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Abstract

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Synthesis of Geranylacetone, 3-Methylgeranylacetone, Pseudoionone, and Pseudoirone

In the course of systematic work in the field of the synthesis of isoprenoid compounds (1), our attention was drawn to a short article by Carroll (2), in which it was reported that, on heating linalool with acetoacetic ester in the presence of a small amount of sodium ethoxide, geranylacetone is formed in a yield of 40-45%. This method was later also used by other authors (3,4) for obtaining geranylacetone and some of its analogues. An interesting variant of the Carroll synthesis was proposed by Kimel and Cope (5). By reacting lanalool with diketene in the presence of metallic sodium, the authors obtained linalyl acetoacetate in 61% yield; pyrolysis of this at 170-235° gave geranylacetone in 78% yield.

We have investigated in detail both variants of the synthesis using linalool and 3-methyllinalool as examples, with the aim of developing a method for obtaining geranylacetone and 3-methylgeranylacetone. It turned out that the reaction between linalool or 3-methyllinalool and acetoacetic ester proceeds best at a temperature of 160-180° without any catalysts (6). The best yields (65-70%) of geranylacetone and 3-methylgeranylacetone were achieved when using a twofold excess of acetoacetic ester and when carrying out the reaction as rapidly as possible. In the course of the reaction, up to 90-95% of the theoretical amount of carbon dioxide is evolved (the CO_2 content, according to analysis, is above 99%), and almost the theoretical amount of alcohol, containing an admixture of acetone, is distilled off.

It should be noted that the distillation of alcohol is completed considerably earlier than the evolution of carbon dioxide. On the basis of these data, it may be assumed that the reaction of formation of geranylacetone and 3-methylgeranylacetone proceeds through the acetoacetate stage according to the scheme:

$$\text{(structural scheme)}$$
$$\mathrm{R} = \mathrm{H},\ \mathrm{CH_3}$$

This mechanism was proved by us (1) in the reaction between dimethylvinylcarbinol and acetoacetic ester, in which it was possible to isolate the acetoacetate of dimethylvinylcarbinol; pyrolysis of this gives methylheptenone.

In studying the second variant of the synthesis, we established that acylation of linalool and 3-methyllinalool with diketene is best carried out in the presence of pyridine or triethylamine, and not metallic sodium. Under the conditions developed by us, the yield of the corresponding acetoacetates is 85–90%. Pyrolysis of the acetoacetates is best carried out as rapidly as possible at a temperature of 160–200°. Both stages of the reaction—acylation and pyrolysis—can be carried out without isolation and purification of the intermediate acetoacetate.

On the basis of the data obtained, we decided to investigate both variants of the reaction using dehydrolinalool and 3-methyldehydrolinalool as examples, with the aim of developing methods for the synthesis of pseudoionone and pseudoirone. At the time of the beginning

of our work an article by Lacey (7) was published, who, using dimethylethynylcarbinol and several other simpler ethynylcarbinols as examples, showed the possibility of synthesizing dienones according to the general scheme:

$$\mathrm{(CH_3)_2C(OH){-}C{\equiv}CH} \xrightarrow{\text{diketene}} \mathrm{(CH_3)_2C(OCOCH_2COCH_3){-}C{\equiv}CH} \xrightarrow[-\mathrm{CO_2}]{t^\circ} \mathrm{(CH_3)_2C{=}CHCH{=}CHCOCH_3}$$

The second stage of the reaction—the pyrolysis of the acetoacetate—was carried out by Lacey in the presence of small amounts of *p*-toluenesulfonic acid. This route to dienones was studied in detail in our laboratory for a whole series of tertiary acetylenic alcohols (8). In the course of our work, a brief note by Naves (9) appeared in print on the possibility of using the reaction between dehydrolinalool or 3-methyldehydrolinalool and acetoacetic ester or diketene for the synthesis of pseudoionone and pseudoirone. Subsequently Naves (10) described in detail the method for obtaining 3-methylpseudoirone from 3-methyldehydrolinalool and α-methylacetoacetic ester. Finally, recently N. A. Preobrazhenskii and co-workers (11) reported the preparation of pseudoionone from dehydrolinalool and diketene via dehydrolinalool acetoacetate.

We studied both of these variants of the synthesis and established that the reaction between dehydrolinalool or 3-methyldehydrolinalool and acetoacetic ester proceeds best on heating in a nitrogen atmosphere at 170–180° in the absence of catalysts. Under these conditions the yield of pseudoionone and pseudoirone is about 55%.

$$\text{R-dehydrolinalool} \xrightarrow[\text{or diketene}]{\text{acetoacetic ester}} \text{R-acetoacetate} \xrightarrow[-\mathrm{CO_2}]{170\text{–}195^\circ} \text{R-pseudoionone/pseudoirone}$$
$$\mathrm{R = H,\ CH_3}$$

Acylation of dehydrolinalool or 3-methyldehydrolinalool with diketene proceeds best in the presence of pyridine or triethylamine at a temperature of 70–80°.

Pyrolysis of the dehydrolinalool and 3-methyldehydrolinalool acetoacetates obtained in this way was carried out at 185-195°. In the course of pyrolysis, approximately 80-85% of the theoretical amount of carbon dioxide is evolved (the CO_2 content according to analysis is above 90%). The yield of pseudoionone and pseudoirone, calculated on the starting dehydrolinalool or 3-methyldehydrolinalool, is 50-55%.

On cyclization of the pseudoionone samples obtained in this way with a mixture of sulfuric and glacial acetic acids (12), ionone was formed in 65% yield.

Experimental Part

1. Preparation of geranylacetone. a) A mixture of 77 g (0.5 mole) of linalool and 130 g (1 mole) of acetoacetic ester was rapidly heated to 160-180° (the air having first been displaced by nitrogen), and this temperature was maintained until gas evolution ceased (approximately 3-4 hours). About 10 l of carbon dioxide was evolved (88% of theory), and 25.8 g of alcohol distilled off (b.p. 75-78°). By double fractionation of the residue, 70 g (about 70%) of geranylacetone was isolated, b.p. 92-94°/3 mm, n_D 1.4674; $\lambda_{\max}$ (in methanol) 291 mμ ($\lg \varepsilon = 2.42$).

Found, %: C 80.55; 80.49; H 11.37; 11.42
$C_{13}H_{22}O$. Calculated, %: C 80.35; H 11.41

Semicarbazone, m.p. 95-96° (from alcohol).

Found, %: N 16.42; 16.42
$C_{14}H_{25}O_3$. Calculated, %: N 16.71

b) To a mixture of 15.4 g (0.1 mole) of linalool and 0.6 g of pyridine, over 15 min, 10 g (0.11 mole) of diketene was added; the mixture was then stirred for 2 hours at room temperature and for 2 hours at 60-65°. The product was washed with bicarbonate solution and water and dried with magnesium sulfate. Distillation gave 20.4 g (85% of theory) of linalyl acetoacetate, b.p. 132-134° at 2 mm; n_D^{20} 1.4706.

18.8 g of the linalyl acetoacetate thus obtained was heated at 165-200° for 30 min. 920 ml of carbon dioxide was evolved. By two distillations, 10.8 g (70% of theory) of geranylacetone was obtained, b.p. 88-89°/1 mm; n_D^{20} 1.4664. The semicarbazone melted at 94-94.5° and gave no depression with the preceding sample.

2. **Preparation of 3-methylgeranylacetone** (I, R=CH_3).

a) From 20 g of 3-methyllinalool and 35 g of acetoacetic ester, analogously to the preceding procedure (experiment 1a), 18 g of 3-methylgeranylacetone was obtained, b.p. 105-107° at 2 mm; n_D^{19} 1.4702.

Found, %:	C 79.48; 79.54; H 11.59; 11.54
$C_{14}H_{24}O$. Calculated, %:	C 80.71; H 11.67

The semicarbazones melted at 101-102° and 138-139°. b) By the interaction of 19 g of 3-methyllinalool and 13 g of diketene in the presence of 0.5 ml of pyridine at 70°, an acetoacetate was obtained, which was subjected to pyrolysis at 160-190°, as described in experiment 1b. By two distillations, 11.5 g of 3-methylgeranylacetone was obtained, b.p. 106-108°/2 mm; n_D^{20} 1.4697.

3. **Preparation of pseudoionone.**

a) The reaction between 152 g of dehydrolinalool and 260 g of acetoacetic ester was carried out at 170-180° for 4.5 hours, analogously to the preceding procedure (experiment 1a). After distillation of the volatile fractions up to 100°/10 mm, the residue was boiled and stirred with a threefold volume of 25% sodium bisulfite for 5 hours. After the mixture had been washed twice with ether, the bisulfite derivative of pseudoionone was decomposed by 10% sodium hydroxide in the presence of ether in the usual way. Distillation of the ethereal extract gave 106 g (55% of theory) of pseudoionone, b.p. 123-125° at 4 mm, n_D^{20} 1.5310; $\lambda_{\max}$ (in isooctane) 280 mμ ($\lg\varepsilon = 4.36$); 2,4-dinitrophenylhydrazone, m.p. 146-146.5° (from alcohol).

Found, %:	N 15.12; 14.97
$C_{14}H_{23}ON_3$. Calculated, %:	N 15.05

b) A mixture of 15.2 g of dehydrolinalool and 10 g of diketene was heated in the presence of triethylamine at 75-80° for 3 hours. The product was dissolved in ether, washed with 5% bicarbonate solution, and dried with magnesium sulfate. Distillation gave 21.2 g (90% of theory) of dehydrolinalool acetoacetate, b.p. 95-96° at 0.07 mm; n_D^{20} 1.4685 / d_4^{20} 0.9879.

Found, %:	C 71.40; 71.60; H 8.60; 8.52
$C_{14}H_{20}O_3$. Calculated, %:	C 71.14; H 8.53

Pyrolysis of 11.8 g of dehydrolinalool acetoacetate was carried out at 185-195° for 25 min. Distillation gave 4.8 g (50% of theory) of pseudoionone, b.p. 89-90° at 0.1 mm; n_D^{20} 1.5285; $\lambda_{\max}$ (in isooctane) 281 mμ ($\lg\varepsilon = 4.38$).

Found, %:	C 80.97; 80.99; H 10.30; 10.43
$C_{13}H_{20}O$. Calculated, %:	C 81.19; H 10.49

2,4-Dinitrophenylhydrazone was obtained in the form of two isomers with m.p. 147-148° (93%) and m.p. 117-118° (7%).

For pseudoionone obtained from natural citral, $\lambda_{\max}$ (in isooctane) 282 mμ ($\lg \varepsilon = 4.37$).

Cyclization of pseudoionone[13]. 96 g of pseudoionone was added dropwise over 35 min at 5-15° to a mixture of 240 g of glacial acetic acid

and 400 g of sulfuric acid (*d* 1.84). The mixture was stirred for 30 min at 28-30°, poured onto ice, and extracted with toluene. The organic layer was washed with a saturated bicarbonate solution, the solvent was distilled off under a slight vacuum, and the residue was steam-distilled at 30-35 mm until the oil had been completely distilled over. The distillate was extracted with ether, the ether layer was dried with magnesium sulfate and fractionated. This gave 63 g (65% of theory) of ionone, b.p. 94-97° at 1 mm; n_D^{20} 1.5190 (β-form content 97%).

Found, %: C 81.07; 80.88; H 10.23; 10.44
$C_{13}H_{20}O$. Calculated, %: C 81.19; H 10.49

The semicarbazone of β-ionone was obtained, m.p. 148-149° (from aqueous methanol).

4. **Preparation of pseudoirone.** a) Heating a mixture of 25 g of 3-methyldehydrolinalool and 40 g of ethyl acetoacetate at 180-190° for 4 h gave a mixture of isomeric pseudoirones. By twofold fractionation, 15.8 g (51% of theory) of pseudoirone was isolated, b.p. 118-129° at 1 mm; n_D^{20} 1.5140-1.5284; d_4^{20} 0.9117-0.9097.

For the fraction with b.p. 118-120° at 1 mm:

Found, %: C 81.08; 80.95; H 10.62; 10.58

For the fraction with b.p. 124-129° at 1 mm:

Found, %: C 81.03; 80.75; H 10.73; 10.63
$C_{14}H_{22}O$. Calculated, %: C 81.49; H 10.74

The 2,4-dinitrophenylhydrazone was separated by crystallization from alcohol and from a mixture of alcohol with ethyl acetate into isomers with m.p. 153-154° and 120-121°. b) By the interaction of 20 g of 3-methyldehydrolinalool and 12 g of diketene in the presence of 0.5 ml of pyridine at 70°, an acetoacetate was obtained; it was washed with a saturated sodium bicarbonate solution, extracted with ether, and dried with magnesium sulfate. After removal of the ether, the residue was subjected, without distillation, to pyrolysis by the usual method at 180-200° for 40 min. After the usual workup, fractionation gave 13.1 g (53% of theory) of a mixture of isomeric pseudoirones, b.p. 102-115° at 1 mm, n_D^{20} 1.5192-1.5280.

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