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PREPARATION OF UNSATURATED KETONES

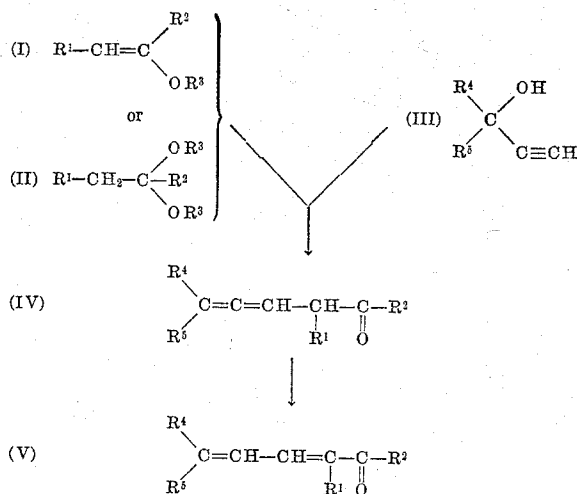
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This invention relates to novel chemical processes. More particularly, it relates to novel processes of making unsaturated ketones having a plurality of double bonds, of the type of pseudoionone and its hydrocarbyl-substituted derivatives, and of the respective cyclization products thereof, e.g. α - and β -ionone and their hydrocarbyl-substituted derivatives.

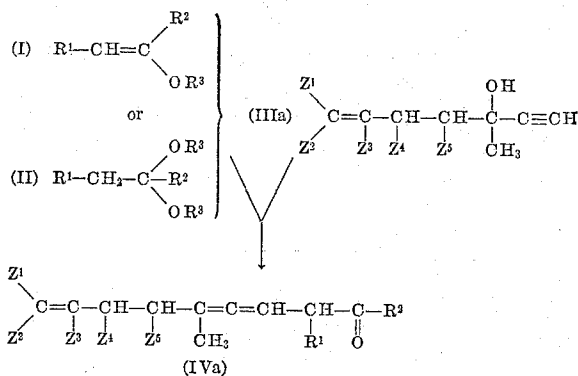
Broadly, the processes of the invention involve the condensation of a ketal—or alternatively, of the dealcoholation derivative thereof, i.e. an enol ether—with a 1,1-disubstituted propargyl alcohol, thereby forming an allenic ketone; rearrangement of the latter to form an α - β , γ - δ doubly unsaturated ketone; and in suitable cases, cyclization of the latter to form a cyclic ketone of the ionone type.

In the description which follows, various aspects of the invention are described with reference to the following flowsheets, wherein Flowsheet A illustrates graphically a broad embodiment of the invention, and Flowsheet B illustrates graphically an especially preferred embodiment thereof.

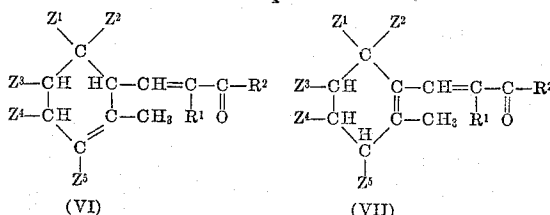
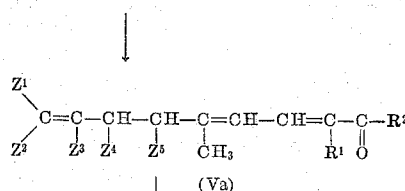
FLWSHEET A



FLWSHEET B



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In the foregoing flowsheets, the symbol R^1 represents hydrogen, a lower alkyl or alkenyl radical, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge; the symbol R^3 represents a lower alkyl radical; and each of the symbols R^4 and R^5 represents a cyclic or acyclic hydrocarbon radical, and R^4 and R^5 taken together represent a polymethylene radical; the symbol Z^1 represents an alkyl radical having from one to five carbon atoms or the phenyl radical, the symbol Z^2 represents the methyl radical, and the symbols Z^1 and Z^2 taken together represent a tetramethylene or pentamethylene radical; and each of the symbols Z^3 , Z^4 and Z^5 represents hydrogen or the methyl radical.

The ketals of general Formula II constitute a known class of compounds, and can be made from the corresponding ketones by ketalization according to methods known per se. The enol ethers of general Formula I likewise constitute a known class of compounds, and can be obtained by acidic pyrolysis of the corresponding ketals II, thereby effecting removal of one mol of alcohol R^3OH , also according to methods known per se. In specific embodiments of the ketals II and the enol ethers I, the symbols R^1 , R^2 and R^3 include such common lower alkyl radicals as methyl, ethyl, propyl, isobutyl and the like. Additionally, the symbols R^1 and R^2 together can represent a polymethylene bridge, e.g. a trimethylene or tetramethylene radical. As typical representatives of compounds included under the ketals of Formula II and the corresponding enol ethers of Formula I, the following are mentioned.

Ketals:

- 2,2-di(lower alkoxy)propane
- 2,2-di(lower alkoxy)butane
- 2,2-di(lower alkoxy)pentane
- 3,3-di(lower alkoxy)pentane
- 4-methyl-2,2-di(lower alkoxy)pentane
- 1,1-di(lower alkoxy)cyclohexane
- 2,2-di(lower alkoxy)-5-hexene

Enol ethers:

- 2-lower alkoxy-1-propene
- 2-lower alkoxy-2-butene
- 2-lower alkoxy-2-pentene
- 3-lower alkoxy-3-pentene
- 4-methyl-2-lower alkoxy-2-pentene
- 1-lower alkoxy-1-cyclohexene
- 2-lower alkoxy-2,5-hexadiene

Advantageously, methoxy-, ethoxy- or butoxy compounds are chosen as specific embodiments of the lower alkoxy ketals and enol ethers listed above.

The 1,1-disubstituted propargyl alcohols of general Formula III above constitute a known class of compounds, and can be made according to methods known per se, e.g. by condensation of acetylene with the appropriate ketone. The cyclic and acyclic hydrocarbon radicals represented by the symbols R^4 and R^5 in general Formula III above, include, illustratively, alkyl radicals having straight or branched chains, e.g. methyl, ethyl, isobutyl, 4-methyl-1-pentanyl, n-heptyl, 3,5-dimethyl-1-pentanyl, 4,8-dimethyl-1-nonanyl and the like; alkenyl radicals (having one or more double bonds), e.g. 3-penten-1-yl, 4-methyl-3-penten-1-yl, 4-methyl-3-hexen-1-yl, 3,4-dimethyl-3-penten-1-yl, 4,6-dimethyl-3-hepten-1-yl, 4,8-dimethyl-3,7-nonadien-1-yl and the like; alicyclic radicals such as cyclohexenyl, cyclohexylmethyl, cyclohexylidenemethyl, 2-(cyclohexen-1-yl)ethyl, 3-cyclohexylidenepropyl and the like; aryl hydrocarbon and araliphatic hydrocarbon radicals, e.g. phenyl, phenylmethyl, 4-methyl-5-phenyl-4-penten-1-yl and the like. Additionally, R^4 and R^5 taken together can represent a polymethylene radical, e.g. tetramethylene or pentamethylene. Typical representatives of 1,1-disubstituted propargyl alcohols suitable for use in the invention include the following:

3-methyl-1-butyn-3-ol
3-phenyl-1-butyn-3-ol
3-methyl-1-pentyn-3-ol
3-ethyl-1-pentyn-3-ol
3,7-dimethyl-1-octyn-3-ol
3,7-dimethyl-8-phenyl-1-octyn-3-ol
3,7,11-trimethyl-1-dodecyn-3-ol
3,7,11,15-tetramethyl-1-hexadecyn-3-ol
1-ethynyl-1-cyclopentanol
1-ethynyl-1-cyclohexanol
3-methyl-4-penten-1-yn-3-ol
3,7-dimethyl-6-octen-1-yn-3-ol
3,6,7-trimethyl-6-octen-1-yn-3-ol
3,7,11-trimethyl-6,10-dodecadien-1-yn-3-ol
3,7,11,15-tetramethyl-6,10,14-hexadecatrien-1-yn-3-ol
3,4,7-trimethyl-6-octen-1-yn-3-ol
3,7-dimethyl-6-nonen-1-yn-3-ol
3,7,9-trimethyl-6-decen-1-yn-3-ol
3-methyl-6-cyclohexylidene-1-hexyn-3-ol
3-methyl-7-phenyl-6-octen-1-yn-3-ol

In an initial stage of the processes of the invention, a ketal of general Formula II—or, preferably, an enol ether of general Formula I—is condensed with a tertiary propargyl alcohol of general Formula III in the presence of an acidic condensing agent. Suitable acidic condensing agents are, for example, strong mineral acids, e.g. sulfuric acid, phosphoric acid and the like; acid-reacting salts, e.g. potassium bisulfate and the like; strong organic acids, e.g. p-toluenesulfonic acid, oxalic acid and trichloroacetic acid; and "Lewis acids," e.g. zinc chloride or boron trifluoride ethyl etherate. The reaction can be effected either with or without a solvent. If a solvent is employed, suitable materials are, for example, hydrocarbons such as benzene, toluene, hexane, heptane, isooctane (2,2,4-trimethylpentane) and petroleum ether. According to a particular mode of execution, a portion of the solvent is distilled off during the reaction, thereby removing, together with the solvent, a portion of the alcohol formed by the condensation reaction. It has proved especially advantageous to add to the reaction mixture an alcohol-binding agent, e.g. an excess of enol ether. In another mode of execution, the enol ether employed as a reactant can be formed in the reaction medium prior to the condensation reaction with the tertiary propargyl alcohol. The product of the condensation reaction is the allenic ketone represented by general Formula IV. Depending upon the reaction conditions which obtain, the allenic ketone of Formula IV suffers rearrangement to the isomer of general Formula V, to a greater or lesser extent, even in the initial condensation stage of the process.

A further stage of the processes of the invention com-

prises effecting the rearrangement of the allenic ketone IV, or completing its rearrangement if it already has been partially isomerized, so as to produce the α - β , γ - δ doubly unsaturated ketone of general Formula V. Such rearrangement or isomerization can be effected by treatment with acidic or basic agents or by the influence of heat. For example, practically complete rearrangement can be effected by heating the allenic ketone for a short time at a temperature between about 100° C. and about 180° C., preferably at about 150° C.; or by heating the allenic ketone with acid, preferably acetic acid; or (the most preferred method) by treating the allenic ketone with a dilute solution of alkali metal hydroxide or alkaline earth metal hydroxide, preferably with dilute methanolic sodium hydroxide, e.g. at room temperature.

An advantageous mode of execution of a two-stage process for the preparation of compounds of general Formula V comprises refluxing the tertiary propargyl alcohol III with an excess of the enol ether II in the presence of p-toluenesulfonic acid, and treating the thus obtained condensation product after evaporation of the excess of enol ether II in solution in methanol, with sodium hydroxide at room temperature.

If desired, the reaction can also be carried out in such a way that even in the stage of condensing the disubstituted propargyl alcohol with the ketal II or enol ether I in the presence of the acidic catalyst, an extensive isomerization is also effected, so that the α - β , γ - δ doubly unsaturated ketone is formed practically in a one-step procedure. The conditions desirable for such a process are: a somewhat lengthy reaction period, and the employment of larger quantities of the acidic condensing agent than would otherwise be necessary for the preparation of the allenic ketone. For example, whereas 1% of p-toluenesulfonic acid (calculated upon the ketal or, respectively, enol ether, employed) suffices in most cases for the formation of the allenic ketone, the use of from about 1% to about 5% of p-toluenesulfonic acid has been found advantageous when effecting the simultaneous isomerization of the allenic ketone formed to the α - β , γ - δ doubly unsaturated ketone. A suitable procedure for such a one-step mode of execution comprises, for example, dissolving the two starting materials in toluene in the presence of p-toluenesulfonic acid as condensing agent and heating for a rather lengthy period at an elevated temperature, thereby forming a mixture of products IV and V in which V predominates. By addition of copper powder or copper salts, the yield of product V, under otherwise identical conditions, can be increased.

In view of the sensitivity to oxygen of the starting materials, the intermediate products and the end products, it is appropriate to carry out all the reactions in an inert atmosphere, for example under nitrogen. In addition, it has been found advantageous to add to the reaction mixture antioxidants, e.g. hydroquinone, butoxyanisole and the like.

It has been found advantageous to follow the reaction from time to time by analytical control methods. By so doing, the reaction can be interrupted as soon as the desired ketone is present in maximal yield. The extent of reaction, as well as the degree of formation of the desired Compound IV or V can be ascertained, for example, by means of ultraviolet and infrared spectra. The disappearance of the disubstituted propargyl alcohol employed as starting material can also be determined by testing with silver nitrate for the presence of the acetylenic radical.

Isolation and purification of the unsaturated ketones formed can be effected according to methods known per se. It has been found that in many cases a particularly efficient purification method is partition between petroleum ether and methanol/water mixtures.

The products of general Formula V belong to a known class of materials having manifold industrial applications. For example, they can be used as odorants, or as inter-

mediates for the preparation of perfume materials, of carotenoid compounds, and of fat-soluble vitamins.

In a further stage of one preferred embodiment of the invention illustrated in Flowsheet B, either the allenic ketone obtained as product IVa or the α - β , γ - δ doubly unsaturated ketone obtained as product Va can be cyclized by treatment with acidic cyclizing agents. Depending upon the nature of the specific cyclizing agents employed, there are thus produced cyclic ketones having α -ionone structure (general Formula VI) or β -ionone structure (general Formula VII). Thus, cyclic ketones of general Formula VI can be obtained by treating the ketones of general Formula V with syrupy phosphoric acid at room temperature or at moderately elevated temperatures, or by treating said ketones V with boron trifluoride at low temperatures. On the other hand, by employing concentrated sulfuric acid as the cyclizing agent, there are obtained cyclization products possessing predominantly the β -ionone structure of general Formula VII. The products of Formulas VI and VII constitute known classes of compounds useful as odorants and as intermediates for pharmaceuticals.

The invention is further disclosed in the following examples, which are illustrative but not limitative thereof. Temperatures are stated in degrees centigrade.

Example 1

4.2 g. of 3-methyl-1-butyn-3-ol and 6.0 g. of 3-ethoxy-3-pentene (B.P. 108–111°; $n_D^{25}=1.4107$; prepared from the diethyl ketal of 3-pentanone by treatment with potassium bisulfate) are mixed with 50 cc. of isooctane (2,2,4-trimethylpentane) and 100 mg. of p-toluenesulfonic acid. Then the reaction mixture is refluxed under nitrogen for 20 hours. At the end of this time the reaction mixture is cooled, washed with sodium bicarbonate solution and water, and then evaporated under a water pump vacuum at 35°. There is thus obtained 5.2 g. of 4,7-dimethyl-4,6-octadien-3-one as a yellow oil having a pleasant fruity odor; $n_D^{21}=1.5159$; U.V. absorption maximum in petroleum ether at 279m μ , $E_1^1=1300$. The semicarbazone melts at 175° and shows a maximum in the U.V. absorption spectrum in ethanol solution at 297m μ , $E_1^1=1830$.

Example 2

(a) To a solution of 200 g. of 3,7-dimethyl-6-octen-1-yn-3-ol in 160 g. of isopropenyl ether (2-ethoxy-1-propene; prepared from acetone diethyl ketal by refluxing with equimolar proportions of acetic anhydride and pyridine) in one liter of high boiling petroleum ether (boiling range 80–110°) is added 100 mg. of p-toluenesulfonic acid. The reaction mixture is refluxed for 15 hours under nitrogen. Then the reaction mixture is cooled, washed with sodium bicarbonate solution, and the solvent is evaporated in a water pump vacuum at 50°, yielding 210 g. of a yellow oil having a refractive index $n_D^{20}=1.4742$ and having only weak absorption

($E_1^1<50$)

in the ultraviolet region around 290 m μ . By distillation in a high vacuum there is obtained, from this crude product, pure 6,10-dimethyl-4,5,9-undecatrien-2-one (B.P. 67–69°/0.04 mm.; $n_D^{20}=1.4875$). By treatment with 4-phenylsemicarbazide in methanolic solution there is obtained the phenylsemicarbazone, which after recrystallization from methanol, melts at 84–86°.

(b) 20 g. of crude 6,10-dimethyl-4,5,9-undecatrien-2-one, 200 cc. of methanol and 20 cc. of 3 N NaOH solution are allowed to stand at room temperature for one hour. Then the pH of the solution is brought to 7 by addition of acetic acid, the methanol is evaporated in a water pump vacuum at 40°, the oil which has separated is taken up in petroleum ether, and the petroleum ether

is distilled off. There is thus obtained 20 g. of crude pseudoionone, which according to its refractive index ($n_D^{20}=1.5138$) and U.V. absorption (in ethanol at 291–292 m μ , $E_1^1=940$) has a purity of about 72%. By distillation in a high vacuum pure pseudoionone is obtained, having B.P. 76–78°/0.02 mm., $n_D^{20}=1.5311$, U.V. absorption at 291 m μ , $E_1^1=1300$. This product yields a semicarbazone melting at 124–126° (U.V. absorption in ethanol at 298 m μ , $E_1^1=2280$).

(c) 50 g. of purified 6,10-dimethyl-4,5,9-undecatrien-2-one is dissolved in 25 cc. of benzene and mixed while cooling at 15–20° with 400 g. of 84% phosphoric acid. Then the reaction mixture is stirred for 30 minutes longer at 20° and then for 15 minutes at 35°. The mixture is thereupon poured into ice water and the crude α -ionone which has been formed is extracted with petroleum ether. The petroleum ether solution is washed once with water and once with sodium bicarbonate solution and then evaporated in a water pump vacuum at 40°. There is thus obtained 48.1 g. of crude α -ionone ($n_D^{20}=1.5103$) which by distillation in a high vacuum is freed of resinous impurities (B.P. 70–75°/0.06 mm.; $n_D^{20}=1.4969$; U.V. absorption in ethanol at 226 m μ). According to the I.R. spectrum, the preparation comprises about 90% of α -ionone. By reaction with 4-phenylsemicarbazide there is obtained a phenylsemicarbazone having M.P. 184–186°.

(d) By cyclization of the pure pseudoionone from Example 2(b) under similar conditions to those in Example 2(c) there is obtained α -ionone having a refractive index $n_D^{20}=1.4998$ and a U.V. maximum at 225–226 m μ . The phenylsemicarbazone melts at 183–185°.

(e) 10 g. of the crude pseudoionone from Example 2(b) is dissolved in 13 cc. of petroleum ether and stirred at 0° for ten minutes with a mixture of 14 cc. of concentrated sulfuric acid and 30 cc. of petroleum ether. Then the mixture is poured onto ice and the petroleum ether layer is separated. The petroleum ether solution is washed with water and sodium bicarbonate solution and then the petroleum ether is driven off, leaving 9.6 g. of crude β -ionone as a dark oil. On distillation in high vacuum, a yellow oil distills over at 0.1 mm. between 88 and 90° ($n_D^{20}=1.5183$), which from its U.V. absorption in ethanol (main maximum 295 m μ) contains about 86% β -ionone. The semicarbazone obtained therefrom melts at 148–150° and absorbs in the U.V. spectrum at 280 m μ , $E_1^1=890$.

Example 3

(a) 400 g. of 3,6,7-trimethyl-6-octen-1-yn-3-ol, 320 g. of isopropenyl ethyl ether and 2 g. of trichloroacetic acid are refluxed under nitrogen for 15 hours while stirring in a flask contained in an oil bath heated to 90°. The crude product obtained is taken up in petroleum ether and washed with sodium bicarbonate solution. After evaporation of the petroleum ether there is obtained 451 g. of a yellow oil having a refractive index $n_D^{20}=1.4824$, which has only very weak absorption in the ultraviolet region at about 290 m μ . By fractional distillation in high vacuum there is obtained therefrom pure 6,9,10-trimethyl-4,5,9-undecatrien-2-one (B.P. 84–85°/0.06 mm.; $n_D^{20}=1.4907$; M.P. of 4-phenylsemicarbazone: 62–64°). This preparation does not absorb in the ultraviolet and shows a typical allene band in the infrared at 5.05 μ as well as a C=O band at 5.80 μ . The same compound can be obtained by using, instead of isopropenyl ethyl ether, a stoichiometrically equivalent quantity of acetone diethyl ketal, under conditions otherwise identical to those set forth above.

(b) The above mentioned crude product, or alternatively pure 6,9,10-trimethyl-4,5,9-undecatrien-2-one, can be isomerized to 6,9,10-trimethyl-3,5,9-undecatrien-2-one (pseudoirone) by proceeding according to the indications in Example 2(b); B.P. of purified pseudoirone product, 80–83°/0.03 mm.; $n_D^{20}=1.5316$; U.V. absorption in

ethanol at 292 $m\mu$, E_1^{1160} . The product forms a semicarbazone having M.P. 158–161° and a U.V. absorption in ethanol at 297 $m\mu$, E_1^{11920} .

(c) By cyclization of pure 6,9,10-trimethyl-4,5,9-undecatrien-2-one, the product of Example 3(a), with phosphoric acid according to the indications in Example 2(c), there is obtained a crude product, which has a refractive index of $n_D^{20}=1.4990$, which absorbs in the ultraviolet at 221 $m\mu$, and which according to its infrared spectrum contains α -irone as its main fraction. The preparation forms a phenylsemicarbazone melting at 61–63°.

(d) By isomerizing 6,9,10-trimethyl-4,5,9-undecatrien-2-one according to the indications in Example 2(b) with methanolic sodium hydroxide solution, there is obtained pseudoirone, which upon purification by distillation in high vacuum at 0.07 mm. boils between 88 and 92°, has a refractive index of $n_D^{20}=1.5269$ and absorbs in the ultraviolet (ethanol) at 293 $m\mu$, E_1^{11000} . The semicarbazone obtained therefrom melts at 158–161° and absorbs in the ultraviolet in ethanol at 297 $m\mu$, E_1^{11920} .

(e) By treatment of pseudoirone with sulfuric acid according to the indications in Example 2(e), there is obtained crude β -irone, which distills in a high vacuum (0.02 mm.) between 73 and 78° and has a refractive index of $n_D^{20}=1.5138$; U.V. maxima at 220 and 293 $m\mu$ in ethanol. According to the I.R. spectrum the product obtained contains 90–95% of β -irone. The semicarbazone obtained therefrom melts at 171–173° and absorbs in the ultraviolet in ethanol at 276 $m\mu$, E_1^{1850} .

Example 4

(a) 15.2 g. of 3,7-dimethyl-6-octen-1-yn-3-ol, 15.0 g. of 2-ethoxy-2-butene and 150 mg. of potassium bisulfate in 100 cc. of toluene are refluxed for two hours under nitrogen. The reaction solution is washed with sodium bicarbonate solution and water, dried over sodium sulfate and evaporated in a water pump vacuum at 40°. The residue (21.0 g.; $n_D^{23}=1.4748$) shows only a weak absorption in the ultraviolet at 275 $m\mu$ (E_1^{130}) and as shown by its infrared spectrum contains, in addition to about 10% of the starting material, 70–80% of 3,6,10-trimethyl-4,5,9-undecatrien-2-one, which is purified by high vacuum distillation: B.P. 95–97°/0.07 mm.; $n_D^{28}=1.4831$. The same product is obtained by the use of 200 mg. of zinc chloride or 0.1 cc. of boron trifluoride ethyl etherate as condensing agent, in lieu of potassium bisulfate under otherwise identical conditions; or by refluxing the starting materials in the presence of 0.35 g. of oxalic acid, using high boiling petroleum ether (boiling range 80–110°) as solvent.

(b) 10.0 g. of the purified 3,6,10-trimethyl-4,5,9-undecatrien-2-one is dissolved in 100 cc. of methanol and 10 cc. of 3 N sodium hydroxide solution is added. Then the mixture is allowed to stand for one hour at 20°. By extraction with petroleum ether, washing with water, drying over sodium sulfate and evaporation of the solvent in vacuo, there is obtained 9.5 g. of crude product having $n_D^{22}=1.5193$, U.V. absorption maximum in petroleum ether solution at 282 $m\mu$, E_1^{11070} . Pure 3,6,10-trimethyl-3,5,9-undecatrien-2-one (isomethylpseudoionone) obtained therefrom by distillation, has the following characteristics: B.P. 105°/0.005 mm.; $n_D^{26}=1.5277$; U.V. absorption maximum in petroleum ether solution at 283 $m\mu$, E_1^{1225} .

(c) 10 g. of 3,6,10-trimethyl-4,5,9-undecatrien-2-one obtained according to part (a) of this example is dissolved in 50 cc. of glacial acetic acid and heated for five hours at 70°. By extraction with petroleum ether there is obtained 9.6 g. of crude isomethylpseudoionone, which is purified as set forth in preceding part (b) of this example.

(d) 5 g. of 3,6,10-trimethyl-4,5,9-undecatrien-2-one obtained according to part (a) of this example is heated under nitrogen for five minutes at 150°, whereupon the temperature in the reaction vessel climbs to about 180°

in consequence of the exothermic reaction. According to its ultraviolet spectrum, the reaction product contains over 80% of isomethylpseudoionone.

(e) 7 g. of 3,6,10-trimethyl-4,5,9-undecatrien-2-one is dissolved in 4 cc. of absolute benzene and reacted with 54 g. of 84% phosphoric acid within a 15 minute period, while stirring and maintaining the reaction temperature at 20° by cooling with water. Then the mixture is stirred for 30 minutes at 20–25° and finally for 15 minutes at 30–35°. At the end of this time the reaction mixture is poured onto 100 g. of ice and is extracted with petroleum ether. The extract is washed twice with sodium bicarbonate solution and three times with water, dried over sodium sulfate, and the solvent is then removed in a water pump vacuum at 45°. There is thus obtained 6.3 g. of crude isomethyl- α -ionone ($n_D^{24}=1.507$) which is purified by high vacuum distillation: B.P. 86–87°/0.5 mm.; $n_D^{24}=1.5004$; U.V. absorption maximum in petroleum ether at 229 $m\mu$. The semicarbazone melts at 199–200°.

(f) The cyclization of isomethylpseudoionone obtained according to part (b) of this example, using syrupy phosphoric acid as cyclizing agent and benzene as solvent, is effected according to the procedure of part (e) of this example, whereupon there is obtained a crude product ($n_D^{24}=1.5007$) which according to its infrared spectrum contains about 80% of isomethyl- α -ionone.

Example 5

A mixture of 6.2 g. of 1-ethynyl-1-cyclohexanol, 6 g. of 3-ethoxy-3-pentene, 62 cc. of heptane and 100 mg. of p-toluene-sulfonic acid is refluxed under nitrogen for 20 hours and worked up according to the indications in Example 1. The residue (8.2 g.; $n_D^{21}=1.5022$), upon treatment with methanolic sodium hydroxide solution according to Example 2(b), yields 8.0 g. of 4-methyl-6-cyclohexylidene-4-hexen-3-one; $n_D^{21}=1.5112$, U.V. absorption maximum in petroleum ether solution at 283 $m\mu$, E_1^{1600} . The semicarbazone obtained therefrom melts at 184–185° and has a maximum in the ultraviolet absorption spectrum in ethanol solution at 298 $m\mu$, E_1^{1780} (shoulders at 290 and 310 $m\mu$).

Example 6

A mixture of 5 g. of 3,6,7-trimethyl-6-octen-1-yn-3-ol, 5 g. of 1-butoxy-1-cyclohexene (prepared according to J. Org. Chem. 20, 1695 [1955]), 50 cc. of benzene, 50 mg. of concentrated sulfuric acid and 10 mg. of hydroquinone is refluxed under nitrogen for 48 hours. Working up according to the indications in Example 1 yields 8.1 g. of crude 1-(2-ketocyclohexylidene)-3,6,7-trimethyl-2,6-octadiene (methylcitrilidene-2-cyclohexanone), having U.V. absorption maximum in petroleum ether solution at 295 $m\mu$. This product is purified by high vacuum distillation; B.P. 120–125°/0.005 mm., $n_D^{25}=1.5463$; U.V. absorption maximum in petroleum ether solution at 293 $m\mu$.

Example 7

A mixture consisting of 15.2 g. of 3,7-dimethyl-6-octen-1-yn-3-ol, 17 g. of 2,2-diethoxybutane, 200 cc. of petroleum ether (boiling range 80–105°) and 20 mg. of potassium bisulfate is refluxed under nitrogen for 2½ days. Working up is effected in accordance with the indications in Example 4(a). The reaction product thus obtained is dissolved in 100 cc. of methanol, mixed with 10 cc. of 3 N sodium hydroxide solution and the mixture is allowed to stand for one hour at 20°. Upon working up the reaction mixture as indicated in Example 4(b), pure isomethylpseudoionone is obtained as the end product.

Example 8

10 g. of 2,2-diethoxypentane (prepared from methyl n-propyl ketone) is dissolved in 100 cc. of benzene and 10 mg. of potassium bisulfate is added. The reaction mixture is refluxed in a nitrogen atmosphere for 20 hours.

Then 5 g. of 3,6,7-trimethyl-6-octen-1-yn-3-ol dissolved in 50 cc. of benzene is added to the reaction mixture and the whole is heated for 20 hours at the boiling point. Working up according to the indications in Example 7 yields isomethylpseudoirone (3-ethyl-6,9,10-trimethyl-3,5,9-undecatrien-2-one). The substance in petroleum ether solution has a U.V. absorption maximum at 284–286 m μ . B.P. 113–115°/0.01 mm.; n_D^{24} =1.5261.

Example 9

(a) 10 g. of 3,7-dimethyl-6-octen-1-yn-3-ol and 10 g. of 2-ethoxy-2-butene are dissolved in 100 cc. of toluene and 200 mg. of p-toluenesulfonic acid is added. Then the reaction mixture is refluxed under nitrogen for 15 hours. Working up according to Example 1 yields 12.7 g. of reaction product, having n_D^{23} =1.5047, which according to its ultraviolet spectrum contains 37% of isomethylpseudoionone.

(b) By processing as described in paragraph (a) above, but with addition of 100 mg. of copper powder, there is obtained 13.0 g. of reaction product having n_D^{23} =1.5159, which according to its U.V. spectrum contains 55% of isomethylpseudoionone.

(c) By proceeding as in paragraph (b) above, but with addition of 100 mg. of cupric acetate instead of copper powder, there is obtained 12.8 g. of crude product having n_D^{23} =1.5129, having a content of 53% of isomethylpseudoionone.

Example 10

(a) 200 g. of 3,7-dimethyl-6-octen-1-yn-3-ol, 320 g. of 2-ethoxy-2-butene and 1 g. of potassium bisulfate are refluxed under nitrogen for two hours in a flask contained in an oil bath heated to 100°. Then the reaction mixture is cooled and shaken with sodium bicarbonate solution. The supernatant mixture is evaporated at 50° in a water pump vacuum. The resulting distillate, according to gas chromatographic investigation, comprises principally 2,2-diethoxybutane, which can be worked up again to 2-ethoxy-2-butene. The oil remaining in the flask, 290 g., has a refractive index n_D^{20} of 1.4748 and, as indicated by titration analysis with silver nitrate, retains at most 10% of the acetylenic compound. By distillation of the residue in high vacuum there is obtained pure 3,6,10-trimethyl-4,5,9-undecatrien-2-one in a yield of about 90%, calculated on the 3,7-dimethyl-6-octen-1-yn-3-ol.

(b) By cyclization of the 3,6,10-trimethyl-4,5,9-undecatrien-2-one obtained in part (a) of this example with phosphoric acid, according to the indications in Example 4(e), there is obtained isomethyl- α -ionone.

Example 11

(a) 10 g. of 3,6,7-trimethyl-6-octen-1-yn-3-ol and 10 g. of 3-ethoxy-3-pentene (B.P. 118–111°; n_D^{25} =1.4107; prepared from diethyl ketal of 3-pentanone by treatment with potassium bisulfate) is dissolved in 100 cc. of isooctane and 100 mg. of concentrated sulfuric acid is added. Then the reaction mixture is refluxed under nitrogen for 30 hours. The reaction mixture is cooled, washed with sodium bicarbonate solution and water, and evaporated in a water pump vacuum at 40°, yielding a product having n_D^{22} =1.5066, which according to its ultraviolet and infrared spectra comprises principally a mixture of 4,7,10,11-tetramethyl-5,6,10-dodecatrien-3-one and 4,7,10,11-tetramethyl-4,6,10-dodecatrien-3-one.

(b) 5 g. of the mixture obtained in part (a) of this example is dissolved in 5 cc. of petroleum ether and is slowly poured into a mixture of 8 cc. of glacial acetic acid and 16 g. of concentrated sulfuric acid while stirring at minus 5°. The reaction mixture is stirred for 15 minutes at minus 5°, 20 minutes at 10° and then is poured onto ice. By extraction with petroleum ether there is obtained 4.5 g. of crude iso-n-dimethyl- β -irone; n_D^{24} =1.5119; B.P. 78–80°/0.02 mm.; U.V. absorption maximum in petroleum ether solution at 283 m μ .

Example 12

(a) 16.6 g. of 3,6,7-trimethyl-6-octen-1-yn-3-ol and 15.0 g. of 2-ethoxy-2-butene are dissolved in 200 cc. of toluene and 200 mg. of zinc chloride is added. Then the reaction mixture is refluxed for three hours under nitrogen and worked up as described in Example 2(a), yielding 21.2 g. of reaction product, n_D^{22} =1.4872, which from its infrared spectrum contains about 60% of 3,6,9,10-tetramethyl-4,5,9-undecatrien-2-one and about 10% of 3,6,9,10-tetramethyl-3,5,9-undecatrien-2-one. This mixture is heated under nitrogen at 160° for ten minutes. By high vacuum distillation of the reaction mixture there is obtained pure isomethylpseudoirone: B.P. 105–108°/0.03 mm.; n_D^{22} =1.5317; U.V. absorption maximum in petroleum ether at 283 m μ , E_1^1 =1220.

(b) 10.7 g. of isomethylpseudoirone is dissolved in 25 cc. of absolute benzene and treated with boron trifluoride gas at 5°, while stirring and cooling, until about 3 g. of gas has been taken up. Then the reaction mixture is stirred for 15 minutes at 15° and poured onto ice. The mixture is extracted with petroleum ether, the organic phase is washed with sodium hydroxide solution and water and dried over potassium carbonate. Then the solvent is removed in vacuo. By high vacuum distillation of the residue there is obtained 8.1 g. of isomethyl- α -irone; B.P. 80–82°/0.1 mm.; n_D^{22} =1.5050; U.V. absorption maximum in petroleum ether at 229.5 m μ .

Example 13

10 g. of 3,6,7-trimethyl-6-octen-1-yn-3-ol and 10 g. of 2-ethoxy-2-butene are dissolved in 100 cc. of toluene, 200 mg. of p-toluenesulfonic acid and 200 mg. of copper powder are added, and the reaction mixture is refluxed under nitrogen for 24 hours. Upon working up the reaction mixture there is obtained 12.7 g. of a product having n_D^{23} =1.5159, which is cyclized to isomethyl- β -irone in accordance with the indications in Example 11; B.P. 77–79°/0.3 mm.; n_D^{25} =1.5109; U.V. absorption maximum in petroleum ether solution at 284 m μ .

Example 14

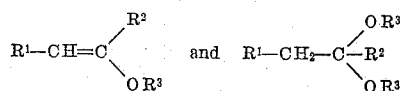
284 g. of 3-ethoxy-3-pentene, 0.36 g. of potassium bisulfate and 72 g. of 3,7-dimethyl-6-octen-1-yn-3-ol are stirred under nitrogen for 21 hours at 120°. Upon working up the reaction mixture there is obtained 100 g. of crude 4,7,11-trimethyl-5,6,10-dodecatrien-3-one; n_D^{20} =1.4755. The product forms a 4-phenyl-semicarbazone having M.P. 72° and a U.V. absorption in ethanol at 240 m μ , E_1^1 =840.

Example 15

40 g. of 3,7-dimethyl-6-octen-1-yn-3-ol and 150 g. of 2-ethoxy-2,5-hexadiene (prepared from 5-hexen-2-one by ketalizing with ortho formic acid ester and boron trifluoride etherate and subsequent treatment with acetic anhydride and pyridine) are refluxed in the presence of 200 mg. of potassium sulfate under nitrogen for 22 hours at 120°. Upon working up the reaction mixture, the 6,10-dimethyl-3-allyl-4,5,9-undecatrien-2-one thus obtained is isomerized as described in Example 2(b). There is thus obtained 41 g. of crude 6,10-dimethyl-3-allyl-3,5,9-undecatrien-2-one as a brown oil, which is purified by fractional distillation; B.P. 94°/0.05 mm.; n_D^{20} =1.5345; U.V. absorption in ethanol at 294–295 m μ , E_1^1 =1110.

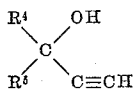
We claim:

1. A process which comprises condensing a member selected from the group consisting of compounds of the general formulas

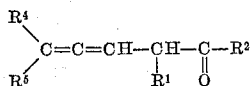


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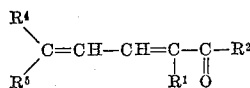
with a 1,1-disubstituted propargyl alcohol of the general formula



in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing an allenic ketone of the general formula

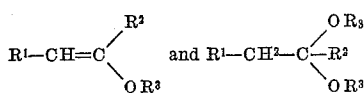


and isomerizing the latter by subjecting it to an isomerizing influence selected from the group consisting of basic reagents and acidic reagents, thereby producing an α - β , γ - δ doubly unsaturated ketone of the general formula

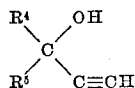


wherein in the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting of hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; the symbol R^3 represents a lower alkyl radical; and each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

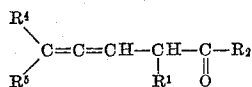
2. A process which comprises condensing a member selected from the group consisting of compounds of the general formulas



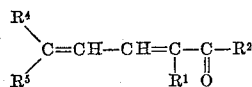
with a 1,1-disubstituted propargyl alcohol of the general formula



in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing an allenic ketone of the general formula



and isomerizing said allenic ketone by heating same, thereby producing an α - β , γ - δ doubly unsaturated ketone of the general formula

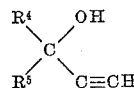


wherein the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting of hydrogen, lower alkenyl and lower alkyl radicals; the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; the symbol R^3 represents a lower alkyl radical; and each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical

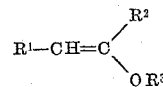
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selected from the group consisting of tetramethylene and pentamethylene radicals.

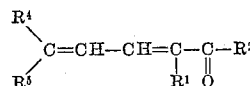
3. A process which comprises refluxing a tertiary propargyl alcohol of the general formula



with an excess of an enol ether of the general formula



in the presence of p-toluenesulfonic acid and treating the condensation product after evaporation of the excess of enol ether with sodium hydroxide, thereby producing an α - β , γ - δ doubly unsaturated ketone of the general formula



wherein the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting of hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; the symbol R^3 represents a lower alkyl radical; and each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

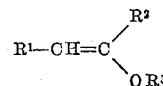
4. A process which comprises condensing isopropenyl lower alkyl ether with 3,7-dimethyl-6-octen-1-yn-3-ol in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing 6,10-dimethyl-4,5,9-undecatrien-2-one; and isomerizing the latter by subjecting it to an isomerizing influence selected from the group consisting of basic reagents and acidic reagents thereby producing 6,10-dimethyl-3,5,9-undecatrien-2-one.

5. A process which comprises condensing isopropenyl lower alkyl ether with 3,6,7-trimethyl-6-octen-1-yn-3-ol in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing 6,9,10-trimethyl-4,5,9-undecatrien-2-one; and isomerizing the latter by subjecting it to an isomerizing influence selected from the group consisting of basic reagents and acidic reagents, thereby producing 6,9,10-trimethyl-3,5,9-undecatrien-2-one.

6. A process which comprises condensing isopropenyl lower alkyl ether with 3,7-dimethyl-6-octen-1-yn-3-ol in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing 6,10-dimethyl-4,5,9-undecatrien-2-one; and isomerizing the latter by heating same thereby producing 6,10-dimethyl-3,5,9-undecatrien-2-one.

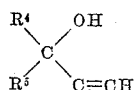
7. A process which comprises condensing isopropenyl lower alkyl ether with 3,6,7-trimethyl-6-octen-1-yn-3-ol in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing 6,9,10-trimethyl-4,5,9-undecatrien-2-one; and isomerizing the latter by heating same, thereby producing 6,9,10-trimethyl-3,5,9-undecatrien-2-one.

8. A process which comprises condensing an enol ether of the general formula

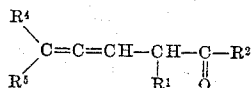


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with a 1,1-disubstituted propargyl alcohol of the general formula

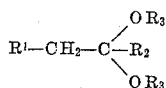


in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing an allenic ketone of the general formula

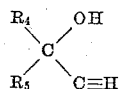


wherein the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting of hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; the symbol R^3 represents a lower alkyl radical; and each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

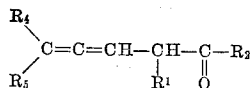
9. A process which comprises condensing a ketal of the general formula



with a 1,1-disubstituted propargyl alcohol of the general formula

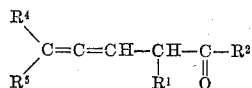


in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid reacting salts, strong organic acids and Lewis acids thereby producing an allenic ketone of the general formula

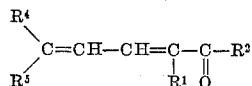


wherein in the foregoing general formulas, the symbol R_1 represents a member selected from the group consisting hydrogen, lower alkenyl and lower alkyl radicals, the symbol R_2 represents a lower alkyl radical, and the symbols R_1 and R_2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; the symbol R_3 represents a lower alkyl radical; and each of the symbols R_4 and R_5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R_4 and R_5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

10. A process which comprises heating an allenic ketone of the general formula



thereby producing an α - β , γ - δ doubly unsaturated ketone of the general formula

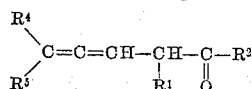


wherein in the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting

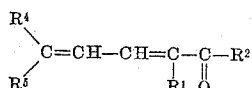
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of hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

11. A process which comprises heating in the presence of acid an allenic ketone of the general formula

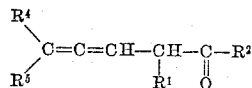


thereby producing an α - β , γ - δ doubly unsaturated ketone of the general formula

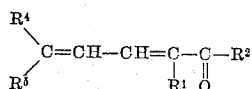


wherein in the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting of hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

12. A process which comprises treating an allenic ketone of the general formula



with a dilute solution of an alkaline hydroxide, thereby producing an α - β , γ - δ doubly unsaturated ketone of the general formula



wherein in the foregoing general formulas, the symbol R^1 represents a member selected from the group consisting hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken together represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

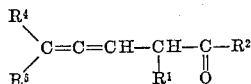
13. A process of making ionone material selected from the group consisting of α -ionone and β -ionone and mixtures thereof which comprises condensing isopropenyl lower alkyl ether with 3,7-dimethyl-6-octen-1-yn-3-ol in the presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing 6,10-dimethyl-4,5,9-undecatrien-2-one, and cyclizing the latter by treating it with an acidic cyclizing agent selected from the group consisting of phosphoric acid, boron trifluoride and sulfuric acid.

14. A process of making iron material selected from the group consisting of α -irone and β -irone and mixtures thereof which comprises condensing isopropenyl lower alkyl ether with 3,6,7-trimethyl-6-octen-1-yn-3-ol in the

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presence of an acidic condensing agent selected from the group consisting of strong mineral acids, acid-reacting salts, strong organic acids and Lewis acids, thereby producing 6,9,10-trimethyl - 4,5,9 - undecatrien-2-one, and cyclizing the latter by treating it with an acidic cyclizing agent selected from the group consisting of phosphoric acid, boron trifluoride and sulfuric acid.

15. A process which comprises treating an allenic ketone of the general formula



with an acidic cyclizing agent selected from the group consisting of phosphoric acid, boron trifluoride, and sulfuric acid, wherein the symbol R^1 represents a member selected from the group consisting of hydrogen, lower alkenyl and lower alkyl radicals, the symbol R^2 represents a lower alkyl radical, and the symbols R^1 and R^2 taken together represent a polymethylene bridge selected from the group consisting of trimethylene and tetramethylene radicals; each of the symbols R^4 and R^5 represents a member selected from the group consisting of monocyclic and acyclic hydrocarbon radicals, and R^4 and R^5 taken to-

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gether represent a polymethylene radical selected from the group consisting of tetramethylene and pentamethylene radicals.

16. A process of making ionone material selected from the group consisting of α -ionone and β -ionone which comprises treating 6,10-dimethyl-4,5,9-undecatrien-2-one with an acidic cyclizing agent selected from the group consisting of phosphoric acid, boron trifluoride, and sulfuric acid.

17. A process of making α -iron which comprises treating 6,9,10-trimethyl-4,5,9-undecatrien-2-one with an acidic cyclizing agent.

18. A process of making isomethyl- α -ionone which comprises treating 3,6,10-trimethyl-4,5,9-undecatrien-2-one with an acidic cyclizing agent.

19. A process of making isomethyl- α -irone which comprises treating 3,6,9,10-tetramethyl-4,5,9-undecatrien-2-one with an acidic cyclizing agent.

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2,902,510	Webb -----	Sept. 1, 1959

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,029,287

April 10, 1962

Roman Marbet et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 9, line 18, for "processing" read -- proceeding --;
line 54, for "118-111°" read -- 108-111° --; column 11, line
10, the right upper antenna "OR₃" read -- OR³ --; line 55, the
end of the formula reading "R₂" read -- R² --; same column 11,
line 65 and column 12, line 22, for "wherein the", each
occurrence, read -- wherein in the --; column 14, line 61,
or "a" read -- of --; line 63, strike out "alkyl", second
occurrence; line 72, for "iron" read -- irone --.

Signed and sealed this 20th day of November 1962.

SEAL)

test:

WINST W. SWIDER

testing Officer

DAVID L. LADD

Commissioner of Patents