CCA-267

547.594.4.07:547.38

Synthesis of an Acyclic Analogue of Ionone*

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Received July 31, 1962

5-*iso*-Propyl-6-methyl-3,5-heptadien-2-one (V) is synthesized by two independent synthetic routes. It shows an odor similar to β-ionone and possesses analogous physical properties.

Many analogues of β- and α-ionone (I and II) are described in the literature. From the relationship between the structure and odor of these compounds rules can be derived which make possible to predict to some extent the odor of an unknown compound.[1] Jitkow and Bogert summarized in 1941 facts about this matter and wrote[2]:

»Based upon the evidence so far accumulated in the literature and upon our own experience it appears that in the ionone group, the violet odor is dependent upon the presence of a cyclohexene nucleus, carrying at least three methyl groups on the ring, two of which must be adjacent to the side chain, either as one *gem*-dimethyl group, or as a single methyl on each side of the chain. The position of the double bond in the nucleus affects the quality but not the type of odor. The introduction of a second double bond into the nucleus, however, destroys the violet odor....« (The presence of a $—CH=CH—CO—CH_3$ side chain is also necessary for the retention of an ionone-like odor).

Most of these rules were confirmed on numerous examples[1-7]. The importance of cyclohexene nucleus itself, however, has not yet been clearly established although compounds of the pseudoionone (III) type, where the cyclohexene ring is open, do not posses an ionone-like odor. However, it has to be pointed out that an important difference exists between the ionones and pseudoionone. The ionones contain a 3,5- (for β-ionone, I) or 3,6- (for α-ionone, II) dienone system subsituted on C-atom 5 and 6 with alkyl groups (forming part of the cyclohexene ring). Since pseudoionone (III) does not have an alkyl group on C-atom 5 it is not a true acyclic analogue of β-ionone in this meaning and it can not be expected to possess a similar odor. This, however, does not mean, that *a priori* all acyclic dienones would not have such an odor. Acyclic dienones substituted on C-atom 5 as *e.g.* 5-alkyl-6-methyl-3,5-heptadien-2-one (IV) with branched alkyl chain, would represent true acyclic analogues of β-ionone.

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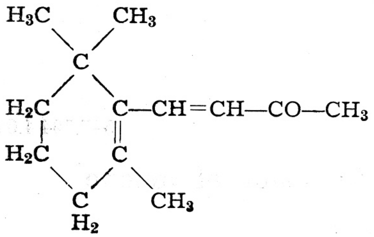
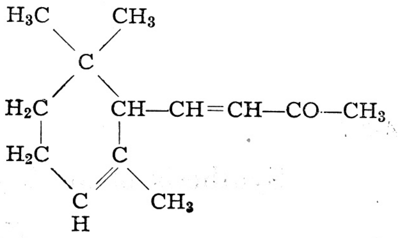
* Part of the Thesis presented to the University of Zagreb (Faculty of Technology) in partial fulfilment of the requirements for the degree of Doctor of Chemistry (Ph. D.)



I



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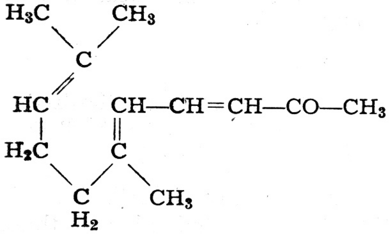

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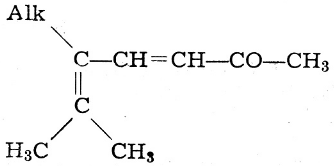
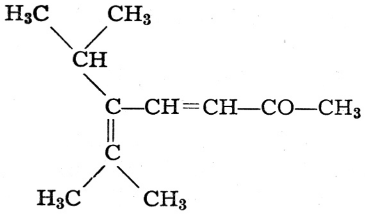


IV

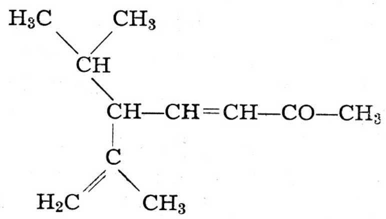
To prove whether such a compound has an ionone-like odor, we chose 5-*iso*-propyl-6-methyl-3,5-heptadien-2-one (V or its 3,6-diene isomer, VI) as the simplest acyclic compound which was, as we believed, enough alike to ionones to possess a similar odor.

This compound has not yet been described and as a simple synthetic approach we considered the condensation of aldehyde VIII with acetone.

In order to synthesize VIII the Lauchenauer-Schinz modification[8] of the Oppenauer oxidation was applied to the known 2-*iso*-propyl-3-methyl-3-buten-1-ol[9] (VII) which should give a mixture of VIII and IX. The presence of a mixture of isomeric aldehydes is of no consequence since the dienone system would isomerize in the course of the condensation with acetone under alkaline conditions.



V



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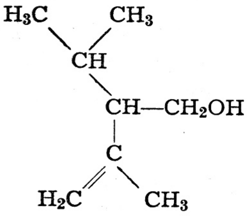
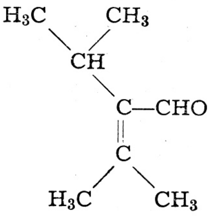
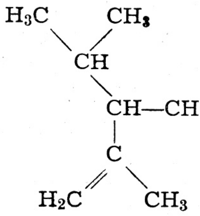


VII



VIII



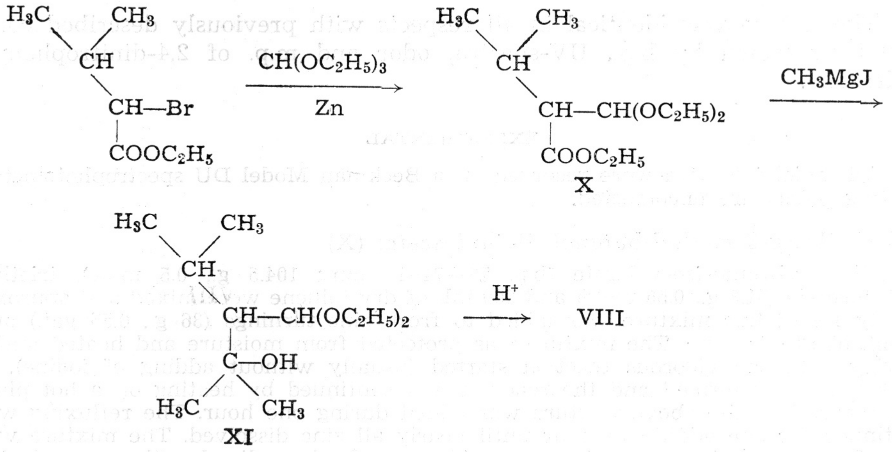
IX

However, this method gave a very low yield and the same unsatisfactory result was also obtained when other oxidation methods were applied.

From the oxidation products always two isomeric 2,4-dinitrophenylhydrazones were isolated (by chromatography on bentonite-kieselgur[10]). Based on the UV-spectra the orange colored derivative belonged to the conjugated aldehyde VIII (λ_{max} 390 mμ, $\varepsilon=28730$), and the yellow one to aldehyde IX (λ_{max} 364 mμ, $\varepsilon=23420$).

The condensation of the crude aldehyde mixture with acetone gave a small amount of a substance with an ionone-like odor. This result encouraged further attempts towards synthesis of compounds V or VI.

By introducing the aldehyde group in a protected form at an early stage of the synthesis aldehyde VIII was successfully synthesized according to the following scheme:

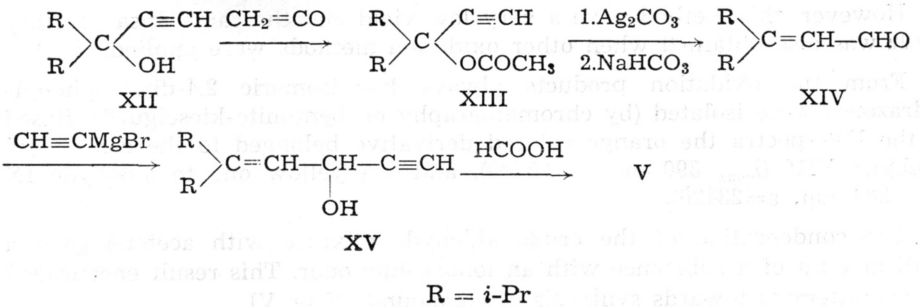


Compound XI was not isolated but hydrolysed with acetic acid and sodium acetate (the method by Isler *et al.*[11]). Aldehyde VIII was charecterised in the form of its orange 2,4-dinitrophenylhydrazone which was identical in all respects with the compound isolated from the oxidation products of alcohol VII (by m.p., mixed m.p. and ultraviolet spectra). This independent synthesis represents another proof of the structure of the aldehyde VIII.

The condensation of the crude aldehyde VIII with acetone gave ketone V which was isolated free of its isomer VI as shown by gas chromatography.

According to the expectations, ketone V had indeed an odor similar to ionone. The physical properties were also comparable to those of β-ionone *e.g.* the ultraviolet spectra showed a shift of the absorption maxima towards longer wave-lengths (λ_{max} 300 mμ, $\varepsilon=11930$; λ_{max} 220 mμ, $\varepsilon=5900$; in ethanol). 2,4-dinitrophenylhydrazone: λ_{max} 394 mμ, $\varepsilon=29600$; λ_{max} 300 mμ, $\varepsilon=12950$; in ethanol. Semicarbazone: λ_{max} 292 mμ, $\varepsilon=25700$, in ethanol.

In the second, independent synthesis of ketone V, we started from 3-*iso*-propyl-4-methyl-1-pentyn-3-ol (XII)[12]:



Acetate XIII was rearranged to aldehyd XIV (the method by Isler *et al.*[13]) from which alcohol XV was obtained (Jones *et al.*[41]). Alcohol XV was heated with formic acid (conditions of Rupe-reaction) and gave the isomeric ketone V.

The ketone was identical in all respects with previously described compound as shown by b.p., UV-spectra, odor and m.p. of 2,4-dinitrophenylhydrazone.

EXPERIMENTAL

Ultraviolet spectra were recorded on a Beckman Model DU spectrophotometer. Melting points are uncorrected.

2-Carbethoxy-3-methyl-butanal diethyl acetal (X)

Ethyl α-bromo-*iso*-valerate (b.p. 73—74^0/10 mm; 104.5 g., 0.5 mole), triethyl orthoformate (81.3 g., 0.55 mole) and 200 ml. of dry toluene were mixed and approximately 1/6 of this mixture was added to fresh zinc turnings (36 g., 0.55 gat.) and 50 ml. of dry toluene. The mixture was protected from moisture and heated under stirring until the vigorous reaction started (usually without adding of iodine). A thick mass was formed and the reaction was continued by heating on a hot plate and the rest of the above mixture was added during one hour. The refluxing was continued for one additional hour until nearly all zinc dissolved. The mixture was poured on ice and ether and acetic acid was added to dissolve the formed zinc hydroxide. The layers were separated and the aqueous layer extracted with ether. The combined ether extracts were washed neutral with sodium hydrogen carbonate and dried over magnesium sulfate. The main product was distilled *in vacuo*, b.p. 56—57^0/0.1 mm, yield 45 g. (40%) (ref. b.p. 80—82^0/2.5 mm[15]).

The analytical sample was three times distilled and the fraction 46—46.5^0/0.06 mm collected.

Anal. $C_{12}H_{24}O_4$ (232.31) calc'd.: C 62.04; H 10.41%
found : C 61.76; H 10.43%

2-Carbethoxy-3-methyl-butanal was prepared by hydrolysis of the acetal ester X with an ethanol-water-sulfuric acid mixture according to Miyazaki *et al.*[15] b.p. 72—76^0/12 mm (rep. b.p. 68—70^0/9 mm); semicarbazone, m.p. 106—108^0 (rep. m.p. 108^0).

2-iso-*Propyl-3-methyl-2-butenal* (VIII)

A) *From 2-carbethoxy-3-methyl-butanal diethyl acetal.* 2-Carbethoxy-3-methyl-butanal diethyl acetal (X, 46 g. 0.2 mole) was dissolved in 100 ml. of dry ether and the solution added to warm methylmagnesium iodide from 10.7 g. (0.44 mole) of magnesium, 62.5 g. (0.44 mole) of methyl iodide and 150 ml. of ether. The reaction was carried out without cooling under reflux during two hours. After the addition was completed the mixture was refluxed one additional hour and then hydrolysed with saturated ammonium chloride solution. The layers were separated and the water layer extracted with ether. The combined ether extracts were washed to neutral and dried over magnesium sulfate.

After evaporating the solvent an oil remained (44 g.) which was hydrolysed with a mixture of 150 ml. of glacial acetic acid, 15 g. of cryst. sodium acetate, 10 ml. of water and 0.5 g. of hydroquinone under nitrogen on the water bath during 3.5 hrs.[11] After addition of 500 ml. of water the mixture was extracted with petroleum ether and the combined extracts washed neutral with sodium hydrogen carbonate and dried over magnesium sulfate.

The crude aldehyde was obtained by distillation at 61—67°/10 mm. The yield was 10 g. (40%).

2.4-Dinitrophenylhydrazone was obtained as usual from 0.5 g. of the crude aldehyde dissolved in 10 ml. of ethanol and 17 ml. of a solution of 2,4-dinitrophenyl-hydrazine (47 mg./ml.) in ethanol and phosphoric acid[16]. One gram of an orange substance was obtained and recrystallized from 50 ml. of ethanol. M.p. 161—162°. Another crystallization from chloroform-petroleum ether mixture raised the m.p. to 162—164°.

The analytical sample was recrystalized from ethanol. The ultraviolet absorption spectrum showed a maximum at 390 mμ (ε=28800, in ethanol).

Anal. $C_{14}H_{18}N_4O_4$ (306.31) calc'd.: C 54.89; H 5.92; N 18.29%
found : C 54.94; H 5.70; N 18.26%

B) *Oxidation of 2-iso-propyl-3-methyl-3-buten-1-ol* (VII). Alcohol VII (8.2 g., 0.064 mole) was mixed with 4.4 g. (0.0213 mole) of aluminum *iso*-propoxide and after distillation of *iso*-propanol at 38—40° and 100 mm the mixture was oxidized with 13.3 g. (0.0975 mole) of freshly distilled anisaldehyde according to the method of Lauchenauer and Schinz[8]. The yield was 1.3 g. of a crude mixture of aldehydes VIII and IX boiling between 57—63°/10 mm.

2,4-Dinitrophenylhydrazones of aldehydes VIII and IX were prepared as usual from 0.55 g. of the crude aldehyde mixture and 19 ml. of 2,4-dinitrophenyl-hydrazine solution (47 mg./ml.). 0.6 g. of crude derivative was obtained and recrystallized from ethanol. 312 mg. of the mixture was dissolved in 15 ml. of petroleum ether-chloroform mixture (2:1) and chromatographed through a bentonite-kieselgur column[10]. After elution with petroleum ether-chloroform (1:1) two fractions were obtained, and recrystallized from ethanol. The orange substance, m.p. 160—162°, corresponded in all respects to the previously described compound; the yellow one, m.p. 121—123°, was isomeric and obviously belonged to the aldehyde IX (λ_{max} 364 mμ, ε=23420).

Anal. $C_{14}H_{18}N_4O_4$ (306.31) calc'd.: N 18.29%
found : N 18.21%

5-iso-*Propyl-6-methyl-3,5-heptadien-2-one* (V)

2-*iso*-Propyl-3-methyl-2-butenal (VIII, 5 g., 0.04 mole) was dissolved in 50 ml. of acetone and a solution of 1.4 g. of potassium hydroxide in 10 ml. of water. About 15 ml. of water was added to homogenize the mixture, followed by 200 mg. of hydroquinone. Nitrogen was bubbled through the mixture for a few minutes, and the bottle was stoppered and shaken during 12 hrs. After acidification with 2*N* hydrochloric acid to *p*H 4, acetone was evaporated *in vacuo*. The residue was extracted with petroleum ether, the organic layer washed neutral and dried over magnesium sulfate. Petroleum ether was evaporated and the remaining oil distilled at 10 mm: 1) 65—99°, 1 g., 2) 100—107°, 2.7 g.

Fraction 2 was transformed into semicarbazone and recrystallized from ethanol. The pure semicarbazone (1.8 g.) was shaken with 20 ml. of petroleum ether and 25 ml. of 2*N* sulfuric acid during 12 hrs. The organic layer was separated and washed with sodium hydrogen carbonate and water to neutral and dried over magnesium sulfate.

After the evaporation of the solvent the ketone was distilled *in vacuo* b.p. 105—107°/10 mm. Gas chromatography showed only one peak. UV-spectrum: λ_{max} 300 mμ, ε=11930; λ_{max} 220 mμ, ε=5900.

Anal. $C_{11}H_{18}O$ (166.25) calc'd.: C 79.46; H 10.92%
found : C 78.87; H 11.10%

2,4-Dinitrophenylhydrazone was obtained as usual from 0.5 g. of the crude ketone and recrystallized (0.8 g.) from ethanol, and the crystals washed with petroleum ether. Another recrystallization from petroleum ether-chloroform gave crystals with m.p. 156—158°. UV-spectrum: λ_{max} 394 mμ, ε=29600; λ_{max} 300 mμ, ε=12950.

Anal. $C_{17}H_{22}N_4O_4$ (346.38) calc'd.: C 58.94; H 6.40; N 16.18%
found : C 59.17; H 6.59; N 16.05%

Semicarbazone, m.p. 155—156.5° from aqueous ethanol. UV-spectrum: λ_{max} 292 mμ, ε=25700.

Anal. $C_{12}H_{21}N_3O$ (223.31) calc'd.: C 64.54; H 9.48; N 18.32%
found : C 64.73; H 9.63; N 18.94%

*3-Acetoxy-3-*iso*-propyl-4-methyl-1-pentyne* (XIII)

3-*iso*-Propyl-4-methyl-1-pentyn-3-ol[12] (14 g., 0.1 mole) was dissolved in 14 ml. of tetrachloromethane, three drops of conc. sulfuric acid were added and the mixture cooled with ice to 2—3°. Ketene was introduced into the mixture under cooling and stirring. After the absorption of ketene ceased, the mixture was washed with sodium hydrogen carbonate to neutral and dried over magnesium sulfate.

The solvent was evaporated and the remaining oil distilled *in vacuo* at 10 mm: b.p. 81—84°; yield 13 g. (71.5%).

The analytical sample was distilled three times *in vacuo*, b.p. 84—84.5°/10 mm.

Anal. $C_{11}H_{18}O_2$ (182.25) calc'd.: C 72.49; H 9.96%
found : C 72.34; H 10.00%

*3-*iso*-Propyl-4-methyl-2-pentenal* (XIV)

3-Acetoxy-3-*iso*-propyl-4-methyl-1-pentyne (11 g., 0.06 mole), 30 ml. of glacial acetic acid and 140 mg. of pure silver carbonate, were mixed and heated on a water bath during 1 hour under nitrogen[13]. The mixture was poured into 200 ml. of water and extracted with petroleum ether, the extract washed with sodium hydrogen carbonate and water to neutral, and dried over magnesium sulfate.

Petroleum ether was evaporated and the remaining oil dissolved in 100 ml. of methanol and refluxed with 10.5 g. of sodium hydrogen carbonate under nitrogen during 1 hour. About 70 ml. of methanol was distilled off and rest poured on ice and extracted with petroleum ether. The organic layer was washed with water to neutral and dried over magnesium sulfate.

After evaporation of petroleum ether, the oil was distilled; b.p. 77—81°/10 mm (rep. b.p. 85—86°/12 mm[17]; 85—91°/19 mm[18]), yield 5.4 g. (64%).

2,4-Dinitrophenylhydrazone melted at 154—156° then solidified and melted again at 176—177° (from petroleum ether-chloroform); m.p. 177—178° (from ethanol).*

*3-Hydroxy-5-*iso*-propyl-6-methyl-4-hepten-1-yne* (XV)

Ethynylmagnesium bromide was prepared according to Jones *et al.*[14] from 1.22 g. (0.05 mole) of magnesium, 5.5 g. (0.05 mole) of ethyl bromide, 55 ml. of dry tetrahydrofurane and acetylene. 3-*iso*-Propyl-4-methyl-2-pentenal (XIV, 5 g., 0.0357 mole) dissolved in 7 ml. of dry tetrahydrofurane was added to the above solution with cooling and stirring under nitrogen. The mixture was hydrolysed with a saturated ammonium chloride solution, the layers separated and the aqueous solution extracted with ether. The ether extract was washed to neutral and dried over magnesium sulfate.

The solvent was evaporated and the oil distilled *in vacuo*: b.p. 90—100°/10 mm, 2.9 g.

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* Young and Roberts[19] gave m.p. 151.5—153°, Ansell and oth.[17] reported m.p. 180° and Takeshima *et al.*[18] obtained this derivative with m.p. 173.5—174°. We found, however, the discrepancy was only feint and melting points depended on solvents used for crystalization. Probably, the substance is dimorphic.

5-iso-*Propyl-6-methyl-3,5-heptadien-2-one* (V)

3-Hydroxy-5-*iso*-propyl-6-methyl-4-hepten-1-yne (XV, 1 g.) was mixed with 5 ml. of formic acid and several milligrams of hydroquinone and the mixture stirred under nitrogen. The clear dark red solution was warmed to 50^0 for 30 minutes. A yellow oil separated and the mixture which contained two layers was poured into water. Formic acid was neutralized with sodium carbonate the oil extracted with petroleum ether and the extract washed to neutral and dried over magnesium sulfate.

The solvent was evaporated and the remaining oil purified with Girard-P reagent. After distillation an oil was obtained, b.p. 104—108^0/10 mm.

2,4-Dinitrophenylhydrazone was obtained as usual and chromatographed through bentonite-kieselgur column[10]. The middle zone was eluated and recrystallized from chloroform-petroleum ether. M.p. 156—158^0, mixed m.p. showed no depression with the sample from the previous preparation.

Acknowledgment. The author is indebted to Dr. R. Seiwerth and to Prof. Dr. V. Hahn for their interest in this work. Thanks are also due to Mrs. B. Živković and Mr. B. Slišković for valuable technical assistance.

REFERENCES

1. H. Schinz, Die Veilchenriechstoffe, *Fortschr. d. Chem. org. Naturstoffe,* **8,** 146.
2. O. N. Jitkow and M. T. Bogert, *J. Am. Chem. Soc.* **63** (1941) 1979.
3. R. Vonderwahl and H. Schinz, *Helv. Chim. Acta* **35** (1952) 1997.
4. R. Vonderwahl and H. Schinz, *Helv. Chim. Acta* **35** (1952) 2005.
5. H. R. Vogt and H. Schinz, *Helv. Chim. Acta* **37** (1954) 2196.
6. B. A. Arbusov and L. A. Mukhamedova, *Izvest. Akad. Nauk SSSR* **1953,** 820.
7. C. A. Vodoz and H. Schinz, *Helv. Chim. Acta* **33** (1950) 1321.
8. A. Lauchenauer and H. Schinz, *Helv. Chim. Acta* **32** (1949) 1265.
9. K. Šestanj, *Croat. Chem. Acta* **33** (1961) 127.
10. J. A. Elvidge and M. Whalley, *Chem. & Ind. (London)* **1955,** 589.
11. O. Isler, M. Montavon, R. Rüegg, and P. Zeller, *Helv. Chim. Acta* **39** (1956) 259.
12. K. Šestanj, *Croat. Chem. Acta* **34** (1962) 246.
13. G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Chimia* **12** (1958) 326; *Helv. Chim. Acta* **42** (1959) 1945.
14. E. R. H. Jones, L. Skatteböl, and M. C. Whithing, *J. Chem. Soc.* **1956,** 4765.
15. M. Miyazaki, C. Mizuno, and S. Umio, Yakugaku Zasshi **77** (1957) 415; *cf. C. A.* **51** (1957) 12068.
16. E. Heuser in Houben-Weyl, *Methoden der org. Chemie* **2.** 449.
17. M. F. Ansell, J. W. Hancock, and W. J. Hickinbottom, *J. Chem. Soc.* **1956,** 911.
18. T. Takeshima, K. Nagaoka, M. Yokoyama, and S. Morita, *Bull. Chem. Soc. Japan* **32** (1959) 547; *cf. C. A.* **54** (1960) 7540.
19. W. G. Young and J. D. Roberts, *J. Am. Chem. Soc.* **67** (1945) 319.

IZVOD

Sinteza jednog acikličkog analoga jonona

K. Šestanj

Opisane su dvije, međusobno nezavisne sinteze 5-izo-propil-6-metil-3,5-heptadien-2-ona (V), acikličkog analoga jonona. Keton V posjeduje miris sličan mirisu jonona, a ima i slična fizikalna svojstva

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ZAGREB

Primljeno 31. srpnja 1962.