UNSATURATED ACIDS AND MACROCYCLIC LACTONES

COMMUNICATION 8. SYNTHESIS OF ACETYLENIC KETO ACIDS

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Study of the structures of the macrolidic antibiotics methymycin, neomethymycin, narbomycin, and carbomycin has shown that in all these substances the macrocyclic lactone ring is built from unsaturated keto acids of the type R-CH=CHCO-[X]-COOH (I) (see the review [1]). In this connection it is interesting that even simple acids of the type CH_2=CHCO$(CH_2)_n$COOH are active antimicrobial compounds notable for their low toxicity, and that their methyl esters have antitumor activity [2, 3]. It is known also that the antibiotic capillin $CH_3C{\equiv}C\text{-}C{\equiv}CCOC_6H_5$ [4] and some other acetylenic ketones [5] have a powerful antifungal action, but the possibilities of using these substances are limited by their high toxicity. It was therefore of interest to synthesize acetylenic analogs of acids of type (I) and study their antimicrobic spectra. A method is described in the literature for the synthesis of acetylenic keto esters by the action of silver acetylides on the acid chlorides of the monoesters of adipic and suberic acids [6]

$$RC{\equiv}CAg + ClCO(CH_2)_nCOOEt \rightarrow RC{\equiv}CCO(CH_2)_nCOOEt \quad (n = 4,8).$$

However, this method gives good results only with derivatives of the higher dicarboxylic acids ($n \geq 4$). Hence, for the preparation of acetylenic keto acids of the type (II) for $n = 2$ and 3 we developed a new method of synthesis based on the condensation of acetylides with cyclic dicarboxylic anhydrides. Attempts to carry out this condensation with chloromagnesium and bromomagnesium derivatives of acetylenes were not successful, but it was carried out in satisfactory yield with the lithium acetylide in tetrahydrofuran.

$$RC{\equiv}CLi + CO\underset{\llcorner\!\!-O-\!\!\lrcorner}{(CH_2)_nCO} \rightarrow \underset{(II)}{RC{\equiv}CCO(CH_2)_nCOOH} \xrightarrow{CH_2N_2}$$

$$\rightarrow \underset{(III)}{RC{\equiv}CCO(CH_2)_nCOOMe} \xrightarrow{H_2,\,Pt} \underset{(IV)}{RCH_2CH_2CO(CH_2)_nCOOMe}$$

A side process that lowers the yield of the keto acids (II) is their further reaction with the lithium acetylide. To suppress this side reaction we carried out the condensation by adding the acetylide to the solution of the anhydride at between -5° and +30°. The optimum temperature varied from one case to another, depending on the structures of the reactants. The exact observance of the temperature schedule is of decisive importance because a departure of even a few degrees from the optimum temperature leads to a sharp reduction in the yield of acetylenic keto acids. In this way, starting with 1-hexyne, trans-3-methyl-4-hexen-1-yne [7], and 3-(tetrahydropyranyloxy)-1-butyne, we synthesized the acetylenic keto acids listed in the table.

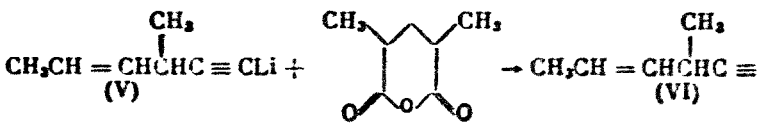
By the condensation of the lithium derivative of the enynic hydrocarbon (V) with meso-2,4-dimethylglutaric anhydride we synthesized trans-2,4 meso-7,8-trimethyl-5-oxo-9-undecen-6-ynoic (VI), the methyl ester of which, on

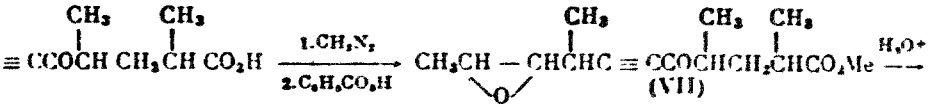
Acetylenic Keto Acids $RC{\equiv}CCO(CH_2)_nCOOH$

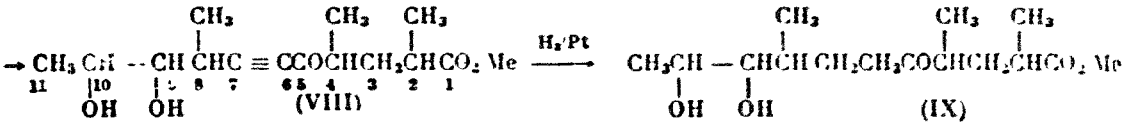
Acid	R	n	Yield (%)*
4-oxo-5-decynoic	n-C_4H_9	2	76
5-oxo-6-undecynoic	n-C_4H_9	3	72
trans-7-methyl-4-oxo-8-decen-5-ynoic	$CH_3CH{=}CHCH(CH_3)$	2	63
trans-8-methyl-5-oxo-9-undecen-6-	$CH_3CH{=}CHCH(CH_3)$	3	62
8-hydroxy-5-oxo-6-nonynoic (-ynoic	$CH_3CH(OH)$	3	61

* Based on the acetylenic derivative.

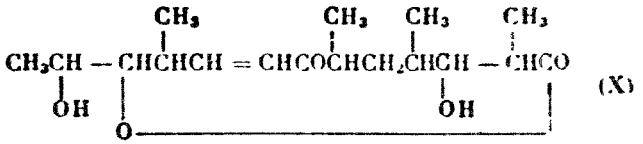
oxidation with peroxybenzoic acid, gave the acetylenic epoxy ester (VII). The hydration of this compound led to the acetylenic dihydroxy ester (VIII), which on hydrogenation gave methyl threo-9,10-dihydroxy-2,4(meso),8-trimethyl-5-oxoundecanoate (IX).







The acetylenic dihydroxy ester (VIII) forms a structural model of the C_3-C_{13} section of the neomethynolide molecule (X), the aglycon of the macrolidic antibiotic neomethymycin [8]



For neomethymycin it has been proved that the 4- and 6-methyl groups have an L,L-orientation [8]. Hence, the configuration of the C_2 and C_4 atoms in the dihydroxy keto ester (VIII) corresponds to the relative configuration of these asymmetric centers in the natural antibiotic. By the hydrogenation of the methyl esters of the acetylenic keto acids synthesized we obtained the corresponding saturated keto esters, and by the partial hydrogenation of methyl 4-oxo-5-undecynoate (III; R = n-C_4H_9, n = 3) in presence of Lindlar's catalyst we synthesized the corresponding ethylenic compound $C_4H_9CH{=}CHCO(CH_3)_2COOMe$ (XI).

The presence of an α,β-unsaturated ketone grouping in the acetylenic keto acids synthesized was confirmed by the ultraviolet spectra. The infrared spectra of their methyl esters contain bands for the triple bond and the two carbonyls (ester and ketonic). The structures of the acetylenic dihydroxy keto ester (VIII) and the enynic acid (VI) were proved by the formation of acetaldehyde in the oxidation of the dihydroxy keto ester (VIII) with periodic acid. When account is taken of the resemblance of the ultraviolet and infrared spectra of all the enynic keto esters that we synthesized and also of the fact that they were prepared under almost indentical conditions, these results can be regarded also as confirmation of the structure of the enynic keto acids [II; R = $CH_3CH=CHCH(CH_3)$, n = 2, 3].

Study of the antimicrobic spectrum* of the compounds that we synthesized showed that the methyl esters of the acetylenic keto acids (III, R = n-C_4H_9, n = 2, 3; III, R = $CH_3CH=CHCH(CH_3)$, n = 2, 3) scarcely affect the growth of bacteria, but are active antifungal substances in vitro they suppress pathogenic dermatophytes Microsporon Lanosum and Achorion schonleini at a concentration of 1-2 γ/ml and Trichophyton gypseum at a concentration of 6 γ/ml. The high antifungal activity of the unsaturated keto ester (III, R = n-C_4H_9, n = 3) depends on the presence of a conjugated acetylenic ketone grouping in its molecule, for its ethylenic analog (XI) is much less active, and the corresponding saturated keto ester does not suppress the growth of these kinds of fungi at all. The antifungal action of acetylenic keto esters (III) disappears on introduction of hydroxy groups into their molecules. Thus, the methyl esters of the acetylenic hydroxy acids (VIII) and (III, R = $CH_3CH(OH)$, n = 3) have scarcely any antifungal action. However, the latter compound has appreciable amebicidal activity and suppresses the growth of Endamoeba histolytica at a concentration of 7-8 γ/ml†. In view of data on the antitumor activity of keto esters of the type $CH_2{=}CHCO(CH_2)_n$-

*The antimicrobic spectrum of the acetylenic keto acids and their esters was investigated by I. D. Ryabova (Biological Testing Laboratory, Institute for the Chemistry of Natural Products, Academy of Sciences, USSR. Director, G. L. Zhdanov). The details of this investigation will be published in a separate paper.

†The data were obtained by N. A. Novitskaya (Chemotherapy Laboratory, Ordzhonikidze All-Union Pharmaceutical Chemistry Research Institute. Director, G. N. Pershin).

COOR [2, 3], it was of interest to study the antitumor activity of the acetylenic keto esters that we had prepared. In tests on two strains of transplanted dense tumors of mice (sarcoma 37 and Crocker sarcoma S-180), the acetylenic keto esters (III; R = n-C_4H_9, n = 2, 3) were found to be devoid of cancerolytic activity on repeated injection in the greatest endurable doses*. In intravenous injection the acetylenic keto esters (III, R = n-C_4H_9, n = 2, 3) were found to be of low toxicity to mice (LD_{50} 230 and 300 mg/kg, respectively), and the hydroxy keto ester [III; R = CH_2CH_2OH), n = 3] was nontoxic for an injection of 1 g/kg.

EXPERIMENTAL

Ultraviolet spectra were determined in alcohol with an SF-4 spectrophotometer; infrared spectra were determined in mineral oil with an IKS-14 spectrograph†. Melting points (uncorrected) were determined in capillaries. Thin-layer chromatography on silica gel was carried out by the procedure described in [3]. For paper chromatography we used "Leningrad B" paper. For development we used a 1% solution of potassium permanganate in 1 N sulfuric acid.

4-Oxo-5-decynoic Acid (II, R = n-C_4H_9, n = 2). An ethereal solution of 1-hexynyllithium (prepared from 2.46 g of lithium, 23.1 g of bromobenzene, and 10.1 g of 1-hexyne in 120 ml of ether) was added dropwise with stirring and cooling with ice and salt to a solution of 14.8 g of succinic anhydride in 150 ml of dry tetrahydrofuran. The addition of the 1-hexynyllithium was carried out at such a rate that the temperature of the reaction mixture did not exceed 10°; this required about two hours. The mixture was stirred further for one hour at 10°, left overnight, and boiled for three hours. It was cooled with ice, 40 ml of moist ether and then 40 ml of water were added, and the mixture was acidified with 5% sulfuric acid. The upper layer was separated, and the lower layer was saturated with ammonium sulfate and extracted with ether (four portions of 50 ml). The combined ether-tetrahydrofuran extract was carefully washed with four 75-ml portions of 5% potassium hydroxide solution. The alkaline extract was acidified to pH 1 with sulfuric acid and extracted with ether, the ether extract was dried with magnesium sulfate. Ether was vacuum-distilled off, benzene was added to the residue (20.7 g), and the succinic acid crystals precipitated were filtered off (0.55 g, m.p. 180°). The dark-yellow filtrate was decolorized by passage through 21 g of neutral activated charcoal and vacuum-evaporated. Part of the acidic substance obtained (8.2 g) was dissolved in 30 ml of benzene and chromatographed on a column (34×980 mm) filled with 300 g of silica gel. Elution with 200 ml of benzene gave a mixture of unidentified substances. By elution with 300 ml of a 5 : 1 mixture of benzene and ether we isolated 5.4 g of 4-oxo-5-decynoic acid as a light-yellow oil, homogeneous according to paper chromatography (R_f 0.83 in chloroform saturated with water and R_f 0.76 in 2 : 1 hexane-benzene) and to chromatography on plates carrying a layer of silica gel (R_f 0.81 in ether). λ_{max} 220 mμ (log ε 3.786). Found C 65.73%, H 7.46%. $C_{10}H_{14}O_3$. Calculated C 65.91%, H 7.60%.

The semicarbazone of 4-oxo-5-decynoic acid melted at 175-176° (from 50% alcohol): λ_{max} 260 mμ (log ε 4.183). Found C 55.22%, H 7.01%. $C_{11}H_{17}O_3N_3$. Calculated C 55.20%, H 7.16%.

By treating 1.51 g of 4-oxo-5-decynoic acid with excess of ethereal diazomethane we obtained its methyl ester (1.36 g, 84%) as a yellow liquid, n_D^{20} 1.4666, λ_{max} 220 mμ (log ε 3.826), ν_{max} (cm^{-1}) 2221 (C≡C), 1746 (CO_2Me), 1681 (conjugated carbonyl). R_f 0.67 (on a plate carrying an unbound layer of alumina in the system 1 : 9 ether-benzene).

0.31 g of methyl 4-oxo-5-decynoate was hydrogenated in 10 ml of 95% alcohol over 21 mg of platinum black (22°, 748 mm). In the course of 20 minutes 80 ml of hydrogen was absorbed (the theoretical volume was 73 ml). Catalyst was then filtered off, alcohol was distilled off, and from the oily residue we prepared the 2,4-dinitrophenylhydrazone of methyl 4-oxodecanoate, m.p. 65-66° (from alcohol). Found C 53.82%, H 6.31%. $C_{17}H_{24}O_6N_4$. Calculated C 53.68%; H 6.31%.

Hydrogenation of methyl 4-oxo-5-decynoate (3 g) over Lindlar's catalyst in ethyl acetate did not proceed selectively and did not stop, but merely slowed down somewhat after the absorption of the first molecular proportion of hydrogen. On chromatography of the resulting mixture of saturated and unsaturated esters in benzene on neutral alumina (Grade II activity) with a mixture of ether and benzene (1 : 1), 1.9 g of methyl 4-oxo-5-decenoate (XI) was

* The tests were carried out by I. B. Sorokina (Biological Testing Laboratory, Institute for the Chemistry of Natural Products, Academy of Sciences, USSR).

† Infrared spectra were determined by S. L. Portnova (Physicochemical Testing Laboratory, Institute for the Chemistry of Natural Products, Academy of Sciences, USSR. Director Yu. N. Sheikner).

eluted as a colorless oil, λ_{max} 228 mμ (log ε 3.877), R_f 0.73 on a plate carrying an unbound layer of alumina in the system 1:9 ether-benzene; R_f 0.68 on paper in 30% aqueous methanol saturated with kerosene. The 2,4-dinitrophenylhydrazone of the ethylenic keto ester (XI) melted at 232-234° (from alcohol). Found: C 53.88%, H 5.62%. $C_{17}H_{22}O_6N_4$. Calculated: C 53.96%; H 5.86%.

5-Oxo-6-undecynoic Acid (II, R = n-C_4H_9, n = 3). Under the conditions used for the synthesis of 4-oxo-5-decynoic acid, from 6.15 g of 1-hexyne and 3.42 g of glutaric anhydride we obtained an ethereal solution of acidic reaction products, which was washed with four 50-ml portions of water to remove glutaric acid (from the wash waters after evaporation we isolated 1.9 g of glutaric acid). The washed ethereal extract was dried with magnesium sulfate, and ether was vacuum-distilled off. By chromatography of the residue (9.4 g) under the above stated conditions we obtained 5.1 g of 5-oxo-6-undecynoic acid as a light-yellow viscous liquid, homogeneous according to chromatography on paper in the system hexane-benzene-ether (5:2:1) (R_f 0.83) or benzene saturated with water (R_f 0.91), λ_{max} 221 mμ (log ε 3.792). Found: C 66.92%, H 8.17%. $C_{11}H_{16}O_3$. Calculated: C 67.33%; H 8.22%.

The semicarbazone of 5-oxo-6-undecynoic acid melted at 110-112° (from 10% aqueous methanol), λ_{max} 262 mμ (log ε 4.174). Found: C 56.70%; H 7.54%. $C_{12}H_{19}O_3N_3$. Calculated: C 56.91%, H 7.45%.

By the methylation of 5-oxo-6-undecynoic acid with diazomethane we obtained its methyl ester as a light-yellow oil (n_D^{20} 1.4681), homogeneous according to chromatography on a plate carrying silica gel in the system 10:1 benzene-ether (R_f 0.63) or on paper in 30% methanol saturated with kerosene (R_f 0.60), λ_{max} 221 mμ (log ε 3.800), ν_{max} (cm^{-1}): 2210 (C≡C), 1744 (CO_2Me), 1680 (conjugated carbonyl). Found: C 68.62%; H 8.52%. $C_{12}H_{18}O_3$. Calculated: C 68.54%; H 8.63%.

0.2 g of methyl 5-oxo-6-undecynoate was hydrogenated in 95% alcohol over 15 mg of platinum black under the above stated conditions. From the hydrogenation product we prepared the 2,4-dinitrophenylhydrazone of methyl 5-oxoundecanoate, m.p. 66-67° (from alcohol). Found: C 54.43%, H 6.44%. $C_{18}H_{26}O_6N_4$. Calculated: C 54.82%; H 6.59%.

3-(Tetrahydropyranyloxy)-1-butyne. To a solution of 7.0 g of 3-butyn-2-ol and 9 g (0.1 mole + 10% excess) of dihydropyran in 40 ml of dry chloroform we added three drops of phosphoryl chloride, and the mixture, which had become dark in color, was left for one day at room temperature, shaken with saturated sodium bicarbonate solution, and dried with potassium carbonate. Solvent was driven off and vacuum-distillation of the residue gave 11.1 g (72%) of 3-(tetrahydropyranyloxy)-1-butyne, b.p. 84-86° (10 mm), n_D^{20} 1.4490, d_4^{20} 0.9646. Found: C 70.36%, H 9.02%, MR 42.87. $C_9H_{14}O_2$. Calculated: C 70.10%, H 9.15%, MR 42.85.

Methyl 8-Hydroxy-5-oxo-6-nonynoate (III, R = $CH_3CH(OH)$, n = 3). A solution of 10.4 g of bromobenzene in 25 ml of dry ether was added with stirring over a period of 30 minutes to 1.1 g of lithium in 40 ml of dry tetrahydrofuran. The mixture was boiled for one hour and then cooled to room temperature. A solution of 10.25 g of 3-(tetrahydropyranyloxy)-1-butyne in 70 ml of dry ether was added over a period of 30 minutes, and the mixture was boiled for 30 minutes. The resulting solution of the lithium derivative was added with stirring to a solution of 8.35 g of glutaric anhydride in 40 ml of dry tetrahydrofuran at such a rate that the temperature of the reaction mixture did not exceed 28-30°, this required about two hours. The mixture was stirred further for two hours at room temperature and left overnight. It was cooled to 0°, and 40 ml of moist ether was added, the mixture was acidified to pH 1 with 5% sulfuric acid and then diluted with alcohol until a homogeneous solution was formed, this was stirred for 12 hours at 40°. The solution was cooled, and ether was added, the aqueous layer was separated and extracted with two 50-ml portions of ether. The combined ether extracts were shaken with 100 ml of 50% potassium hydroxide solution, and the alkaline solution was carefully acidified with sulfuric acid and extracted with five 50-ml portions of ether. The extract was dried with magnesium sulfate and solvent was vacuum-distilled off, we then obtained 8.8 g of acidic substances, which were methylated with ethereal diazomethane at room temperature. 2 g of the unpurified methyl ester in 10 ml of benzene was chromatographed on a column (24 × 80 mm) filled with 150 g of neutral alumina (Grade II activity). 1 g of methyl 8-hydroxy-5-oxo-6-nonynoate was eluted with a 4:1 mixture of petroleum ether and ethyl acetate as a yellow oil, R_f 0.83 (on paper in t-butyl alcohol saturated with water), λ_{max} 210 mμ (log ε 3.802), ν_{max} (cm^{-1}): 3601 (OH), 2221 (C≡C), 1734 (CO_2Me), 1682 (conjugated carbonyl).

0.3 g of methyl 8-hydroxy-5-oxo-6-nonynoate was hydrogenated, as indicated above, over 15 mg of platinum black until 108 ml of hydrogen had been absorbed (theoretical volume 98 ml). From the hydrogenation product we prepared the 2,4-dinitrophenylhydrazone of methyl 8-hydroxy-5-oxononanoate, m.p. 115-116° (from alcohol). Found: C 50.54%; H 4.63%. $C_{16}H_{18}O_7N_4$. Calculated: C 50.79%, H 4.80%.

trans-7-Methyl-4-oxo-8-decen-5-ynoic Acid (II; R = $CH_3CH=CHCH(CH_3)$, n = 2). A solution of 15 g of trans-3-methyl-4-hexen-1-yne [7] in 30 ml of dry ether was added to a solution of phenyllithium (from 2.4 g of lithium and 25.1 g of bromobenzene) in 80 ml of dry ether, and the mixture was boiled for one hour. The resulting solution of 3-methyl-4-hexen-1-ynyllithium was added over a period of 90 minutes at 0° to a solution of 16 g of succinic anhydride in 150 ml of dry tetrahydrofuran. The mixture was then stirred further for one hour at 0° and left overnight. It was cooled with ice and, after the addition of 40 ml of moist ether and 50 ml of water, it was acidified with 5% sulfuric acid. The upper layer was separated, and the lower layer was saturated with ammonium sulfate and extracted with four 50-ml portions of ether. The combined ether-tetrahydrofuran extract was washed with four 100-ml portions of saturated sodium bicarbonate solution, and, after acidification to pH 1 with 20% sulfuric acid, the aqueous extract was extracted with five 75-ml portions of ether; the ether extract was dried with magnesium sulfate. After the separation of succinic acid (1.5 g) as indicated above, part of the product (5 g) was dissolved in 20 ml of benzene and chromatographed on a column (34×980 mm) filled with 350 g of silica gel. With a 10 : 1 mixture of benzene and ether 3.8 g of trans-7-methyl-4-oxo-8-decen-5-ynoic acid was eluted as a light-yellow oil. R_f 0.80 on a plate with a bound layer of silica gel in 2 : 1 benzene-ether. The 2,4-dinitrophenylhydrazone of the acid melted at 158-160°. Found: C 54.37%; H 5.01%. $C_{17}H_{18}O_6N_4$. Calculated: C 54.54%; H 4.85%.

2 g of the acid was treated at room temperature with excess of ethereal diazomethane, and the oil obtained (1.85 g) was dissolved in 10 ml of benzene and chromatographed on a column (24×180 mm) filled with 150 g of neutral alumina. With a 5 : 1 mixture of benzene and ether 1.4 g of methyl trans-7-methyl-4-oxo-8-decen-5-ynoate was eluted as a pale-yellow oil. n_D^{20} 1.4994. λ_{max} 272 mμ (log ε 3.887); ν_{max} (cm^{-1}) 2125 (C≡C), 1734 (CO_2Me), 1680 (conjugated carbonyl). The substance was homogeneous according to chromatography on a plate carrying an unbound layer of alumina in the system 4 : 1 ether-benzene (R_f 0.75) and on paper impregnated in kerosene in a system of heptane saturated with methanol (R_f 0.80). Found: C 68.13%; H 7.58%. $C_{12}H_{16}O_3$. Calculated: C 68.26%; H 7.69%.

trans-8-Methyl-5-oxo-9-undecen-6-ynoic Acid (II, R = $CH_3CH=CHCH(CH_3)$, n = 3). Under the above stated conditions from 7.5 g of trans-3-methyl-4-hexen-1-yne [7] and 10 g of glutaric anhydride we obtained an ethereal solution of acidic reaction products, which, to remove glutaric acid, were washed with four 50-ml portions of water (from the wash waters, after evaporation, we isolated 1.2 g of glutaric acid). The washed ether extract was dried with magnesium sulfate and ether was vacuum-distilled off. By chromatography of the residue (12.2 g) as indicated above on 400 g of silica gel we obtained 10.4 g of trans-8-methyl-5-oxo-9-undecen-6-ynoic acid as a viscous liquid having R_f 0.83 (on a plate carrying a bound layer of silica gel in 3 : 1 benzene-ether). The 2,4-dinitrophenylhydrazone of this acid, after crystallization from a mixture of alcohol and ethyl acetate, melted at 153-154°. Found: C 55.42%; H 5.07%. $C_{18}H_{20}O_6N_4$. Calculated: C 55.66%; H 5.19%.

Methyl trans-8-methyl-5-oxo-9-undecen-6-ynoate was obtained, after chromatography on neutral alumina (elution with 4 : 1 benzene-ether) as a pale-yellow oil. n_D^{20} 1.4898. R_f 0.70 (on a plate carrying an unbound layer of alumina in 10 : 1 benzene-ether) and 0.85 (on paper impregnated in kerosene, in hexane saturated with methanol). λ_{max} 270 mμ (log ε 3.844). ν_{max} (cm^{-1}) 2225 (C≡C), 1739 (CO_2Me), 1636 (conjugated carbonyl). Found: C 69.97%; H 8.34%. $C_{13}H_{18}O_3$. Calculated: C 70.27%; H 8.10%.

trans-2,4,8-Trimethyl-5-oxo-9-undecen-6-ynoic Acid (VI). Under the conditions of the preceding experiment from 10 g of trans-3-methyl-4-hexen-1-yne [7] and 15.1 g of meso-2,4-dimethylglutaric anhydride we obtained 7 g of trans-2,4,8-trimethyl-5-oxo-9-undecen-6-ynoic acid as a yellow oil. R_f 0.75 (on a plate carrying a bound layer of silica gel in 2 : 1 benzene-ether). After being crystallized from a mixture of alcohol and ethyl acetate the 2,4-dinitrophenylhydrazone of this keto acid had m.p. 160-162° (decomp.). Found: C 57.51%; H 5.61%. $C_{20}H_{24}O_6N_4$. Calculated: C 57.68%; H 5.81%.

The methyl ester of the keto acid (VI), after being purified in a column (72×1440 mm) filled with 500 g of neutral alumina (elution with 4 : 1 benzene-ether), consisted of an oil having R_f 0.75 (on a plate carrying an unbound layer of alumina in 10 : 1 benzene-ether) and R_f 0.80 (on paper impregnated with kerosene, in hexane saturated with methanol). λ_{max} 271 mμ (log ε 3.875). ν_{max} (cm^{-1}) 2228 (C≡C), 1741 (CO_2Me), 1676 (conjugated carbonyl).

Methyl 9-10-Dihydroxy-2,4,8-trimethyl-5-oxo-6-undecynoate (VIII). A solution of 3 g of peroxybenzoic acid in 30 ml of dry chloroform was added to a solution of 5 g of the methyl ester of the keto acid (VI) in 15 ml of chloroform with water-cooling of the reaction mixture so that its temperature did not exceed 25-30°. After 60 hours (when, according to titration results, only excess of peroxybenzoic acid remained in the solution) the mixture was washed several times with 10% sodium bicarbonate solution and then with water, it was dried with magnesium sulfate. The un-

purified methyl 9,10-epoxy-2,4,8-trimethyl-5-oxo-6-undecynoate (VII) [4.8 g; ν_{max} (cm^{-1}). 2238 (C≡C), 1744 (CO_2Me), 1634 (conjugated carbonyl), 1224 (epoxy group)] was heated with 1% sulfuric acid at 55-60° for three hours (in the course of which the mixture became homogeneous). The mixture was cooled, neutralized with dry sodium bicarbonate, and extracted with six 75-ml portions of ether. The combined ether extracts were dried with magnesium sulfate, and ether was distilled off. The residue (4 g) was dissolved in 5 ml of ethyl acetate and chromatographed on silica gel (300 g). With a 9 : 1 mixture of petroleum ether and ethyl acetate 2 g of methyl 9,10-dihydroxy-2,4,8-trimethyl-5-oxo-6-undecynoate (VIII) was eluted as a yellow oil. R_f 0.58 (on a plate carrying a bound layer of silica gel in 9 : 1 petroleum ether and ethyl acetate); ν_{max} (cm^{-1}). 3413 (OH), 2208 (C≡C), 1729 (CO_2Me), 1682 conjugated carbonyl). After being crystallized from a mixture of alcohol and ethyl acetate the 2,4-dinitrophenylhydrazone of (VIII) melted at 171-173°. Found C 54.14; H 6.39%. $C_{21}H_{30}O_8N_4$. Calculated C 54.30%; H 6.08%.

By the hydrogenation of 0.28 g of the keto ester over 10 mg of platinum black in alcohol we obtained methyl 9,10-dihydroxy-2,4,8-trimethyl-5-oxoundecanoate (0.25 g); 3,5-dinitrobenzoate, m.p. 175-177° (from alcohol). Found: C 51.93%; H 4.53%. $C_{29}H_{34}O_{15}N_4$. Calculated. C 51.47%; H 4.73%.

Oxidation of the Dihydroxy Keto Ester (VIII) with Sodium Periodate. A solution of 0.43 g of sodium periodate in 10 ml of water was added with stirring over a period of ten minutes to a solution of 0.568 g of the ester (VIII) in 5 ml of 95% alcohol. Stirring was continued for 20 minutes at room temperature. The mixture was filtered, and excess of an alcoholic solution of 2,4-dinitrophenylhydrazine sulfate was added to the filtrate. According to the results of paper chromatography (system heptane saturated with methanol) in presence of reference compounds, the crystalline precipitate contained the 2,4-dinitrophenylhydrazone of acetaldehyde (R_f 0.18) and did not contain the 2,4-dinitrophenylhydrazone of propionaldehyde.

SUMMARY

1. A description is given of a synthesis of acetylenic keto acids of the type RC≡CCO-[X]-COOH, based on the condensation of lithium acetylides with cyclic dicarboxylic anhydrides.

2. By this method acetylenic keto esters having low toxicity and considerable antifungal activity were prepared.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
