CHEMISTRY

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1958

SovietRxiv

Abstract

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CONDENSATION OF THE ACETAL OF β-CYCLOCITRAL WITH 1-ETHOXYISOPRENE

The method we developed earlier for the synthesis of unsaturated aldehydes of the isoprenoid type, based on the condensation of acetals with 1-alkoxydienes (^{1}), makes it possible to lengthen the isoprenoid carbon chain at once by five or ten carbon atoms.

By means of this method such polyenals as octatrienal, dehydrocitral, farnesinal, and others were obtained, and a series of α, β-unsaturated ether-aldehydes was also synthesized: 4-ethoxycitral, 4,8-diethoxyfarnesal, and others.

This interesting reaction opens a simple route for the synthesis of β-ionylideneacetic aldehyde and vitamin A aldehyde, and to this end we studied the condensation of the acetal of β-cyclocitral (I) with 1-ethoxyisoprene (II).

The previously unknown acetal of β-cyclocitral (I) was obtained by the action of ethyl orthoformate on β-cyclocitral.

In the presence of zinc chloride, condensation of the acetal of β-cyclocitral (I) with ethoxyisoprene (II) leads to a mixture of ether-acetals of the aldehyde C_{15} (III) and the aldehyde C_{20} (IV), with yields of 44.6 and 25%, respectively, which are readily separated by distillation in vacuo.

The best yields of ether-acetals (III) and (IV) were obtained with a ratio of acetal (I) to ethoxyisoprene (II) of 2 : 1 and at a temperature of 40–45°.

$$\text{(reaction scheme: acetal of } \beta\text{-cyclocitral (I)} + \mathrm{CH_2=C(CH_3)-CH=CHOC_2H_5} \text{ (II)} \longrightarrow \text{ ether-acetal } C_{15} \text{ (III) and ether-acetal } C_{20} \text{ (IV)}$$

On saponification of ether-acetal (III) with dilute orthophosphoric acid, ethoxydihydro-β-ionylideneacetic aldehyde (V) is obtained smoothly; its reduction with sodium borohydride gave the corresponding ethoxydihydro-β-ionylidenethyl alcohol (VI).

From ether-acetal (III), under the action of orthophosphoric acid in dioxane, β-ionylideneacetic aldehyde (VII) was obtained in satisfactory yield.

$$\text{(VII)} \longleftarrow \text{(III)} \longrightarrow \text{(V)} \longrightarrow \text{(VI)}$$

$$(IV) \longrightarrow (VIII) \longrightarrow (IX)$$

By similar transformations, starting from the ether acetal (IV), it was possible to carry out in high yields the synthesis of diethoxybisdihydroaldehyde of vitamin A (VIII) and diethoxybisdihydrovitamin A (IX)—important intermediates for the synthesis of vitamin A, which may be of independent biological interest.

Experimental Part

Diethyl acetal of β-cyclocitral (I). A solution of 104 g of β-cyclocitral (b.p. 93-95°/10 mm; n_D^{20} 1.4958), 130 g of ethyl orthoformate, and 14.3 mg of p-toluenesulfonic acid in 48 ml of abs. ethyl alcohol was left for 3 days at room temperature, and after neutralization with sodium ethylate the mixture was distilled in vacuo.

As a result of twofold distillation there were obtained:

1st fraction (67-70°/36 mm, n_D^{17} 1.3960), 70 g—ethyl orthoformate;

2nd fraction (93-104°/10 mm; n_D^{19} 1.4880), 62 g—starting β-cyclocitral;

3rd fraction (104-112°/10 mm, n_D^{17} 1.4710), 58 g—a mixture of β-cyclocitral and its acetal.

The 3rd fraction obtained from several experiments (103 g) was subjected to distillation on a rectification column with glass packing. After separation of β-cyclocitral, the still residue was distilled from a Favorskii flask, and in this way 32.5 g of β-cyclocitral acetal (I) were isolated, b.p. 105-107°/7 mm, n_D^{20} 1.4615.

Found %:	C 74.43; 74.47; H 11.40; 13.41
$C_{14}H_{26}O_2$. Calculated %:	C 74.29; H 11.58

From acetal (I) a semicarbazone was obtained, m.p. 164-166° (from ethanol), which gave no depression with the semicarbazone of β-cyclocitral.

Condensation of β-cyclocitral acetal (I) with ethoxyisoprene (II). To a mixture of 40 g (0.177 mole) of acetal (I) and 4 ml of a 10% solution of zinc chloride in ethyl acetate, there was slowly added (over 3.5 hours), at a temperature of 42° and with stirring, 10 g (0.089 mole) of ethoxyisoprene (II). The mixture was then stirred for another 1 hour 15 min at 42-45°, after which it was cooled, diluted with ether, washed with 5% caustic soda solution, water, dried, and distilled. As a result of twofold fractional distillation in vacuo there were obtained:

1) 24.7 g of starting acetal (I), b.p. 68-73°/0.7 mm, $n_D^{19.5}$ 1.4670;

2) 10 g (yield* 44.6%) of the ether acetal of aldehyde C_{15} (III) as a colorless liquid, b.p. 105-107°/0.08 mm, n_D^{20} 1.4740, d_4^{20} 0.9466, MR found 100.5, calculated 100.97.

Found %: C 74.13; 74.16; H 11.17; 11.03
$C_{21}H_{38}O_3$. Calculated %: C 74.50; H 11.32

3) 7.4 g (yield* 25%) of the ether acetal of aldehyde C_{20} (IV) as a yellowish viscous liquid, b.p. 152-156°/0.07 mm, n_D^{20} 1.4828.

Found %: C 74.92; 75.04; H 11.06; 11.15
$C_{28}H_{50}O_4$. Calculated %: C 74.61; H 11.18

* The yield is based on the acetal (I) that entered into the reaction.

Ethoxydihydro-β-ionylideneacetic aldehyde (V) *(3-methyl-5-ethoxy-5-(2,6,6-trimethylcyclohexen-1-yl-1)pent-2-enal).* A mixture of 10 g of effiroacetal (III), 25 ml of 5% orthophosphoric acid, and 5 ml of ethyl alcohol was stirred at 95° in a stream of nitrogen for 1 hr. After cooling, ether was added to the reaction mixture; the organic layer was separated, washed with sodium bicarbonate solution and with water, dried over magnesium sulfate, and distilled in vacuo. There was obtained 6.2 g of effiroaldehyde (V) with b.p. 98-99°/0.07 mm, $n_D^{21.5}$ 1.5045.

λ_{max} (in ethanol) 240 mμ (lg ε 4.086).

Found, %: C 77.45; 77.18; H 10.88; 10.82
$C_{17}H_{28}O_2$. Calculated, %: C 77.21; H 10.67

2,4-Dinitrophenylhydrazone of effiroaldehyde (V) was obtained in the form of a mixture of geometrical isomers with m.p. 137-145° (after two recrystallizations from ethanol).

λ_{max} (in heptane) 368 mμ (lg ε 4.14), 290 mμ (lg ε 3.79), 256 mμ (lg ε 4.107).

Found, %: C 62.01; 62.29; H 7.29; 7.01; N 13.02; 12.58
$C_{23}H_{32}N_4O_5$. Calculated, %: C 62.13; H 7.26; N 12.6

Semicarbazone of effiroaldehyde (V) was likewise obtained in the form of a mixture of geometrical isomers with m.p. 153-161° (after recrystallization from 90% methanol).

Found, %: N 13.28; 13.30
$C_{18}H_{31}O_2N_3$. Calculated, %: N 13.07

β-Ionylideneacetic aldehyde (VII). A mixture of 2.5 g of effiroacetal (III), 1 ml of 90% orthophosphoric acid, 20 ml of dioxane, and 6 ml of water was heated for 5 hr at 88-90° in a stream of nitrogen in the presence of traces of hydroquinone. During heating, distillation of dioxane and water proceeded slowly; at the same time a mixture of dioxane and water (4 : 1) was added to the flask so that the volume of the reaction mass remained constant. The reaction mixture was cooled, poured into ice water (30 ml), and the reaction product was extracted with ether. The ethereal extract was washed with sodium bicarbonate solution and with water, dried, and distilled. There was obtained 1.4 g of an orange-yellow liquid with b.p. 91-97°/0.09 mm.

The product obtained, in a mixture with 2 ml of 90% orthophosphoric acid, 20 ml of dioxane, and 6 ml of water, was again subjected to the operation described above. After distillation, 0.7 g of a substance was obtained with b.p. 91-94°/0.09 mm, representing β-ionylideneacetic aldehyde (VII), the 2,4-dinitrophenylhydrazone of which had m.p. 195-196° (from a mixture of ethanol with ethyl acetate).

λ_{max} (in ethanol) 319 mμ (lg ε 4.191), 408 mμ (lg ε 4.599).

Found, %: C 63.35; 63.18; H 6.50; 6.48; N 14.30; 14.31
$C_{21}H_{26}O_4N_4$. Calculated, %: C 63.31; H 6.53; N 14.07

According to literature data, the 2,4-dinitrophenylhydrazone of β-ionylideneacetic aldehyde melts at 199-201°; λ_{max} (in ethanol) 260 mμ (lg ε 4.1987), 320 mμ (lg ε 4.1461), 400 mμ (lg ε 4.5635) (^{2}); at 198-200°, λ_{max} 405 mμ (lg ε 4.5966) (^{3}).

Ethoxydihydro-β-ionylideneethyl alcohol (VI) *(3-methyl-5-ethoxy-5-(2,6,6-trimethylcyclohexen-1-yl-1)pent-2-enol).* To a solution of 2.2 g of effiroaldehyde (V) in 18 ml of 96% ethyl alcohol, with stirring and at a temperature of 10-12°, 370 mg of sodium borohydride (85% content) was added over the course of 1 hr in a stream of nitrogen.

The mixture was then stirred for another 1 hr at this temperature and left overnight at room temperature. The excess sodium borohydride was decomposed with acetic acid (7-8 drops), the alcohol was distilled off in a weak vacuum, water and ether were added to the residue, the ethereal layer was separated, and the aqueous layer—double-

The liquids were extracted with ether. The combined ethereal extract was washed with water, dried over calcined magnesium sulfate, and distilled.

This gave 1.65 g of ethoxydihydro-β-ionylideneethyl alcohol (VI), b.p. 87-88°/0.025 mm, n_D^{20}1.4943.

Found, %:	C 76.60; 76.85;	H 11.49; 11.44
$C_{17}H_{30}O_2$. Calculated, %:	C 76.66;	H 11.35

Found number of active hydrogens: 0.99; 1.06.

Diethoxybisdihydroaldehyde of vitamin A (VIII) (3,7-dimethyl-5,9-diethoxy-9-(2,6,6-trimethylcyclohexen-1-yl-1)nonadien-2,6-al). A mixture of 13.7 g of ether acetal (IV), 29 ml of 5% orthophosphoric acid, and 6 ml of ethyl alcohol was stirred in a stream of nitrogen at 95° for 1 hour and worked up as described above for the preparation of ether aldehyde (V). This afforded 9 g of ether aldehyde (VIII), b.p. 155–157°/0.1 mm, n_D^{20}1.5070.

$$\lambda_{\text{max (in ethanol)}}\ 240\ \text{m}\mu\ (\lg\varepsilon\ 4.123),\quad 340\ \text{m}\mu\ (\lg\varepsilon\ 3.677)$$

Found, %: C 76.92; 76.91; H 10.55; 10.54

$C_{24}H_{40}O_3$. Calculated, %: C 76.52; H 10.70

The 2,4-dinitrophenylhydrazone and semicarbazone of ether aldehyde (VIII) could not be obtained in the crystalline state.

Diethoxybisdihydro vitamin A (IX) (3,7-dimethyl-5,9-diethoxy-9-(2,6,6-trimethylcyclohexen-1-yl-1)nonadien-2,6-ol). To a solution of 3.1 g of ether aldehyde (VIII) in 18 ml of 97% ethyl alcohol at a temperature of 10–12° and with stirring, 370 mg of sodium borohydride was added over the course of 2 hours. After the workup described above and distillation, 2.4 g of diethoxybisdihydro vitamin A (IX) was obtained as a viscous, almost colorless liquid, b.p. 143–145°/0.025 mm, n_D^{20}1.5020.

Found, %: C 75.85; 75.90; H 11.11; 11.20

$C_{24}H_{42}O_3$. Calculated, %: C 76.12; H 11.18

Found number of active hydrogens: 0.85; 0.85.

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Academy of Sciences of the USSR

Received
13 V 1958

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