $184^{\circ}$ — $186^{\circ}$ C (benzene);

by replacing (a) by 3-chlorophenylhydrazine and by replacing (b) by cyclohexane-3-acetic acid there is obtained 7-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $189^{\circ}$ — $192^{\circ}$ C (ethyl acetate);

by replacing (a) by 2-chlorophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 9-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

by replacing (a) by 4-bromophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-bromo-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $191^{\circ}$ — $201^{\circ}$ C (ethyl acetate);

by replacing (a) by 4-methylphenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $184^{\circ}$ — $186^{\circ}$ C (ethyl acetate);

by replacing (a) by 4-methoxyphenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-methoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $187^{\circ}$ — $188^{\circ}$ C (ethyl acetate);

by replacing (b) by cyclohexanone-4-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid of melting point  $186^{\circ}$ — $188^{\circ}$ C (ethyl acetate);

by replacing (a) by 3-chlorophenylhydrazine and by replacing (b) by cyclohexanone-4-carboxylic acid there is obtained 7-chloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid of melting point  $186^{\circ}$ — $188^{\circ}$ C (hexane/ethyl acetate);

by replacing (a) by 1-methyl-1-(4-chlorophenyl)-hydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point  $202^{\circ}$ — $204^{\circ}$ C (ethyl acetate);

by replacing (a) by 1-methyl-1-(4-chlorophenyl)-hydrazine there is obtained 6-chloro- $\alpha$ ,9-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid (diastereomers) of melting point  $197^{\circ}$ — $203^{\circ}$ C (ethyl acetate);

by replacing (a) by 1-benzyl-1-(4-methylphenyl)-hydrazine and by replacing (b) by cyclohexanone-1-acetic acid ethyl ester there is obtained 6-methyl-9-benzyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

by replacing (a) by 1-methyl-1-(4-chlorophenyl)-hydrazine and by replacing (b)

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by cyclohexanone-1-acetic acid ethyl ester there is obtained 6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

by replacing (a) by 4-dimethylsulfamoylphenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 1,2,3,4-tetrahydro-6-dimethylsulfamoyl-carbazole-2-acetic acid of melting point 159°—161°C (ethyl acetate);

by replacing (a) by 4-cyanophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

by replacing (a) by 3,4-dichlorophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 192°—193°C (ethyl acetate);

by replacing (a) by 4-nitrophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 233°—234°C (methanol);

by replacing (a) by phenylhydrazine there is obtained  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

by replacing (a) by phenylhydrazine and by replacing (b) by  $\alpha$ -methyl-4-oxocyclohexane-acetic acid there is obtained  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid of melting point 162.5°—163.5°C (benzene);

by replacing (a) by 4-trifluoromethylphenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 186°—187°C (ethanol/water);

by replacing (a) by 2,3-dichlorophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 167°—169°C (benzene);

by replacing (a) by 3,4-dichlorophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 194°—196°C (acetonitrile);

by replacing (a) by 4-methylthiophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 1,2,3,4-tetrahydro-6-methylthio-carbazole-2-acetic acid of melting point 204°—205°C (ethyl acetate);

by replacing (a) by 4-carboxyphenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 306°—307°C (ethanol);

by replacing (a) by 4-fluorophenylhydrazine and by replacing (b) by cyclohexanone-2-acetic acid there is obtained 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 189°—190°C (ethyl acetate);

by replacing (b) by  $\alpha,\alpha$ -dimethyl-3-oxo-cyclohexane-acetic acid there is obtained 6-chloro- $\alpha,\alpha$ -dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid of melting point 242°—243°C (ethyl acetate);

by replacing (a) by 4-acetamidophenylhydrazine and by replacing (b) by cyclohexanone-3-acetic acid there is obtained 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

by replacing (a) by 1-ethyl-1-(4-chlorophenyl)-hydrazine and by replacing (b) by cyclohexanone-2-acetic acid there is obtained 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

by replacing (b) by cyclohexanone-3-propionic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid of melting point 211°—212°C (ethyl acetate); and

by replacing (b) by cyclohexanone-2-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid of melting point 141°—142.5°C.

D) Alternative method for the preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid.

a) Preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid diethyl ester. To a stirred solution of 18.8 g of 6-chloro-1,2,3,4-tetrahydrocarbazole, 20 g of pyridine and 320 ml of dry benzene are added over the course of 30 minutes 18.8 g of freshly recrystallized N-bromosuccinimide. After the addition, the reaction mixture is stirred for 2.5 hours at room temperature and then stirred for 45 minutes at 60°C. After cooling to room temperature, the reaction mixture is concentrated to dryness under reduced pressure. To the stirred residue is added a solution of 42.5 g of diethylmalonate in 265 ml of anhydrous ethanol. The stirred mixture is cooled in an ice bath to 5°C and 21.5 g of anhydrous potassium carbonate are added slowly over

30 minutes. The reaction mixture is stirred for an additional 16 hours at room temperature and glacial acetic acid is added slowly until the reaction mixture is slightly acidic. The mixture is then concentrated to dryness under reduced pressure and the residue is partitioned between ether and water. The organic layer is separated, washed four times by extraction with water and dried over anhydrous sodium sulfate. After the desiccant has been removed by filtration and the ether evaporated, the residue slowly crystallizes. The supernatant liquor is decanted and the remaining crystals are dried on a porous plate to yield 8 g of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid diethyl ester of melting point 142°—144°C.

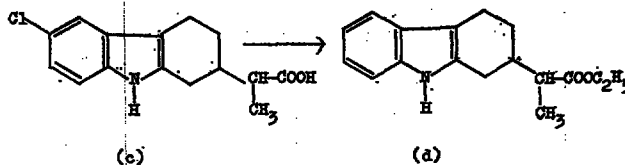
b) Preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid

A solution of 5 g of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid diethyl ester, 8 g of potassium hydroxide, 38 ml of ethanol and 2 ml of water is stirred and heated to reflux temperature under an atmosphere of nitrogen. After 2 hours under reflux, the reaction mixture is concentrated to dryness under reduced pressure. The residue is dissolved in 1.5 litres of warm water and filtered through a Celite filter pad. (The word "Celite" is a registered Trade Mark). Concentrated hydrochloric acid is added to the cooled filtrate until precipitation is complete and the mixture is then extracted with ether. In turn, the ether extract is washed by extraction with water and dried over anhydrous magnesium sulfate. After filtration of the desiccant and evaporation of the ether solution, 4.7 g of product are obtained. A small portion is recrystallized from benzene to yield 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid of melting point 159°—160°C (decomposition).

c) Preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid

4.3 g of anhydrous 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid are heated with stirring under an atmosphere of dry nitrogen. The temperature is raised to 195°C over 20 minutes and then held at 195°C for 0.5 hour to complete the decarboxylation. Carbon dioxide starts to evolve when the temperature reaches 160°C. After cooling, the reaction mixture is crystallized from benzene to yield 1.8 g of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid of melting point 141°—142.5°C.

E) Preparation of 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (diastereomers)



36 g of 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid (diastereomers) are dissolved in 1500 ml of ethanol. The slightly turbid solution is filtered and 10 g of hydrogen chloride gas are introduced into the clear filtrate. The solution is refluxed under an atmosphere of nitrogen for 12 hours and allowed to remain at room temperature for 48 hours. 100 ml of benzene are added and the reaction mixture is concentrated under reduced pressure to dryness. The residue is dissolved in 1 litre of ethanol, 11 g of hydrogen chloride gas are introduced and the solution is again refluxed. After 12 hours at reflux, the heating is stopped and 200 ml of benzene are added. Thereafter, the reaction mixture is concentrated to dryness. The residue is dissolved in 800 ml of ether (a faint turbidity remains) and extracted with 200 ml of cold 2-N sodium hydroxide. After the ether solution has been washed by extraction with water, it is dried over powdered anhydrous magnesium sulfate. After filtration of the desiccant and evaporation of the ether, a gummy solid remains. Yield 35.9 g (91.2 per cent theory) of 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester.

In an analogous manner, when the 1,2,3,4-tetrahydrocarbazole of formula (c) is replaced as hereinafter set forth, the corresponding carbazoles are obtained:

by replacing (c) by 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester of melting point 125°—126°C (ethanol);

by replacing (c) by 1,2,3,4-tetrahydro-6-dimethylsulfamoyl-carbazole-2-acetic acid there is obtained 1,2,3,4-tetrahydro-6-dimethylsulfamoyl-carbazole-2-acetic acid ethyl ester;

by replacing (c) by 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester of melting point 159°—160°C (benzene);

by replacing (c) by 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 1,2,3,4-tetrahydro-6-methylthiocarbazole-2-acetic acid there is obtained 1,2,3,4-tetrahydro-6-methylthio-carbazole-2-acetic acid ethyl ester;

by replacing (c) by 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 6-chloro- $\alpha,\alpha$ -dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-chloro- $\alpha,\alpha$ -dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester of melting point 169°—171°C (ethyl acetate);

by replacing (c) by  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid there is obtained  $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid ethyl ester;

by replacing (c) by 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid ethyl ester;

by replacing (c) by 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

by replacing (c) by 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid there is obtained 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

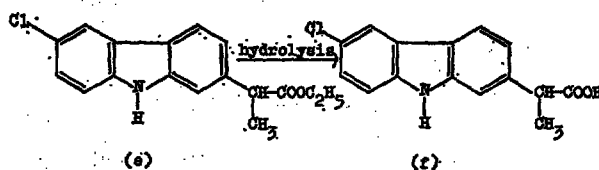
by replacing (c) by 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid there is obtained 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

by replacing (c) by 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid ethyl ester; and

by replacing (c) by 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester.

### Example 2

#### Preparation of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid (racemic)



A stirred mixture of 11 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester, 100 ml of ethanol and 100 ml of 3-N sodium hydroxide is heated under an atmosphere of nitrogen. After 2 hours at reflux, the reaction mixture is concentrated to dryness under reduced pressure. 300 ml of water and 200 g of ice are added to the residue and then concentrated hydrochloric acid is added until the mixture is strongly acid. The acidic mixture is extracted three times with 200 ml of ether each time. The ether extracts are combined, washed by extracting three times with 100 ml of water each time and dried over anhydrous magnesium sulfate. After filtration of the desiccant and evaporation of the solvent, a yield of 9.8 g (98.2%) of product is obtained. Crystallization from chloroform yields 6.2 g (62.0%) of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid of melting point 197°—198°C. A second crop of 1.6 g of melting point 195°—199°C is obtained from the mother liquors.

In an analogous manner, when the carbazole of formula (e) is replaced as hereinafter set forth, the corresponding carbazole of formula (f) are obtained:

by replacing (e) by 6-chloro-carbazole-2-acetic acid ethyl ester there is obtained 6-chloro-carbazole-2-acetic acid of melting point 255°—257°C (ethyl acetate);

- by replacing (e) by 7-chloro-carbazole-2-acetic acid ethyl ester there is obtained 7-chloro-carbazole-2-acetic acid of melting point 252°—254°C (methanol);
- by replacing (e) by 8-chloro-carbazole-2-acetic acid ethyl ester there is obtained 8-chloro-carbazole-2-acetic acid of melting point 210°—211°C (chloroform);
- 5 by replacing (e) by 6-bromo-carbazole-2-acetic acid ethyl ester there is obtained 6-bromo-carbazole-2-acetic acid of melting point 249°—250°C (methanol);
- by replacing (e) by 6-methyl-carbazole-2-acetic acid ethyl ester there is obtained 6-methyl-carbazole-2-acetic acid of melting point 272°—274°C (decomposition) (ethyl acetate);
- 10 by replacing (e) by 6-methoxy-carbazole-2-acetic acid ethyl ester there is obtained 6-methoxy-carbazole-2-acetic acid of melting point 205°—206°C (decomposition) (ethyl acetate);
- by replacing (e) by 6-methyl-9-benzyl-carbazole-1-acetic acid ethyl ester there is obtained 6-methyl-9-benzyl-carbazole-1-acetic acid of melting point 182°—185°C (methanol);
- 15 by replacing (e) by 6-chloro-9-methyl-carbazole-1-acetic acid ethyl ester there is obtained 6-chloro-9-methyl-carbazole-1-acetic acid of melting point 223°—225°C (ethyl acetate);
- by replacing (e) by 6-chloro-9-methyl-carbazole-2-acetic acid ethyl ester there is obtained 6-chloro-9-methyl-carbazole-2-acetic acid of melting point 235°—236°C (ethyl acetate);
- 20 by replacing (e) by racemic 6-chloro- $\alpha$ ,9-dimethyl-carbazole-2-acetic acid ethyl ester there is obtained racemic 6-chloro- $\alpha$ ,9-dimethyl-carbazole-2-acetic acid of melting point 176°—178°C (benzene);
- 25 by replacing (e) by 6-chloro-carbazole-3-acetic acid ethyl ester there is obtained 6-chloro-carbazole-3-acetic acid of melting point 246°—247°C (ethyl acetate);
- by replacing (e) by 7-chloro-carbazole-3-acetic acid ethyl ester there is obtained 7-chloro-carbazole-3-acetic acid of melting point 236°—237°C (ethyl acetate);
- by replacing (e) by 6-acetamido-carbazole-2-acetic acid ethyl ester there is obtained 6-acetamido-carbazole-2-acetic acid of melting point 300°C (ethanol);
- 30 by replacing (e) by 6-methyl-9-benzyl-carbazole-1-acetic acid ethyl ester there is obtained 6-methyl-9-benzyl-carbazole-1-acetic acid of melting point 182°—185°C (methanol);
- by replacing (e) by 6-chloro-9-ethyl-carbazole-1-acetic acid ethyl ester there is obtained 6-chloro-9-ethyl-carbazole-1-acetic acid of melting point 192°—193°C (methanol);
- 35 by replacing (e) by 6-chloro-carbazole-2-propionic acid ethyl ester there is obtained 6-chloro-carbazole-2-propionic acid of melting point 230°—231°C (methanol);
- by replacing (e) by 6-chloro- $\alpha$ , $\alpha$ -dimethyl-carbazole-2-acetic acid ethyl ester there is obtained 6-chloro- $\alpha$ , $\alpha$ -dimethyl-carbazole-2-acetic acid of melting point 221°—222.5°C (ethyl acetate/hexane);
- 40 by replacing (e) by 6-chloro-carbazole-1-acetic acid ethyl ester there is obtained 6-chloro-carbazole-1-acetic acid of melting point 155°—157°C (decomposition). The piperidine salt has a melting point of 118°—120°C (acetone/ether);
- 45 by replacing (e) by 6-chloro-carbazole-4-acetic acid ethyl ester there is obtained 6-chloro-carbazole-4-acetic acid of melting point 175°—176°C (decomposition) (benzene);
- by replacing (e) by 6-methylthio-carbazole-2-acetic acid ethyl ester there is obtained 6-methylthio-carbazole-2-acetic acid of melting point 202°—204°C (ethyl acetate);
- 50 by replacing (e) by 6-carboxy-carbazole-2-acetic acid ethyl ester there is obtained 6-carboxy-carbazole-2-acetic acid of melting point 301°—302°C (acetone);
- by replacing (e) by 6-chloro-9-carboxymethyl- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester there is obtained 6-chloro-9-carboxymethyl- $\alpha$ -methyl-carbazole-2-acetic acid of melting point 248°—250°C (decomposition) (acetone);
- 55 by replacing (e) by  $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester there is obtained  $\alpha$ -methyl-carbazole-2-acetic acid of melting point 246°—447°C (decomposition) (chloroform);
- by replacing (e) by  $\alpha$ -methyl-carbazole-3-acetic acid ethyl ester there is obtained  $\alpha$ -methyl-carbazole-3-acetic acid of melting point 213°—216°C (decomposition) (ethyl acetate);
- 60 by replacing (e) by 6-nitro-carbazole-2-acetic acid ethyl ester there is obtained 6-nitro-carbazole-2-acetic acid of melting point 262°—264°C (methanol); and
- by replacing (e) by 6-chloro-9-ethoxycarbonylmethyl- $\alpha$ -methyl-carbazole-2-acetic

acid ethyl ester there is obtained 6-chloro-9-carboxymethyl- $\alpha$ -methyl-carbazole-2-acetic acid of melting point 248°—250°C (acetone).

#### Example 3

##### Preparation of (–)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid

A solution of 8.0 g of (+)- $\alpha$ -methylbenzylamine ( $[\alpha]_D^{20} = +39^\circ$ ) in 40 ml of acetone is carefully added to a warmed solution of 18.0 g of racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid in 360 ml of acetone. After standing at room temperature for 3 days, the mixture is filtered and the filter cake is washed with a small amount of cold acetone to yield, upon drying, 10.6 g of (–)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid (+)- $\alpha$ -methylbenzylamine salt;  $[\alpha]_D^{20} = +9.9^\circ$  (the filtrate and washings are combined, concentrated to dryness and the free acid is liberated for use in further resolution). A recrystallization of the salt from 200 ml of acetone gives 6.0 g of product;  $[\alpha]_D^{22} = +11.1^\circ$ . After two additional recrystallizations of the salt there are obtained 1.85 g of product;  $[\alpha]_D^{22} = +13.2^\circ$ . Further recrystallization of the salt from acetone does not increase the specific rotation. 1.85 g of the salt are dissolved in 50 ml of warm methanol, filtered from any insolubles, and then poured into a stirred mixture of ice and hydrochloric acid. After filtration and drying, 1.2 g of the acid are obtained which yield upon crystallization from chloroform 1.0 g of (–)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid of melting point 198°—201°C;  $[\alpha]_D^{22} = -53.0^\circ$ , ( $c = 1.4$  in methanol).

#### Example 4

##### Preparation of (+)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid

A solution of 4.3 g of (–)- $\alpha$ -methylbenzylamine in 20 ml of acetone is added to a solution of 9.7 g of partially resolved 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid (recovered from the filtration of a previous resolution of the racemate). After standing at room temperature for 24 hours, the mixture is filtered and the filter cake is washed with cold acetone to yield, after drying, 7.3 g of product. After two additional recrystallizations from acetone, there are obtained 1.9 g of (+)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid (–)- $\alpha$ -methylbenzylamine salt;  $[\alpha]_D^{22} = -13.6^\circ$ . Further recrystallizations from acetone do not change the specific rotation. The salt is dissolved in 50 ml of warm acetone and the solution is poured, after filtration, into 500 ml of dilute hydrochloric acid. After filtration and drying, 1.4 g are obtained, which upon crystallization from chloroform give 0.9 g of (+)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid of melting point 198°—201°C;  $[\alpha]_D^{22} = +53.2^\circ$ , ( $c = 1.33$  in methanol).

#### Example 5

##### Preparation of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid *tert*butyl ester

A solution of 2 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid (which can be prepared according to the procedure in Example 2) in 10 ml of tetrahydrofuran is added dropwise to a stirred solution of 1.4 g of 1,1-carbonyldiimidazole in 10 ml of tetrahydrofuran. The stirred reaction mixture is heated to reflux. After the reaction has been stirred at reflux temperature for 1 hour (carbon dioxide is given off by the reaction mixture), it is cooled to 25°C and a solution of 0.5 g of sodium *tert*butoxide, 5 g of *tert*butyl alcohol and 10 ml of tetrahydrofuran is added dropwise over the course of 5 minutes. After the last addition, the stirred reaction mixture is heated to reflux and maintained at reflux for 4 hours. When the reaction has cooled to room temperature, it is concentrated to dryness under reduced pressure. The residue is partitioned between ether and 2-*N* potassium carbonate. The ether layer is separated, washed by extraction with water and dried over anhydrous magnesium sulfate. After filtration of the desiccant and evaporation of the ether, 2.2 g are obtained. Crystallization from aqueous ethanol gives 1.7 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid *tert*butyl ester of melting point 152°—154°C.

#### Example 6

##### Preparation of 9-acetyl-6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid

A solution of 4 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid *tert*butyl ester (which can be prepared according to the procedure in Example 5), 70 ml of chloroform, 3 ml of acetic anhydride and 1 drop of concentrated sulfuric acid is stirred at reflux temperature for 3 hours. The reaction mixture is concentrated to dryness under reduced pressure, and the residue is partitioned between chloroform and cold dilute potassium bicarbonate. The chloroform layer is separated, washed by extraction with water and dried over magnesium sulfate. After filtration of the desiccant and evaporation of the ether solution, 1.9 g of the acetylated ester are obtained. Without further purification, the crude product is stirred and heated between 210°—220°C under an

atmosphere of dry nitrogen for 30 minutes. Upon cooling to room temperature, the reaction mixture is partitioned between ether and cold dilute potassium bicarbonate. The aqueous portion is separated and the ether is again extracted with cold dilute potassium bicarbonate. Ice is added to the combined potassium bicarbonate extracts and the solution is made slightly acidic with cold 6-N hydrochloric acid. The acid that separates is removed by filtration, washed with cold water and air dried, yielding 0.7 g of product. After recrystallization from ethyl acetate, there are obtained 0.5 g of 9-acetyl-6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid of melting point 180°—182°C.

#### Example 7

##### Preparation of 6-acetamido-carbazole-2-acetic acid ethyl ester

A mixture of 1.8 g of 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (which can be prepared according to the procedure in Example 1E), 0.3 g of 10% palladium on carbon black and 30 ml of dry xylene is refluxed and stirred under an atmosphere of dry nitrogen for 48 hours. The mixture is cooled to 70°C, diluted with warm ethanol and filtered through Celite. The filter cake is washed several times with warm ethanol. The filtrate and washings are combined and concentrated to dryness under reduced pressure; yielding 1.6 g of product. Upon crystallization from ethanol, there are obtained 0.8 g of 6-acetamido-carbazole-2-acetic acid ethyl ester of melting point 208°—210°C.

#### Example 8

##### Preparation of 6-amino-carbazole-2-acetic acid ethyl ester hydrochloride

A solution of 6-acetamido-carbazole-2-acetic acid ethyl ester (which can be prepared according to the procedure in Example 7) and 40 ml of 1-N alcoholic hydrogen chloride is refluxed and stirred under an atmosphere of dry nitrogen for 6 hours. The solution is concentrated to dryness under reduced pressure and the residue is crystallized from a solution of ethyl acetate and ethanol, yielding 0.5 g of 6-amino-carbazole-2-acetic acid ethyl ester hydrochloride of melting point 231°—232°C (decomposition).

#### Example 9

##### Preparation of racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid methyl ester

A mixture of 1 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid (which can be prepared according to the procedure in Example 1), 100 ml of methanol and 3 drops of concentrated sulfuric acid is stirred thoroughly and allowed to stand at room temperature for 24 hours. The solution is concentrated to dryness under reduced pressure and the residue is partitioned between ether and dilute sodium carbonate. The ether layer is separated and washed by extraction with water and dried over anhydrous sodium sulfate. After filtration of the desiccant and evaporation of the ether, 1.2 g of ester are obtained. Recrystallization from hexane yields 0.7 g of racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid methyl ester of melting point 111°—112°C.

#### Example 10

##### Preparation of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid 2-dimethylamino-ethyl ester

A solution of 3 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid in 10 ml of dimethylformamide is added to a stirred mixture of 0.48 g of 54.5% dispersion of sodium hydride (in mineral oil) in 30 ml of dimethylformamide. After the addition, the mixture is stirred for 1 hour at room temperature and a solution of freshly liberated dimethylaminoethyl chloride in 10 ml of dimethylformamide is added dropwise over the course of 10 minutes. After the last addition, the reaction mixture is stirred and heated with the temperature maintained at about 70°C for 4 hours. The warm reaction mixture is poured on to 300 g of ice and when the ice has melted the mixture is extracted with ether. The ether solution is in turn extracted with dilute potassium carbonate followed by water and the washed ether solution is dried over anhydrous magnesium sulfate. After the desiccant has been removed by filtration and the ether evaporated under reduced pressure, there remain 2.7 g of product. Crystallization of the residue from a solution of ether and hexane gives 2.1 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid 2-dimethylaminoethyl ester of melting point 89°—90°C.

## Example 11

Preparation of 6-chloro-9-ethoxycarbonylmethyl- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester

5 A solution of 1.5 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester (pre-  
pared according to the procedure in Example 9) in 10 ml of dimethylformamide is  
slowly added to a stirred mixture of 0.25 g of a 54.5% dispersion of sodium hydride  
(in mineral oil) in 10 ml of dimethylformamide. After the addition, the mixture is  
10 stirred for 30 minutes at room temperature under an atmosphere of dry nitrogen and  
a solution of 1 g of ethyl chloroacetate in 5 ml of dimethylformamide is added drop-  
wise over the course of 10 minutes. After the last addition, the reaction mixture is  
stirred and heated to about 60°C for 7 hours and then poured into 300 ml of ice  
water. The mixture is extracted with ether. The ether extract is washed by extrac-  
tion with water and dried over anhydrous magnesium sulfate. After filtration of the  
15 desiccant and evaporation of the ether, there remain 1.6 g of product. Trituration  
of the residue with a mixture of hexane and ether followed by filtration gives 1.0 g  
of product of melting point 80°—87°C. Recrystallization from methanol gives 0.7 g  
of 6-chloro-9-ethoxycarbonylmethyl- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester of  
melting point 87°—88°C.

## Example 12

Preparation of 9-acetyl-6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid methyl ester

20 A solution of 2.0 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid methyl ester, 20  
ml of chloroform, 1 ml of acetic anhydride and 1 drop of concentrated sulfuric acid  
is stirred and heated at reflux temperature. After 3 hours at reflux, the reaction mix-  
25 ture is cooled and concentrated to dryness under reduced pressure. The residue is  
partitioned between ether and cold dilute sodium bicarbonate. The ether layer is  
separated, washed by extraction with water and dried over anhydrous magnesium  
sulfate. After filtration of the desiccant and evaporation of the ether, there are ob-  
tained 1.9 g of product. Crystallization from a solution of ether and hexane gives  
30 1.1 g of 9-acetyl-6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid methyl ester of melting  
point 86°—87°C.

## Example 13

## Preparation of 6-dimethylamino-carbazole-2-acetic acid ethyl ester hydrochloride

35 A mixture of 1.5 g of 6-amino-carbazole-2-acetic acid ethyl ester (which can be  
prepared according to the procedure in Example 8), half a teaspoon of Raney nickel,  
100 ml of methanol and 1.3 g of 30% aqueous formaldehyde is shaken for 4 hours  
in a Parr bomb under an atmosphere of hydrogen (3.8 atmospheres) at room tem-  
perature. The catalyst is removed by filtration through Celite and the filtrate is con-  
40 centrated to dryness under reduced pressure. (The word "Celite" is a registered Trade  
Mark). The residue is partitioned between chloroform and dilute sodium bicarbonate.  
The chloroform layer is separated, washed by extraction with water and dried over  
anhydrous sodium sulfate. After the desiccant has been removed by filtration, dry  
hydrogen chloride is introduced into the filtrate. The salt is filtered and washed with  
45 ether. Upon air drying, there are obtained 0.8 g of product. Recrystallization from  
a mixture of methanol and ethyl acetate gives 0.3 g of 6-dimethylamino-carbazole-2-  
acetic acid ethyl ester hydrochloride of melting point 129°—131°C.

## Example 14

## Preparation of 6-hydroxy-carbazole-2-acetic acid

50 A mixture of 1 g of 6-methoxy-carbazole-2-acetic acid ethyl ester, 5 ml of glacial  
acetic acid and 5 ml of 40% aqueous hydrobromic acid is stirred at reflux tempera-  
ture for 5 hours and the warm solution is then poured into 800 ml of water with stir-  
ring. The mixture is stirred for a further 20 minutes. The mixture is filtered, washed  
with water and air dried, yielding 0.6 g of a tan solid which gives a slight positive  
55 test with ferric chloride. Recrystallization from methanol yield 0.3 g of 6-hydroxy-  
carbazole-2-acetic acid of melting point 280°—282°C.

## Example 15

Preparation of racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester

60 A mixture of 10 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid and 400 ml of  
ethanol (in which 2 g of hydrogen chloride gas has been introduced) is refluxed and

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5 stirred under an atmosphere of nitrogen for 12 hours and allowed to remain over-  
night at room temperature. 50 ml of benzene are added and the reaction mixture is  
concentrated to dryness under reduced pressure. The residue is dissolved in 200 ml  
of ethanol (2B). Then, 2 g of hydrogen chloride gas are introduced and the solution  
is refluxed again for 5 hours. The reaction mixture is cooled to about 50°C, 50 ml  
of benzene are added and the solution is concentrated to dryness. The residue is dis-  
solved in 400 ml of ether. The ether solution is extracted once with 100 ml of 0.01-M  
dilute potassium carbonate and then twice with 100 ml of water. After drying over  
anhydrous magnesium sulfate, the desiccant is removed by filtration and the ether  
evaporated, yielding 10.6 g (96%) of product. Recrystallization from methanol yields  
8.1 g of racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester (74%) of melt-  
ing point 106°—107°C.

Example 16

Preparation of 2-(6-chloro-2-carbazolyl)-propanol

15 There are placed 30 ml of ether and 0.5 g of lithium aluminium hydride in a  
500 ml 3-necked flask equipped with a stirrer, condenser, thermometer, dropping fun-  
nel and under an atmosphere of dry nitrogen. The mixture is stirred and a solution  
of 1 g of 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester in 80 ml of ether is  
added dropwise over the course of 20 minutes. After the addition is completed, the  
20 reaction mixture is heated on a water bath to reflux and allowed to reflux for 10 hours  
with stirring. Then, the reaction mixture is cooled by means of an ice/water bath and  
30 ml of cold water are added dropwise at such a rate that the temperature never  
exceeds +10°C. After the addition of water, the mixture is stirred for 1.5 hours at  
room temperature and filtered. The filter cake and the flask are washed twice with  
25 25 ml of ether each time. The combined filtrates and washings are dried over an-  
hydrous magnesium sulfate. Filtration of the desiccant and evaporation of the ether  
gives a residue of 0.8 g (93.3%). Recrystallization of the product from benzene gives  
0.7 g (81.5%) of 2-(6-chloro-2-carbazolyl)-propanol of melting point 170°—171.5°C.

Example 17

30 In accordance with the procedure in Example 15, (—)6-chloro- $\alpha$ -methyl-carb-  
azole-2-acetic acid is converted to the corresponding optically active 6-chloro- $\alpha$ -methyl-  
carbazole-2-acetic acid ethyl ester. Then, in accordance with the procedure in Example  
16, the optically active 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester is con-  
verted to the (+)2-(6-chloro-2-carbazolyl)-propanol of melting point 186°—187.5°C  
35 (benzene);  $[\alpha]_D^{22} = +20.6$  ( $c = 1.81$  in methanol).

Example 18

40 In accordance with the procedure in Example 15, (+)6-chloro- $\alpha$ -methyl-carb-  
azole-2-acetic acid is converted to the corresponding optically active 6-chloro- $\alpha$ -  
methyl-carbazole-2-acetic acid ethyl ester. Then, in accordance with the procedure in  
Example 16, the optically active 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid ethyl ester  
is converted to the (—)2-(6-chloro-2-carbazolyl)-propanol of melting point 186°—  
186.5°C;  $[\alpha]_D^{22} = -20.6$  ( $c = 1.6$  in methanol).

The following Examples illustrate pharmaceutical preparations provided by the  
present invention:

Example A

45 Suppositories of the following composition are manufactured in a conventional  
manner:

|                                                       | Per 1.3 g<br>suppository |    |
|-------------------------------------------------------|--------------------------|----|
| 50 6-Chloro- $\alpha$ -methyl-carbazole-2-acetic acid | 0.025 g                  | 50 |
| Wecobee M*                                            | 1.230 g                  |    |
| Carnauba wax                                          | 0.045 g                  |    |

\* E. F. Drew Company, 522 Fifth Avenue, New York, New York.

Example B

55 Tablets of the following composition are manufactured in a conventional man-  
ner:

|                                                       | Per tablet |    |
|-------------------------------------------------------|------------|----|
| 60 6-Chloro- $\alpha$ -methyl-carbazole-2-acetic acid | 25.00 mg   | 60 |
| Lactose                                               | 64.50 mg   |    |
| Corn starch                                           | 10.00 mg   |    |
| Magnesium stearate                                    | 0.50 mg    |    |

## Example C

Capsules of the following composition are manufactured in a conventional manner:

|   |                                                    |                      |   |
|---|----------------------------------------------------|----------------------|---|
| 5 | 6-Chloro- $\alpha$ -methyl-carbazole-2-acetic acid | Per capsule<br>50 mg | 5 |
|   | Lactose                                            | 125 mg               |   |
|   | Corn starch                                        | 30 mg                |   |
|   | Talc                                               | 5 mg                 |   |
|   | Total weight                                       | 210 mg               |   |

## Example D

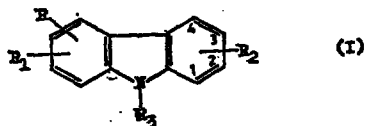
## Parenteral Formulation

Each 1 cm<sup>3</sup> ampoule contains:

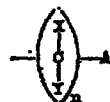
|    |                                                    |                                |    |
|----|----------------------------------------------------|--------------------------------|----|
| 10 | 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid | Per cm <sup>3</sup><br>10.2 mg | 10 |
| 15 |                                                    | (2 per cent excess)            | 15 |
|    | Methylparaben                                      | 1.8 mg                         |    |
|    | Propylparaben                                      | 0.2 mg                         |    |
| 20 | Sodium hydroxide, <i>q.s.</i> ph                   | 9.0                            | 20 |
|    | Water for injection, <i>q.s.</i> ad                | 1 cm <sup>3</sup>              |    |

## WHAT WE CLAIM IS:—

## 1. Compounds of the general formula



wherein R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy(lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-(lower alkoxy), nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group and R<sub>1</sub> represents a halogen atom or a hydroxy, cyano, lower alkyl, hydroxy-(lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-(lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R<sub>1</sub> together represent a lower alkylenedioxy group, R<sub>2</sub> represents the grouping



in which A represents a cyano, hydroxy, lower alkoxy, amino(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy), di(lower alkyl)amino-(lower alkoxy) group or the grouping —C(O)—B wherein B represents a hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino, amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy), di(lower alkyl)-amino-(lower alkoxy) group, Y and X each represent a hydrogen atom or a lower alkyl group and n stands for 1 to 7, and R<sub>3</sub> represents a hydrogen atom or a lower alkyl, acyl, halo-substituted acyl, carboxy-(lower alkyl), (lower alkoxy-carbonyl)-(lower alkyl), aralkyl or haloaralkyl group, or R<sub>1</sub> represents a hydrogen atom when R, X and R<sub>3</sub> each represent a hydrogen atom, Y represents a lower alkyl group and B represents a hydroxy or lower alkoxy group, and, when R or R<sub>1</sub> represents a carboxy and/or when B represents a hydroxy or carboxy group, salts thereof with bases and, when R or R<sub>1</sub> represents an amino or mono(lower alkyl)amino or di(lower alkyl) amino group and/or when B or A represents an amino-(lower alkoxy) or mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, addition salts thereof with acids.

## 2. Compounds of formula I given in claim 1, wherein R represents a hydrogen



## Example C

Capsules of the following composition are manufactured in a conventional manner:

|   |                                                    |                      |   |
|---|----------------------------------------------------|----------------------|---|
| 5 | 6-Chloro- $\alpha$ -methyl-carbazole-2-acetic acid | Per capsule<br>50 mg | 5 |
|   | Lactose                                            | 125 mg               |   |
|   | Corn starch                                        | 30 mg                |   |
|   | Talc                                               | 5 mg                 |   |
|   | Total weight                                       | 210 mg               |   |

## Example D

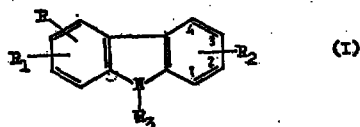
## Parenteral Formulation

Each 1 cm<sup>3</sup> ampoule contains:

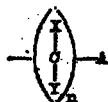
|    |                                                    |                                                       |    |
|----|----------------------------------------------------|-------------------------------------------------------|----|
| 15 | 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid | Per cm <sup>3</sup><br>10.2 mg<br>(2 per cent excess) | 15 |
|    | Methylparaben                                      | 1.8 mg                                                |    |
|    | Propylparaben                                      | 0.2 mg                                                |    |
|    | Sodium hydroxide, <i>q.s.</i> ph                   | 9.0                                                   |    |
| 20 | Water for injection, <i>q.s.</i> ad                | 1 cm <sup>3</sup>                                     | 20 |

## WHAT WE CLAIM IS:—

## 1. Compounds of the general formula



wherein R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy(lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-(lower alkoxy), nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group and R<sub>1</sub> represents a halogen atom or a hydroxy, cyano, lower alkyl, hydroxy-(lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-(lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R<sub>1</sub> together represent a lower alkylenedioxy group, R<sub>2</sub> represents the grouping

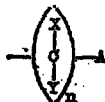


in which A represents a cyano, hydroxy, lower alkoxy, amino(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy), di(lower alkyl)amino-(lower alkoxy) group or the grouping —C(O)—B wherein B represents a hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino, amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy), di(lower alkyl)-amino-(lower alkoxy) group, Y and X each represent a hydrogen atom or a lower alkyl group and n stands for 1 to 7, and R<sub>3</sub> represents a hydrogen atom or a lower alkyl, acyl, halo-substituted acyl, carboxy-(lower alkyl), (lower alkoxy-carbonyl)-(lower alkyl), aralkyl or haloaralkyl group, or R<sub>1</sub> represents a hydrogen atom when R, X and R<sub>3</sub> each represent a hydrogen atom, Y represents a lower alkyl group and B represents a hydroxy or lower alkoxy group, and, when R or R<sub>1</sub> represents a carboxy and/or when B represents a hydroxy or carboxy group, salts thereof with bases and, when R or R<sub>1</sub> represents an amino or mono(lower alkyl)amino or di(lower alkyl) amino group and/or when B or A represents an amino-(lower alkoxy) or mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, addition salts thereof with acids.

## 2. Compounds of formula I given in claim 1, wherein R represents a hydrogen



or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy-(lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo(lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group and  $R_1$  represents a halogen atom or a hydroxy, cyano, lower alkyl, hydroxy-(lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo(lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or  $R$  and  $R_1$  together represent a lower alkylenedioxy group,  $R_2$  represents the grouping



in which A represents a cyano, hydroxy or lower alkoxy group or the grouping  $-C(O)-B$  wherein B represents a hydroxy, carboxy, lower alkoxy, amino, hydroxy-amino, mono(lower alkyl)amino, di(lower alkyl)amino, amino-(lower alkoxy), mono-(lower alkyl)amino-(lower alkoxy), di(lower alkyl)amino-(lower alkoxy) group, Y and X each represent a hydrogen atom or a lower alkyl group and  $n$  stands for 1 to 7, and  $R_2$  represents a hydrogen atom or a lower alkyl, acyl, halo-substituted acyl, aralkyl or haloaralkyl group, or  $R_1$  represents a hydrogen atom when  $R$ , X and  $R_2$  each represent a hydrogen atom, Y represents a lower alkyl group and B represents a hydroxy or lower alkoxy group, and, when  $R$  or  $R_1$  represents a carboxy and/or when B represents a hydroxy or carboxy group, salts thereof with bases and, when  $R$  or  $R_1$  represents an amino or mono(lower alkyl)amino or di(lower alkyl)amino group and/or when B or A represents an amino-(lower alkoxy) or mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, addition salts thereof with acids.

3. Carbazoles according to claim 1 or claim 2, wherein A represents a cyano, hydroxy or lower alkoxy group or the grouping  $-C(O)-B$  as defined in said claims.

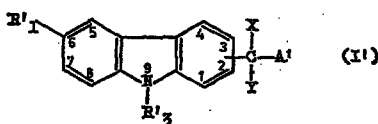
4. Carbazoles according to any one of claims 1 to 3 inclusive, wherein  $n$  stands for 1 or 2.

5. Carbazoles according to any one of claims 1 to 4 inclusive, wherein A or B represents a hydroxy group.

6. Carbazoles according to any one of claims 1 to 5 inclusive, wherein  $R$  represents a hydrogen atom.

7. Carbazoles according to any one of claims 1 to 6 inclusive, wherein  $R_1$  represents a halogen atom.

8. Carbazoles according to any one of claims 1, 2 and 4 to 7 inclusive of the general formula



wherein  $A'$  represents a carboxy or hydroxymethyl group,  $R'_1$  represents a halogen atom or a lower alkyl or lower alkoxy group and  $R'_3$  represents a hydrogen atom or a lower alkyl group,

and salts of said compounds in which  $A'$  represents a carboxy group.

9. Racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid.

10. (+)6-Chloro- $\alpha$ -methyl-carbazole-2-acetic acid.

11. (-)6-Chloro- $\alpha$ -methyl-carbazole-2-acetic acid.

12. 6-Chloro-carbazole-2-acetic acid.

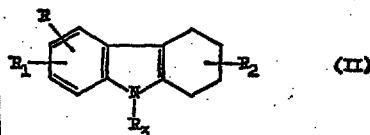
13. 2-(6-Chloro-2-carbazolyl)-propanol.

14. (+)2-(6-Chloro-2-carbazolyl)-propanol.

15. (-)2-(6-Chloro-2-carbazolyl)-propanol.

16. 6-Chloro-9-methyl-carbazole-1-acetic acid.

17. A process for the manufacture of the carbazoles claimed in claim 1, which process comprises reacting a compound of the general formula



wherein  $R$ ,  $R_1$ ,  $R_2$  and  $R_3$  have the significance given in claim 1,



(34)

with an aromatizing agent, for the manufacture of an ester of formula I in which R or R<sub>1</sub> represents a carbo-(lower alkoxy) group or B represents a lower alkoxy group esterifying an acid of formula I in which R or R<sub>1</sub> represents a carboxy group or B represents a hydroxy group, for the manufacture of an acid of formula I in which R or R<sub>1</sub> represents a carboxy group, R<sub>3</sub> represents a carboxy-(lower alkyl) group or B represents a hydroxy group hydrolysing an ester of formula I in which R or R<sub>1</sub> represents a carbo-(lower alkoxy) group, R<sub>3</sub> represents a (lower alkoxycarbonyl)-(lower alkyl) group or B represents a lower alkoxy group, for the manufacture of a compound of formula I in which R<sub>1</sub> represents an amino group reacting a compound of formula I in which R<sub>1</sub> represents an acylamido group with an inorganic acid, if desired replacing a hydrogen atom denoted by R<sub>3</sub> in a compound of formula I by an acyl or (lower alkoxycarbonyl)-(lower alkyl) group, for the manufacture of a compound of formula I in which R or R<sub>1</sub> represents a di(lower alkyl)amino group alkylating a compound of formula I in which R or R<sub>1</sub> represents an amino group, for the manufacture of a compound of formula I in which R, R<sub>1</sub> or A represents a hydroxy group hydrolysing an ether of formula I in which R, R<sub>1</sub> or A represents a lower alkoxy group, if desired converting a compound of formula I in which A represents a hydroxy group into a compound of formula I in which A represents a lower alkoxy, amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, for the manufacture of an alcohol of formula I in which A represents a hydroxy group reducing an ester of formula I in which B represents a lower alkoxy group, if desired converting a hydroxy group denoted by B in an acid of formula I or in a salt of such an acid with a base into an amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, for the manufacture of an optically active isomer of a compound of formula I resolving a racemate of formula I into its optically active isomers and isolating the desired isomer and for the manufacture of a salt of a compound of formula I in which R or R<sub>1</sub> represents a carboxy group and/or B represents a hydroxy or carboxy group or in which R or R<sub>1</sub> represents an amino, mono(lower alkyl)amino or di(lower alkyl)amino group and/or B represents an amino(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group reacting such a compound of formula I with a base or an acid.

18. A process according to claim 17 for the manufacture of the carbazoles claimed in claim 2, which process comprises reacting a compound of formula II in which R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the significance given in claim 2 with an aromatizing agent, for the manufacture of an acid of formula I in which R or R<sub>1</sub> represents a carboxy group or B represents a hydroxy group hydrolysing an ester of formula I in which R or R<sub>1</sub> represents a carbo-(lower alkoxy) group or B represents a lower alkoxy group, for the manufacture of an alcohol of formula I in which A represents a hydroxy group hydrolysing an ether of formula I in which A represents a lower alkoxy group, if desired converting a hydroxy group denoted by B in an acid of formula I or in a salt of such an acid with a base into an amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group, for the manufacture of an optically active isomer of a compound of formula I resolving a racemate of formula I into its optically active isomers and isolating the desired isomer and for the manufacture of a salt of a compound of formula I in which R or R<sub>1</sub> represents a carboxy group and/or B represents a hydroxy or carboxy group or wherein R or R<sub>1</sub> represents an amino, mono(lower alkyl)amino or di(lower alkyl)amino group and/or B represents an amino-(lower alkoxy), mono(lower alkyl)amino-(lower alkoxy) or di(lower alkyl)amino-(lower alkoxy) group reacting such a compound of formula I with a base or an acid.

19. A process according to claim 17 or claim 18 for the manufacture of the carbazoles claimed in claim 3, wherein a compound of formula II in which A has the significance given in claim 3 is used as the starting material.

20. A process according to any one of claims 17 to 19 inclusive for the manufacture of the carbazoles claimed in claim 4, wherein a compound of formula II in which n stands for 1 or 2 is used as the starting material.

21. A process according to any one of claims 17 to 20 inclusive for the manufacture of the carbazoles claimed in claim 5, wherein a compound of formula II in which A or B represents a hydroxy group is used as the starting material.

22. A process according to any one of claims 17 to 21 inclusive for the manufacture of the carbazoles claimed in claim 6, wherein a compound of formula II in which R represents a hydrogen atom is used as the starting material.

23. A process according to any one of claims 17 to 22 inclusive for the manu-

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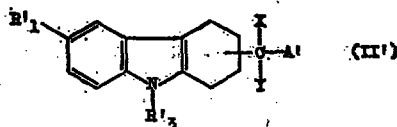
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facture of the carbazoles claimed in claim 7, wherein a compound of formula II in which  $R_1$  represents a halogen atom is used as the starting material.

24. A process according to any one of claims 17, 18 and 20 to 23 inclusive for the manufacture of the carbazoles claimed in claim 8, wherein a compound of the general formula



wherein  $R'_1$ ,  $R'_3$  and  $A'$  have the significance given in claim 8, is used as the starting material.

25. A process according to any one of claims 17 to 24 inclusive for the manufacture of racemic 6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid, wherein 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

26. A process according to any one of claims 17 to 24 inclusive for the manufacture of (+)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid, wherein 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

27. A process according to any one of claims 17 to 24 inclusive for the manufacture of (-)6-chloro- $\alpha$ -methyl-carbazole-2-acetic acid, wherein 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

28. A process according to any one of claim 17 to 24 inclusive for the manufacture of 6-chloro-carbazole-2-acetic acid, wherein 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

29. A process according to any one of claims 17, 18 and 20 to 24 inclusive for the manufacture of 2-(6-chloro-2-carbazolyl)-propanol, wherein 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

30. A process according to any one of claims 17, 18 and 20 to 24 inclusive for the manufacture of (+)2-(6-chloro-2-carbazolyl)-propanol, wherein 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

31. A process according to any one of claims 17, 18 and 20 to 24 inclusive for the manufacture of (-)2-(6-chloro-2-carbazolyl)-propanol, wherein 6-chloro- $\alpha$ -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is used as the starting material of formula II.

32. A process according to any one of claims 17 to 24 inclusive for the manufacture of 6-chloro-9-methyl-carbazole-1-acetic acid, wherein 6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester is used as the starting material of formula II.

33. A process for the manufacture of the carbazoles claimed in claim 1, substantially as hereinbefore described with reference to Examples 1 to 18.

34. Carbazoles as set forth in claim 1, when manufactured by the process claimed in any one of claims 17 to 33 inclusive.

35. A pharmaceutical preparation containing a compound as set forth in any one of claims 1 to 16 inclusive or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier.

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