

PATENT SPECIFICATION

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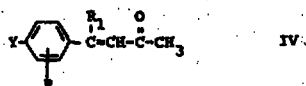
(72) Inventor EUGENE ERVIN GALANTAY



(54) PHENYL-ALKENONES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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:—

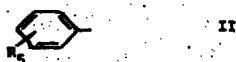
This invention relates to phenyl-alkenones. More particularly, this invention provides compounds of formula IV,



in which

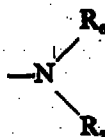
R signifies hydrogen, fluorine, chlorine or bromine,

R₁ signifies alkyl of 1 to 3 carbon atoms, and Y signifies bromine, iodine, isobutyl, tert. butyl, cyclohexyl, cyclohexenyl, a radical of formula II,



in which

R₅ is hydrogen, fluorine, chlorine or bromine, or alkoxy of 1 to 4 carbon atoms, or a radical of formula III,



III

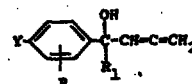
in which either R₆ and R₇ are the same or different and each signifies an alkyl radical of 1 to 3 carbon atoms, or R₆ and R₇ together signify the radical

—(CH₂)_n—, in which n is 4 or 5, the radical —CH₂—CH₂—O—CH₂—CH₂—, the radical —CH₂—CH=CH—CH₂—, or a radical



in which R₈ is hydrogen or alkyl of 1 to 3 carbon atoms.

The invention also provides a process for the production of compounds of formula IV, characterised by treatment of a compound of formula V,



in which R, R₁ and Y are as defined above, with a strong protonating agent, in the presence of water.

The process may suitably be effected using a strong protonating agent in the presence of water and also in the presence of hydroxy, C₂₋₄ acyloxy or C₁₋₄ alkoxy ions. Suitable protonating agents include mineral acids, such as hydrochloric, hydrobromic or sulphuric acid, and aromatic or lower aliphatic sulphonic acids containing up to 10 carbon atoms, such as *p*-toluenesulphonic acid. Suitable hydroxy, C₂₋₄ acyloxy and C₁₋₄ alkoxy anion contributing agents, include C₁₋₄ alkanols such as methanol, esters, such as ethyl orthoformate, and organic acids and anhydrides, such as acetic acid or acetic anhydride. If appropriate, an excess of such agents may be employed to provide a reaction medium or, alternatively, an inert organic solvent may be used. The process is conveniently effected at a temperature of from 10° to 100° C., preferably 15° to 35° C. When hydrochloric acid or hydrobromic acid is employed, a mixture of the

desired compound of formula IV, and the corresponding 4-substituted phenyl-4-alkyl-2-chloro- (or bromo)-1,3-butadiene may be formed. Such products may be separated in conventional manner.

The resulting compounds of formula IV may be isolated and purified using conventional techniques.

The compounds of formula V are either known or may be produced in conventional manner from available materials.

The compounds of formula IV exist as geometric isomers and may be produced in the form of *cis* or *trans* isomers or in the form of isomeric mixtures which may, if desired, be separated in conventional manner into individual isomers. Compounds of formula IV substantially or predominantly in *trans* form result directly from the process described above. Other forms may be produced by conventional methods, for example by stereospecific synthesis from available materials, or by "scrambling" the compounds obtained predominantly or substantially in *trans* form as described above, e.g. by UV irradiation, and, if desired, separating the resulting isomeric mixtures using conventional techniques.

It is to be appreciated that while the invention is not intended to be limited to any particular form of the compounds of formula IV, the compounds are preferably predominantly or substantially in *trans* form.

The compounds of formula IV are useful as intermediates for the production of pharmaceutically active compounds, in particular those described in our co-pending application No. 36481/74 (Serial No. 1,483,352).

The following Examples illustrate the invention.

EXAMPLE 1.

2-(*p*-Biphenyl)-2-penten-4-one.

To a solution of 10 g 2-(*p*-biphenyl)-3,4-pentadien-2-ol in 200 ml of anhydrous methanol is added 3 ml of concentrated hydrochloric acid (12N). The resulting mixture is stirred at room temperature for 3 hours and then in an ice bath for 2 hours. Solids formed are filtered off and recrystallised from pentane to obtain 2-(*p*-biphenyl)-2-penten-4-one, m.p. 130° to 133° C., substantially in *trans* form. 2-(*p*-Biphenyl)-4-chloro-2,4-pentadiene, a by-product, remains in the mother liquor.

EXAMPLE 2.

In manner analogous to Example 1, employing appropriate starting materials in approximately equivalent amounts, the following compounds may be obtained:—

2 - (*p* - tert.butylphenyl) - 2 - penten - 4 - one,
2 - (*p* - bromophenyl) - 2 - penten - 4 - one,

2 - (*p* - cyclohexyl - *m* - chlorophenyl) - 2-penten - 4 - one,

2 - (*p* - isobutylphenyl) - 2 - penten - 4 - one, 65

4 - (*p* - biphenyl) - 3 - hepten - 2 - one,

2 - [*p* - (1' - cyclohexenyl)phenyl] - 2-penten - 4 - one,

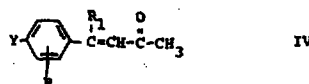
2 - (*p* - morpholinophenyl) - 2 - penten - 4-one, hydrochloride form, 70

2 - [*p* - (N - methylpiperazinyl)phenyl] - 2-penten - 4 - one, hydrochloride form,

2 - [*p* - (3 - pyrrolin - 1 yl)phenyl] - 2-penten - 4 - one, and all substantially in *trans* form. 75

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula IV,



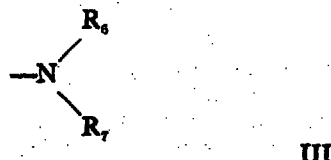
in which

R signifies hydrogen, fluorine, chlorine or bromine; 80

R₁ signifies alkyl of 1 to 3 carbon atoms, and Y signifies bromine, iodine, isobutyl, tert. butyl, cyclohexyl, cyclohexenyl, a radical of formula II, 85



in which R₂ is hydrogen, fluorine, chlorine or bromine, or alkoxy of 1 to 4 carbon atoms, or a radical of formula III, 90



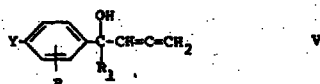
in which either R₆ and R₇ are the same or different and each signifies an alkyl radical of 1 to 3 carbon atoms,

or R₆ and R₇ together signify the radical —(CH₂)_n—, in which n is 4 or 5, the radical —CH₂—CH₂—O—CH₂—CH₂—, the radical —CH₂—CH=CH—CH₂—, or a radical 95

—CH₂—CH₂—N(R₈)—CH₂—CH₂—, 100

in which R₈ is hydrogen or alkyl of 1 to 3 carbon atoms,

characterised by treatment of a compound of formula V,



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desired compound of formula IV, and the corresponding 4-substituted phenyl-4-alkyl-2-chloro- (or bromo)-1,3-butadiene may be formed. Such products may be separated in conventional manner.

The resulting compounds of formula IV may be isolated and purified using conventional techniques.

The compounds of formula V are either known or may be produced in conventional manner from available materials.

The compounds of formula IV exist as geometric isomers and may be produced in the form of *cis* or *trans* isomers or in the form of isomeric mixtures which may, if desired, be separated in conventional manner into individual isomers. Compounds of formula IV substantially or predominantly in *trans* form result directly from the process described above. Other forms may be produced by conventional methods, for example by stereospecific synthesis from available materials, or by "scrambling" the compounds obtained predominantly or substantially in *trans* form as described above, e.g. by UV irradiation, and, if desired, separating the resulting isomeric mixtures using conventional techniques.

It is to be appreciated that while the invention is not intended to be limited to any particular form of the compounds of formula IV, the compounds are preferably predominantly or substantially in *trans* form.

The compounds of formula IV are useful as intermediates for the production of pharmaceutically active compounds, in particular those described in our co-pending application No. 36481/74 (Serial No. 1,483,352).

The following Examples illustrate the invention.

EXAMPLE 1.

2-(*p*-Biphenyl)-2-penten-4-one.

To a solution of 10 g 2-(*p*-biphenyl)-3,4-pentadien-2-ol in 200 ml of anhydrous methanol is added 3 ml of concentrated hydrochloric acid (12N). The resulting mixture is stirred at room temperature for 3 hours and then in an ice bath for 2 hours. Solids formed are filtered off and recrystallised from pentane to obtain 2-(*p*-biphenyl)-2-penten-4-one, m.p. 130° to 133° C., substantially in *trans* form. 2-(*p*-Biphenyl)-4-chloro-2,4-pentadiene, a by-product, remains in the mother liquor.

EXAMPLE 2.

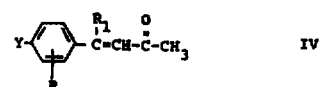
In manner analogous to Example 1, employing appropriate starting materials in approximately equivalent amounts, the following compounds may be obtained:—

2 - (*p* - tert.butylphenyl) - 2 - penten - 4 - one,
2 - (*p* - bromophenyl) - 2 - penten - 4 - one,

2 - (*p* - cyclohexyl - *m* - chlorophenyl) - 2-penten - 4 - one,
2 - (*p* - isobutylphenyl) - 2 - penten - 4 - one,
4 - (*p* - biphenyl) - 3 - hepten - 2 - one,
2 - [*p* - (1' - cyclohexenyl)phenyl] - 2-penten - 4 - one,
2 - (*p* - morpholinophenyl) - 2 - penten - 4-one, hydrochloride form,
2 - [*p* - (N - methylpiperazinyl)phenyl] - 2-penten - 4 - one, hydrochloride form,
2 - [*p* - (3 - pyrrolin - 1 yl)phenyl] - 2-penten - 4 - one, and all substantially in *trans* form.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula IV,



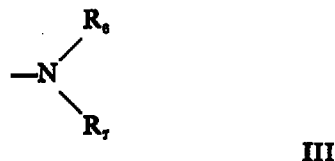
in which

R signifies hydrogen, fluorine, chlorine or bromine,

R₁ signifies alkyl of 1 to 3 carbon atoms, and Y signifies bromine, iodine, isobutyl, tert. butyl, cyclohexyl, cyclohexenyl, a radical of formula II,

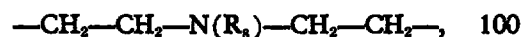


in which R₅ is hydrogen, fluorine, chlorine or bromine, or alkoxy of 1 to 4 carbon atoms, or a radical of formula III,



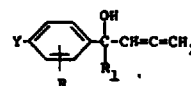
in which either R₆ and R₇ are the same or different and each signifies an alkyl radical of 1 to 3 carbon atoms,

or R₆ and R₇ together signify the radical —(CH₂)_n—, in which n is 4 or 5, the radical —CH₂—CH₂—O—CH₂—CH₂—, the radical —CH₂—CH=CH—CH₂—, or a radical



in which R₆ is hydrogen or alkyl of 1 to 3 carbon atoms,

characterised by treatment of a compound of formula V,





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in which R, R₁ and Y are as defined above, with a strong protonating agent, in the presence of water.

2. A process for the production of a compound of formula IV, stated in Claim 1, substantially as herein described with reference to any one of the Examples.

3. A compound of formula IV, stated in Claim 1, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula IV, stated in Claim 1.

5. 2 - (p - Biphenyl) - 2 - penten - 4 - one.

6. 2 - (p - Tert.butylphenyl) - 2 - penten - 4 - one.

7. 2 - (p - Bromophenyl) - 2 - penten - 4 - one.

8. 2 - (p - Cyclohexyl - m - chlorophenyl) - 2 - penten - 4 - one.

9. 2 - (p - Isobutylphenyl) - 2 - penten - 4 - one.

10. 4 - (p - Biphenyl) - 3 - hepten - 2 - one.

11. 2 - p - [(1' - Cyclohexenyl)phenyl] - 2 - penten - 4 - one.

12. 2 - (p - Morpholinophenyl) - 2 - penten - 4 - one.

13. 2 - [p - (N - Methylpiperazinyl)phenyl] - 2 - penten - 4 - one.

14. 2 - [p - (3 - Pyrrolin - 1 - yl)phenyl] - 2 - penten - 4 - one.

15. 4 - (p - Cyclohexylphenyl) - 3 - penten - 2 - one.

16. 4 - (p - Biphenyl) - 3 - hexen - 2 - one.

17. A compound according to any one of Claims 3 to 16, predominantly or substantially in *trans*-isomeric form.

18. A compound according to Claims 3 or 4, in which Y signifies a radical of formula III, stated in Claim 1.

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