CHEMISTRY OF POLYENIC AND POLYACETYLENIC COMPOUNDS

COMMUNICATION 4. USE OF ETHOXYACETYLENE FOR THE SYNTHESIS OF ESTERS OF ISOPRENOID ACIDS

Zh. A. Krasnaya and V. F. Kucherov

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences, USSR

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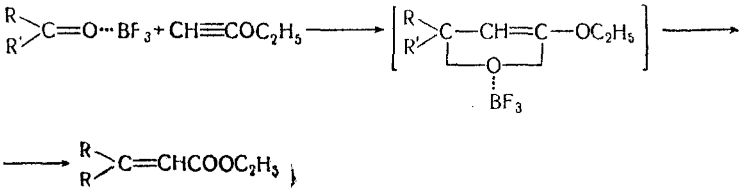
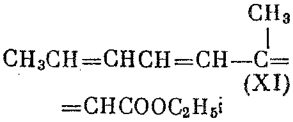
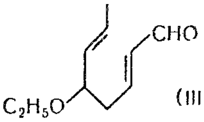
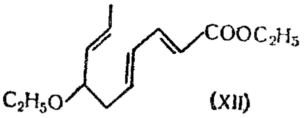
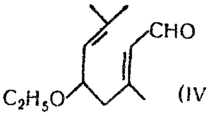
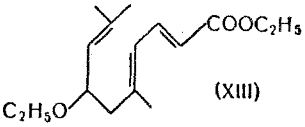
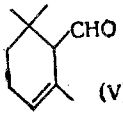
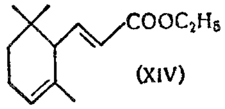
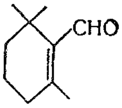
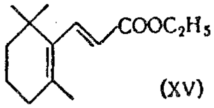
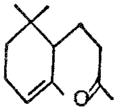
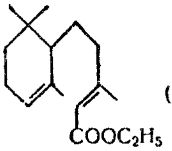
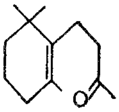
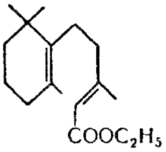
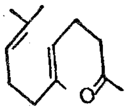
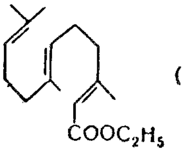
In connection with our investigations on the synthesis of polyenic isoprenoid compounds we were interested in recently published short communications by Arens and co-workers [1, 2], which refer to the possibility of preparing esters of α,β-unsaturated acids by the reaction of carbonyl compounds with ethoxyacetylene under the influence of boron trifluoride etherate. According to these authors, the reaction consists in the electrophilic addition of a molecule of the carbonyl compound to the β-carbon atom of the acetylenic bond of ethoxyacetylene and proceeds in accordance with the following scheme



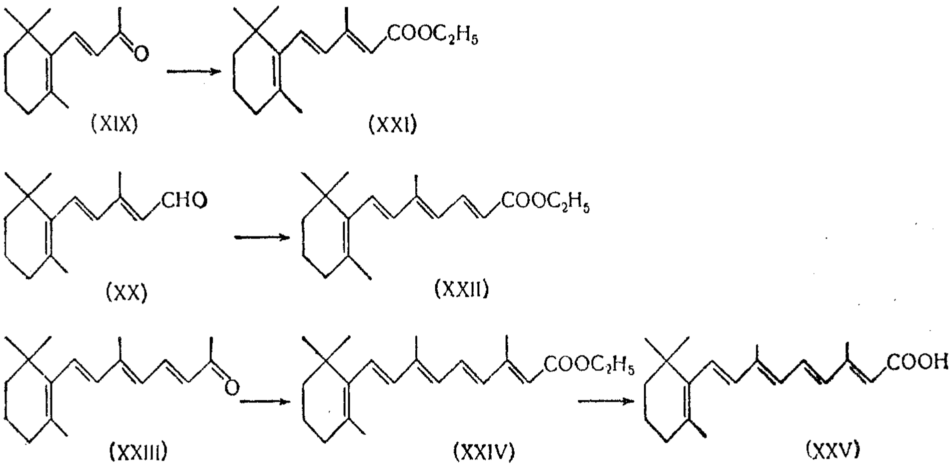
Unlike the generally known Wittig method, based on the use of [(ethoxycarbonyl)methylene]phosphoranes, this reaction proceeds fairly smoothly not only with aldehydes, but also with ketones, which is an undoubted advantage in synthesis.

With the object of studying the possibility of using this method for the synthesis of polyenic acids we effected the condensation of ethoxyacetylene with various unsaturated aldehydes and ketones: Crotonaldehyde (I), 3,5-heptadien-2-one (II), 5-ethoxy-2,6-octadienal (III), 5-ethoxycitral (IV), α- and β-cyclocitrals (V) and (VI), α- and β-dihydroionones (VII) and (VIII), and geranylacetone (IX). In all cases, in ether solution in presence of an equimolecular amount of BF_3 etherate at 0° we readily obtained esters of the corresponding unsaturated acids (X)—(XVIII), the yields and constants of which are given in the table. In some cases the esters of the polyenic acids were hydrolyzed to the corresponding acids. Reduction in the amount of boron trifluoride etherate led to reduced yields. When ferric chloride and zinc chloride were used as catalysts, the condensation did not go. Replacement of ether as solvent by tetrahydrofuran led to a reduction in the yields of the unsaturated esters. As a result of the mild reaction conditions, the original positions of the double bonds were preserved in the condensation products, which made it possible, for example, to prepare the ethyl esters of α-cyclocitrylidene- and α-dihydroionolidene-acetic acids with ease.

The above-described method for the synthesis of α, β-unsaturated acids was used by us for the preparation of some polyenic acids, including the acid of vitamin A. Thus, by the condensation of ethoxyacetylene with β-ionone (XIX) and β-ionolideneacetaldehyde (XX) in presence of born trifluoride etherate we obtained good yields of the ethyl esters of β-ionolideneacetic acid (XXI) and β-ionolidenecrotonic acid (XXII), the hydrolysis of which gave the corresponding cyrstalline acids. It is particularly important that the esters (XXI) and (XXII) formed in this reaction have normal structures, whereas in the Reformatskii reaction compounds of "retro" structure are formed preferentially.

Original carbonyl compound	yield (%)	Reaction product	Constants of products
$CH_3CH{=}CHCHO$ (I)	50	$CH_3CH{=}CHCH{=}CHCOOC_2H_5$ (X)	Ethyl ester: b.p. 69-70° (8 mm): n_D^{20} 1.4920: sorbic acid, yield 80%, m.p 133-135° [3]
$CH_3CH{=}CHCH{=}CHCOCH_3$ (II)	30	 $CH_3CH{=}CHCH{=}CH{-}\overset{CH_3}{\overset{\vert}{C}}{=}CHCOOC_2H_5$ (XI)	Ethyl ester: b.p. 71-72° (1 mm) n_D^{18} 1.5532: 3-methyl-2,4,6-octatrienoic acid, yield 72%, m.p. 159-160° [4]
 (III)	43	 (XII)	See Experimental
 (IV)	40	 (XIII)	
 (V)	40	 (XIV)	Ethyl ester: b.p 74-75° (0.25 mm) α-cyclocitrylideneacetic acid, yield 73%; b.p. 143-150° (1 mm): n_D^{25} 1.5080
 (VI)	67,5	 (XV)	Ethyl ester: b.p. 70-74° (0.07 mm): n_D^{19} 1.5015: β-cyclocitrylideneacetic acid, yield 86%, b.p. 105-107° [5]
 (VII)	76	 (XVI)	Ethyl ester: b.p. 131-133° (1 mm): n_D^{17} 1.4880 [6, 7]
 (VIII)	75	 (XVII)	Ethyl ester: b.p. 138-142° (1 mm): n_D^{16} 1 4930 [7]
 (IX)	70	 (XVIII)	Ethyl ester: b.p. 132-133° (1 mm): n_D^{16} 1.4820 [6]

Taking the condensation of β-ionone with ethoxyacetylene as our example we showed that the reaction is to a considerable extent stereospecific, for the β-ionolideneacetic ester (XXI) then formed gives on hydrolysis mainly the acid of m.p. 127-129°, which has the trans configuration at the double bond formed [8].



The reaction of ethoxyacetylene with the C_{18} ketone (XXIII) proceeds analogously. There is then formed the ethyl ester of the acid of vitamin A (XXIV), which, according to spectrographic data, does not contain the "retro" form. The ethyl ester of the acid of vitamin A, without isolation in the pure state, may be hydrolyzed directly to the acid of vitamin A, which is formed in about 70% yield, based on the original C_{18} ketone. Since the original C_{18} ketone is a mixture of cis and trans isomers, the crystalline acid of vitamin A (XXV) formed after the hydrolysis of the ester (XXIV) is not an individual geometric isomer. However, after its irradiation with ultraviolet radiation in presence of iodine and crystallization from ethanol we may isolate the acid of vitamin A of m.p. 178-179°, which consists entirely of trans isomer [8]. The ethyl ester of the acid of vitamin A (XXIV) may be readily reduced with $LiAlH_4$ to vitamin A [11].

EXPERIMENTAL*

Ethyl 7-Ethoxy-2,4,8-decatrienoate (XII). A solution of 4.9 g of 5-ethoxy-2,6-octadienal (III) in 5 ml of dry ether was cooled to -15° and stirred while simultaneous gradual addition was made of 4.2 g of BF_3 etherate and 2.1 g of ethoxyacetylene from two dropping funnels. The reaction mixture was then stirred for 15 minutes at room temperature, after which it was poured into 75 ml of 20% aqueous sodium acetate solution. The ether layer was washed with water and dried with magnesium sulfate.

After distillation we obtained 3 g (43%) of ethyl 7-ethoxy-2,4,8-decatrienoate; b.p. 89-94° (0.1 mm); n_D^{22} 1.5035; λ_{max} 261.5 mμ; ε 22450; λ_{max} 328 mμ; ε 3970.

Saponification of the ester (XII) by 10% caustic potash solution in methanol gave 7-ethoxydecatriene-2,4,8-carboxylic acid, b.p. 132-133° (0.4 mm); n_D^{25} 1.5230; λ_{max} 257 mμ; ε 3420. Found: C 68.37; 68.21; H 8.92; 8.61%. $C_{12}H_{18}O_3$. Calculated: C 68.6; H 8.58%.

Ethyl 7-Ethoxycitrylideneacetate (XIII). A solution of 3 g of 5-ethoxycitral (IV) in 3 ml of dry ether was cooled to -15° and stirred while simultaneous addition was made of 1.2 g of ethoxyacetylene and 2.4 g of BF_3 etherate. The reaction mixture was then treated as described above. Distillation gave 1.6 g (40%) of ethyl 7-ethoxycitrylideneacetate (XIII); b.p. 85-87° (0.06 mm); n_D^{20} 1.5000; λ_{max} 277.5 mμ; ε 17650.

On hydrolysis of the ester (XIII) with 10% methanolic potassium hydroxide we obtained 7-ethoxycitrylideneacetic acid; b.p. 124-125° (0.1 mm); $n_D^{23.5}$ 1.5190; λ_{max} 268.5 mμ; ε 18050. Found: C 70.20; 70.35; H 9.00; 9.12%. $C_{14}H_{22}O_3$. Calculated: C 70.6; H 9.24%.

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* The ultraviolet spectra of all compounds were determined in ethanol.

Ethyl β-Ionolideneacetate (XXI). To a solution of 70 g of β-ionone in 70 ml of dry ether we added, with stirring and cooling (bath temperature -5°), 51.6 g of boron trifluoride etherate in one portion; then, over a period of three hours, 28 g of ethoxyacetylene was added, in the course of which the temperature of the reaction mixture rose to 7°. When the ethoxyacetylene had been added, the reaction mixture was diluted with 70 ml of dry ether and heated at 35° for ten minutes; after being cooled, the reaction mixture was treated with 20% sodium acetate solution. The ether solution was washed with water and dried with magnesium sulfate; ether was distilled off, and the residue was vacuum-distilled: Fraction I (10 g), b.p. 82-116° (0.37 mm) and n_D^{20} 1.5130; Fraction II (58 g) b.p. 116-118° (0.25 mm) and n_D^{20} 1.5380; residue (15 g), a resin. Fraction II was ethyl β-ionolideneacetate (XXI); yield 61%; λ_{max} 298.5 mμ; ε 14420; λ_{max} 260 mμ; ε 11220.

β-Ionolideneacetic Acid. A mixture of 52 g of ethyl β-ionolideneacetate, 12.5 g of potassium hydroxide, and 125 ml of 90% ethanol was boiled for two hours. Alcohol was vacuum-distilled off, and the residue was dissolved in water. The aqueous solution was extracted with ether and acidified to Congo Red with dilute sulfuric acid. The β-ionolideneacetic acid that separated was extracted with ether. The ether solution was washed with water, dried, and evaporated. We obtained 43 g of a yellow crystalline residue, and by recrystallization of this from acetonitrile we isolated 17.3 g of trans-β-ionolideneacetic acid, m.p. 127-129°. The literature [8] gives m.p. 127-128°. When the mother liquor was cooled we isolated 12 g of a crystalline mixture of cis- and trans-β-ionolideneacetic acid, which, after two crystallizations from methanol, had m.p. 80-88°

Ethyl β-Ionolidenecrotonate (XXII). A solution of 6.2 g of β-ionolideneacetaldehyde (XX) in 25 ml of dry ether was cooled to -5°, and 4 g of BF_3 etherate in 4 ml of dry ether was added; then, gradually with stirring at 0° in a stream of nitrogen we added 2 g of ethoxyacetylene. After this addition the cooling bath was removed and the reaction mixture was brought, with stirring, to room temperature; it was given the usual treatment. After distillation we obtained: Fraction I (1.8 g), b.p. 115-140° (0.11 mm); and $n_D^{18.5}$ 1.5580; Fraction II (4 g). b.p. 140-145° (0.11 mm); and $n_D^{18.5}$ 1.5860. Fraction II was ethyl β-ionolidenecrotonate (XIII); λ_{max} 332 mμ; ε 26 600. Found C 78.62; 78.76; H 9.65; 9.40%. $C_{19}H_{28}O_2$. Calculated: C 79.12; H 9.78%.

9.6 g of the ester (XXII) was hydrolyzed with 10% methanolic potassium hydroxide (50 ml) at room temperature. After the usual treatment we obtained 7.6 g of the crude crystalline acid, from which, after recrystallization from acetone, we isolated 3.5 g of "trans"-β-ionolidenecrotonic acid; m.p. 157-159°; λ_{max} 327.5 mμ; ε 30 800. According to the literature [9] "trans"-β-ionolidenecrotonic acid has m.p. 154-156°; λ_{max} 323 mμ; ε 36 310. From the mother solution we isolated 2 g of an acid of m.p. 145-153°.

Acid of Vitamin A (XXV). The starting compound, the C_{18} ketone (XXIII) prepared by the condensation of β-ionolideneacetaldehyde with acetone [8], had: b.p. 123-127° (0.06 mm); n_D^{25} 1.6080; λ_{max} 343.5 mμ; ε 21400. To a solution of 12.9 g of the C_{18} ketone in 40 ml of dry ether, cooled to -5°, 6.45 ml of boron trifluoride etherate was added. The reaction mixture was then stirred for 30 minutes at 0° while 3.56 g of ethoxyacetylene was added in a stream of nitrogen. Stirring was continued at 0° for 30 minutes, and 20 ml of ether was then added; the mixture was stirred further for 30 minutes at room temperature. A solution of 34 g of sodium acetate in 110 ml of water was then added. The ethereal solution was washed with water, dried with anhydrous magnesium sulfate, and evaporated. To the residue* (16.3 g), which formed a thick red oil, we added 110 ml of a 2 N solution of sodium hydroxide in ethanol. The reaction mixture was heated at the boil for two hours and, after cooling, was poured into 1.5 liters of water. The aqueous solution was extracted twice with an isopentane-ether mixture and acidified with 2 N H_2SO_4; the acid that separated (XXV) was extracted with ether. The ether extract was washed with water, dried with anhydrous magnesium sulfate, and evaporated. The residue (13.35 g) was a yellowish-red greasy material. It was dissolved in ether, 5% aqueous potassium hydroxide was added, and the aqueous solution was extracted with a mixture of petroleum ether and hexane. On acidification of the aqueous layer with 2 N H_2SO_4 there separated a yellow precipitate of the acid of vitamin A, which was dissolved in ether, washed with water, and dried. Ether was distilled off, and we obtained 10.7 g of a crystalline acid (yield 71%, based on the C_{18} ketone). Recrystallization from methanol gave 4.6 g of a yellow substance containing orange flecks, m.p. 153-161° (λ_{max} 349 mμ; ε 38 000), which was a mixture of the isomer of the acid of vitamin A**.

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* The residue may be vacuum-distilled: The ester (XXIV) was then obtained as a thick yellow oil; b.p. 168-175° (0.35 mm); n_D^{25} 1.6115; λ_{max} 351 mμ; ε 29700. The literature [8] give: λ_{max} 353.5 mμ; ε 40 000.

** From the mother liquor on long standing there separated a little of an acid of m.p. 184-187° (λ_{max} 343 mμ; ε 26200), which was probably the 6-cis acid of vitamin A [10].

A solution of 1 g of the acid (m.p. 153-161°) in a mixture of 10 ml of benzene and 15 ml of ether containing 10 mg of iodine was irradiated at 25-26° with a mercury lamp for four hours. When the solution was cooled in a refrigerator there separated a precipitate (0.35 g) of m.p. 168-173°. After two recrystallizations from absolute ethanol we obtained the "trans" acid of vitamin A (XXV) in the form of tiny glistening lemon-yellow needles; m.p. 178-179°; λ_{max} 360 mμ; ε 41 400 (in heptane). According to the literature [10] this acid has: m.p. 179-180°; λ_{max} 350 mμ; ε 45200. From the mother solutions we isolated a mixture of the isomers of the acid of vitamin A, m.p. 152-167°.

In the determination of the ultraviolet spectrum of the acid of vitamin A in ethanol there was a shift in the absorption maximum from 353 to 334 mμ, depending on the quality of the ethanol used. This phenomenon has also been observed previously [10].

SUMMARY

1. The reaction of ethoxyacetylene with various unsaturated aldehydes and ketones in presence of boron trifluoride ether provides a simple and convenient method for the synthesis of esters of α, β-unsaturated acids.

2. This method was used for the preparation of esters of important polyenic isoprenoid acids: β-ionolideneacetic and β-ionolidenecrotonic acids, and also the acid of vitamin A.

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