THE CHEMISTRY OF POLYENE AND POLYACETYLENE COMPOUNDS

COMMUNICATION 3*. γ -HYDROXYACETYLENIC CARBOXYLIC AND VINYLACETYLENECARBOXYLIC ACIDS AND SOME OF THEIR CONVERSIONS

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As has been shown [2,3], acetylenic alcohols can be used successfully for the synthesis of various γ -hydroxyacetylenic carboxylic acids, which are interesting starting materials for the production of a number of unsaturated oxygencontaining compounds. In order to find new routes for the synthesis of such systems, we have systematically studied the reaction of magnesium halide derivatives of a series of readily accessible acetylenic alcohols [4] and vinylacetylenes with carbon dioxide. It has been found that the reaction of lotsich's complexes obtained from dimethyl, methyl ethyl, cyclopentyl, and cyclohexyl ethinyl carbinols, dehydrolinalool, isopropenylacetylene, and ethinylcyclohexene with CO₂ under pressure leads to good yields of the corresponding γ -hydroxyacetylenic carboxylic (I)-(V) and vinylacetylenecarboxylic (VI), (VII) acids, esterification of which readily gives the methyl esters corresponding to them

As has been shown earlier [5], the selective hydrogenation of γ -hydroxyacetylenic acids (as a result of the cisaddition of hydrogen) inevitably leads to unsaturated γ -lactones, which considerably narrows the synthetic possibilities of the initial acetylenic acids. In order to find routes for the synthesis of trans-addition products, we have made a detailed study of the reaction of esters of some γ -hydroxyacetylenic carboxylic acids with sodium phenoxide, which, in the case of β -(1-hydroxycyclohexyl)-propiolic acid leads to a mixture of cis- and trans-products of addition to the acetylenic bond [3]. We have found that the reaction of sodium phenoxide with the methyl esters of 4-methyl-4-hydroxypent-2-ynoic acid (VIII), 4-methyl-4-hydroxyhex-2-ynoic acid (IX), and β -(1-hydroxycyclopentyl)-propiolic (X) acids gives a 70% yield of a mixture of reaction products, containing about 50% of the corresponding β -phenoxy derivatives of trans-acrylic esters (XI)-(XIII) and 15% of the phenoxylactones (XIV)-(XVI) corresponding to cis-addition. Separation of this mixture can be accomplished relatively simply by crystallization and high-vacuum distillation



[•] Preceding communication of this series, see [1].



The phenoxy group in the esters (XI)-(XIII) is fairly stable in an alkaline medium, and on saponification in aqueous-alcoholic alkali at room temperature the corresponding substituted trans-acrylic acids (XVII)-(XIX) have been obtained. However, acid hydrolysis readily leads to saponification of the phenoxy group and under these conditions the trans-acid (XVII) gives 5,5-dimethyltetronic acid (XX). The same acid is formed by saponification of the lactone (XIV), which is a direct proof of the structure of both series of compounds



Dehydration of the ester of the trans-acid (XI) using phosphoryl chloride readily yields the ester of 3-methyl-2phenoxybutadiene-1-carboxylic acid (XXI) which is also formed by the direct addition of phenol to the ester of isopropenylpropiolic acid (XXII). Alkaline saponification then gave a good yield of the 3-methyl-2-phenoxybutadiene-1-carboxylic acid (XXIII) itself. The presence of the diene system in the ester (XXI) was shown by the UV spectrum and the reaction with maleic anhydride, which forms the adduct (XXIV), which on saponification with water gives the corresponding acid (XXV).

The most highly selective trans-addition of phenol takes place in the case of the ester of cyclohexenylpropiolic acid (XXVI), and the corresponding β -phenoxydienic ester (XXVII) is formed with a yield of 85%; when it is saponified with aqueous-alcoholic alkali, the dienic acid (XXVIII) is readily formed, but this does not give an adduct with maleic anhydride.

The addition of water to the triple bond of the acetylenic acids was studied on the basis of the ester of β -(1-hydroxycyclohexyl)-propiolic acid (XXIX). However, in this case, only the lactone (XXX) was formed, with a yield of 40%; this was also formed in an attempt to cyclize trans- β -phenoxy- β -(1-hydroxycyclohexyl)-acrylic acid (XXXI) to form a chromanone system.



General method of the synthesis of γ -hydroxyacetylenic and vinylacetylenic carboxylic acids. Dry benzene (400 ml) was added to the Grignard reagent obtained from 2 moles of magnesium and 2 moles of ethyl bromide in 800 ml of absolute ether, and 1 mole of tertiary acetylenic alcohol or 2 moles of the corresponding vinylacetylene derivative was added to this mixture at 4-6° with vigorous stirring over 3-4 hours. The reaction mixture was stirred for 2 hours and transferred to a dry steel reactor fitted with a stirrer, which had been cooled to 4-5°, and was slowly (over 3-4 hours) saturated with dry carbon dioxide to a pressure of 30-40 atm. with stirring. After decomposing the complex with a slight excess of 20% sulfuric acid, the reaction product was extracted with ether and dried with Mg₂SO₄, the ether was distilled off, and the crystalline acids obtained were filtered off and washed with petroleum ether or n-hexane. In those cases where the acids obtained were not isolated in the crystalline state, the reaction product was neutralized with saturated sodium carbonate solution, the neutral product was extracted with ether, and the aqueous solution was acidified with 2 N sulfuric acid. After extraction with ether and distillation of the ether, the residual acid either crystallized or was converted into its methyl ester (by heating with a mixture of benzene and methanol in the presence of a small amount of sulfuric acid), which was then distilled in a high vacuum.

<u>3-Methyl-3-hydroxypent-1-ynecarboxylic acid (II) and its methyl ester (IX)</u>. Ninety-eight grams of methyl ethyl ethinyl carbinol [4], by the above-described method, yielded 108 g of acid in the form of an oil which partially crystallized. Crystallization from a mixture of benzene and petroleum ether (1:3) yielded 57 g of the crystalline acid (II) which, after vacuum sublimation, melted at 57°, which corresponds to data in the literature [6]. The residual liquid reaction product, consisting mainly of the same acid, was converted without further purification into the ester and after conventional working up and vacuum distillation yielded 40.5 g of the methyl ester (IX) with b.p. 60-62° (0.07 mm); $n_D^{18.5}$ 1.4612. Found: C 60.73, 60.89; H 7.60, 7.54%. C₈H₁₂O₃. Calculated: C 60.52; H 7.75%.

The methyl ester of 3-methyl-3-hydroxypent-1-ynecarboxylic acid (IX) obtained from the pure acid (II) had b. p. 58-59.5° (0.02 mm); n_D^{20} 1.4605.

<u>B-(1-Hydroxycyclopentyl)-propiolic acid (III) and its methyl ester (X)</u>. By the method described above, 55 g of ethinylcyclopentanol yielded 46 g of the acid (III) in the form of a viscous dark oil; purification via the sodium salt yielded 21 g of the acid (III) with m.p. 107-108.5° (from a mixture of benzene and petroleum ether). Found: C 62.12, 61.96; H 6.73, 6.88%. C₈H₁₀O₃. Calculated: C 62.32; H 6.54%.

To obtain the methyl ester, 29.5 g of the acid (III) was boiled in solution in methanol and benzene for 30 hours in the presence of sulfuric acid and, after conventional working up and vacuum distillation, this gave 21 g (a 70% yield) of the ester of β -(1-hydroxycyclopentyl)-propiolic acid (X) with b.p. 75° (0.05 mm); n_D^{19} 1.4919. Found: C 64.40, 64.68; H 7.31, 7.43%. C₉H₁₂O₃. Calculated: C 64.27; H 7.19%.

Cyclohexenylpropiolic acid (VII) and its methyl ester (XXIV). By the method described above, 100 g of ethinylcyclohexene [7] [b.p. 52-54° (30 mm); n_D^{25} 1.4934] gave 60 g (a 42% yield) of the acid (VII) with m.p. 66-67° (from a mixture of benzene and petroleum ether) and 28 g of an oil which was converted without purification into the methyl ester. This gave 18 g of the ester of cyclohexenylpropionic acid (XXVI) with b.p. 52-55° (0.03 mm); n_D^{21} 1.5192. Found: C 73.43, 73.49; H 7.29, 7.25%. C₁₀H₁₂O₂. Calculated: C 73.14; H 7.37%.

<u>3,7-Dimethyl-3-hydroxyoct-6-enynecarboxylic acid (V)</u>. From 152 g of dehydrolinalool, 108 g of the acid (V) was obtained in the form of a dark oil which could not be crystallized even after purification through the sodium salt. Esterification of 24 g of this acid by the method described above and vacuum-distillation of the reaction product yielded 6.7 g of a substance with b.p. 39-46° (0.03 mm) (bath temperature 53-55°); n_D^{20} 1.4692, which, from the results of elementary analysis, was the methyl ester of the acid (V). Found: C 68.3, 68.25; H 8.67, 8.88%. C₁₂H₁₈O₃. Calculated: C 68.54; H 8.63%.

In addition to this product, distillation gave 2.9 g of a substance with b.p. 57-59° (0.015 mm) (bath temperature 95°); n_D^{20} 1.4840, which was not investigated more closely. 3-Methyl-3-hydroxybutynecarboxylic acid (I), β -(1-hydroxycyclohexyl)-propiolic acid (IV) and isopropenylpropiolic acid (VI), and their methyl esters, the constants of which correspond to data in the literature [2, 3, 8] were obtained by the method described above.

Addition of phenol to the methyl ester of 4-methyl-4-hydroxypent-2-ynoic acid (VIII). Ten grams of the methyl ester (VIII) was added to a solution of sodium phenoxide in phenol obtained from 26 g of phenol and 0.6 g of sodium and heated to 90°, whereupon the temperature of the reaction mixture rose to 112°. The reaction product was kept at 20° for 2 hours and was then dissolved in ether and carefully washed with 4 N caustic soda solution, and the ethereal solution was dried with magnesium sulfate. After the ether had been distilled off, the residue partially crystallized; it was filtered off from the oil and washed with n-hexane. This gave 3.5 g (22.5%) of the methyl ester of trans-4-methyl-4-hydroxy-3-phenoxypent-2-enoic acid (XI) with m.p. 58-59° (from n-hexane). Found: C 66.40, 66.51; H 6.85, 6.98%. C₁₃H₁₆O₄. Calculated: C 66.08; H 6.83%. The filtrate after the removal of the ester of the hydroxy acid (XI) and the mother liquors from its crystallization were combined and the solvent was distilled off, and the residue (7.6 g) was saponified with a solution of 5 g of caustic soda in 70 ml of 50% aqueous methol at room temperature (48 hours). The methanol was distilled off in vacuum and the aqueous solution was acidified with 2 N sulfuric acid and extracted with ether; the ethereal solution was carefully washed with saturated sodium bicarbonate solution to remove acidic products and dried with magnesium sulfate. After evaporating off the ether, the residue was distilled in a vacuum of 4×10^{-3} mm at 80-85° (bath temperature 105-110°) to yield 3.6 g (24.6%) of the lactone (XIV); n_D^{20} 1.5222, which crystallized on standing; λ_{max} 215.5 m μ ; log ϵ 4.011 (heptane). Found: C 69.98, 70.13; H 5.69, 5.80%. C₁₂H₁₂O₃. Calculated: C 70.57; H 5.92%.

The alkaline solution after isolation of the lactone (XIV) was acidified with 2 N sulfuric acid and extracted with ether and the extract was dried with magnesium sulfate. After removal of the ether, 3.97 g (21.5%) of trans-4-methyl-4-hydroxy-3-phenoxypent-2-enoic acid (XVII) with m.p. 157° (from aqueous ethanol) was obtained. Found: C 64.55, 64.60; H 6.58, 6.47%. C₁₂H₁₄O₃. Calculated: C 64.45; H 6.35%.

The same acid was obtained with a yield of 75% by saponification of the pure trans-ester (XI) with aqueous-alcoholic alkali at room temperature using a solution of 0.5 g of caustic soda in 7 ml of 50% aqueous methanol at 20° for 48 hours.

<u>Hydrolysis of the trans-acid (XVII) and the lactone (XIV).</u> a) A solution of 1 g of the acid (XVII) in a mixture of 10 ml of methanol and 10 ml of concentrated hydrochloric acid was boiled for 2 hours. The reaction product was diluted with water and extracted with ether, and the ethereal solution was washed with saturated sodium carbonate solution. Acidification of the alkaline solution yielded 0.3 g of 5,5-dimethyltetronic acid (XX) with m.p. 147° (from a mixture of ethyl acetate and petroleum ether), which gave no depression of the melting point in admixture with an authentic sample. b) One gram of the lactone (XIV) was heated at 70-80° with 1.5 ml of methanol and 1 drop of sulfuric acid for 1 hour. After working up as described above, 0.2 g of 5,5-dimethyltetronic acid (XX) with m.p. 147° , giving no depression with the previous sample, was obtained.

Addition of phenol to the methyl ester of 4-methyl-4-hydroxyhex-2-ynoic acid (IX). The interaction of 10 g of the ester (IX) with a solution of 0.5 g of sodium in 24 g of phenol by the method described above gave 11.5 g of a substance distilling at 5×10^{-3} mm (bath temperature 110-120°). On standing, this reaction product partially crystallized and 3.5 g (38%) of the methyl ester of trans-4-methyl-4-hydroxy-3-phenoxyhex-2-enoic acid (XII) was obtained; after recrystallization from n-hexane it had m.p. 53-54°. Found: C 67.24, 66.97; H 7.11, 7.21%. C₁₄H₁₆O₄. Calculated: C 67.18; H 7.25%.

The liquid mixture of products obtained after the removal and recrystallization of the ester (XII) (7.9 g) was saponified with a solution of 2 g of caustic potash in 20 ml of 30% aqueous methanol at room temperature for 5 days. The reaction product was acidified with 2 N sulfuric acid, and extracted with ether, the ethereal solution was carefully washed with sodium bicarbonate solution and water, and dried with magnesium sulfate. After evaporating off the ether and distillation at 5×10^{-3} mm, 2.5 g of the lactone (XV) with n_{2}^{19} 1.5215, which crystallized on long standing, was obtained. Found: C 71.23; H 6.72%. C₁₃H₁₄O₃. Calculated: C 71.54; H 6.47%.

The aqueous solution was acidified with 2 N sulfuric acid and extracted with ether, and the extract was dried with sodium sulfate. After the ether had been distilled off, 2.35 g (14%) of trans-4-methyl-4-hydroxy-3-phenoxyhex-2-enoic acid (XVIII) with m.p. 124° (from aqueous ethanol) was obtained. Found: C 66.0, 66.20; H 6.88, 6.98%. $C_{13}H_{16}O_4$. Calculated: C 66.08; H 6.83%. The same acid is formed in the alkaline saponification of the pure transester (XII).

Addition of phenol to the methyl ester of β -(1-hydroxycyclopentyl)-propiolic acid (X). Ten grams of the methyl ester (X) was added at 90° to a solution of sodium phenoxide in phenol (from 0.4 g of sodium and 22.4 g of phenol). Working up as described above gave 9.2 g of a liquid product which distilled in a vacuum of 9×10^{-3} mm (bath temperature 140-150°) but which could not be crystallized. A solution of 1 g of this product in a mixture of 5 ml of methanol, 1 ml of water, and 0.2 g of caustic soda was allowed to stand at room temperature for 48 hours and was then acidified and extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate, dried with sulfate, and the ether was evaporated off. A yield of 0.3 g of the lactone (XVI) with m.p. 61-62° (from petroleum ether) was obtained. Found: C 73.52, 73.55; H 6.34, 6.51%. C₁₄H₁₄O₃. Calculated: C 73.02; H 6.13%.

The alkaline aqueous solution was acidified with 2 N sulfuric acid and the crystalline product which separated was filtered off. This yielded 0.35 g of trans- β -phenoxy- β -(1-hydroxycyclopentyl)-acrylic acid (XIX) with m.p. 148-149° (from aqueous ethanol). Found: C 67.69, 67.52; H 6.45, 6.47%. C₁₄H₁₆O₄. Calculated: C 67.79; H 6.50%.

Dehydration of the methyl ester of trans-4-methyl-4-hydroxy-3-phenoxypent-2-enoic acid (XI). A solution of 3 ml of phosphoryl chloride in 6 ml of pyridine was added at room temperature to a solution of 3.5 g of the ester (XI) in 6 ml of dry pyridine (in the presence of hydroquinone). The temperature rose to 40° and was then kept at 80-85° for 4 hours. The reaction product was poured onto ice, acidified with hydrochloric acid, and extracted with ether, and

the extract was dried with magnesium sulfate. After evaporation of the ether and distillation of the residue at 4×10^{-3} mm (bath temperature 100°), 1.1 g (32%) of the methyl ester of 3-methyl-2-phenoxy-butadienecarboxylic acid (XXI) was obtained; after redistillation it had n_D^{20} 1.5380, λ_{max} 245.5 mµ, log ϵ 4.087 (heptane). A solution of 1.1 g of the diene (XXI) and 0.4 g of maleic anhydride was boiled in xylene in the presence of hydroquinone for 6 hours. After distillation of the solvent, 0.16 g of the adduct (XXIV) with m.p. 160-161° (from benzene), was obtained. Found: C 64.39, 64.09; H 4.83, 5.12%. C₁₇H₁₆O₆. Calculated: C 64.55; H 5.15%.

On boiling 1 g of the adduct (XXIV) with 15 ml of water for 5 hours, 1 g of a crystalline product with m.p. 184-185° (from water) was obtained, which, by analysis, corresponds to the acid (XXV). Found: C 61.26, 61.21; H 5.47, 5.44%; titration equivalent 119. $C_{17}H_{18}O_7$. Calculated: C 61.07; H 5.43%; titration equivalent 117.

Addition of phenol to the methyl ester of isopropenylpropiolic acid (XXII). Twenty grams of the ester (XXII) was added to a solution of sodium phenoxide (from 1.3 g of sodium in 70 g of phenol) at 90°. The reaction mixture was heated to 100°, after which the temperature rose spontaneously to 126°. After 30 minutes, heating was discontinued, and the product was cooled to 20°, dissolved in ether, and washed with 20% caustic soda solution. The ethereal solution was washed with water and dried with magnesium sulfate and, after evaporation of the ether, 29.65 g of reaction product was left, which was distilled in a vacuum of 2×10^{-8} mm. This gave 13.5 g of a product distilling at a bath temperature of 75-100°; n_D^{26} 1.5340. On redistillation, 10.5 g (30%) of the above-described methyl ester of 3-methyl-2-phenoxybutadiene-carboxylic acid (XXI), n_D^{20} 1.5373, was obtained. Found: C 70.97; H 6.42%. C₁₃H₁₄O₃. Calculated: C 71.54; H 6.47%.

Condensation of this acid with maleic anhydride in xylene solution yielded the adduct (XXIV) with m.p. 160-161°, giving no depression of the melting point with the sample described above. For saponification, 1.6 g of the dienci ester (XXI) was allowed to stand in a solution of 0.5 g of caustic potash in 35 ml of 50% aqueous methanol at 20° for 48 hours. The reaction product was diluted with water, acidified with 2 N sulfuric acid, and extracted with ether, and the extract was dried with magnesium sulfate. Evaporation of the ether yielded 0.9 g of the acid (XXIII) with m.p. 111° (from aqueous alcohol). Found: C 70.40; H 6.08%. $C_{12}H_{12}O_3$. Calculated: C 70.57; H 5.92%.

Addition of phenol to the methyl ester of cyclohexenylpropiolic acid (XXVI). Twenty grams of the ester (XXVI) was added at 120° to a solution of 1 g of sodium in 40 g of phenol, after which the mixture was slowly heated during 30 min to 145°. The reaction product was rapidly cooled to 15° and treated as described above. Vacuum distillation yielded 27.8 g (89%) of the methyl ester of β -phenoxy- β -cyclohexenylacrylic acid (XXVII), with b.p. 108-112° (5 × 10⁻³ mm) (bath temperature 130-140°); n²⁰_D 1.555; λ_{max} 258 mµ, log ϵ 4.146 (isooctane). Found: C 74.05, 74.12; H 6.99, 7.0%. C₁₆H₁₈O₃. Calculated: C 74.39; H 7.02%.

For saponification, 3.5 g of the dienic ester (XXVII), 35 ml of methyl alcohol, and 8 ml of a 50% aqueous solution of caustic soda was shaken at room temperature for 48 hours. Conventional working up yielded 2.2 g of the acid (XXVIII) with m.p. 128-129° (from isooctane); λ_{max} 262.5 m μ , log ϵ 4.291 (alcohol). Found: C 73.85, 73.94; H 6.31, 6.24%. C₁₅H₁₆O₃. Calculated: C 73.75; H 6.60%.

Attempts to cyclize β -phenoxy- β -(1-hydroxycyclohexyl)-acrylic acid (XXXI). One gram of the acid (XXXI) was added slowly to 22 ml of 80% sulfuric acid cooled to 0°, and the mixture was allowed to stand at room temperature until the crystals had completely dissolved (2.5 hours). The reaction product was poured onto ice, and the oil which separated crystallized. A yield of 0.35 g of the lactone (XXX) with m.p. 197-198° (from ethyl acetate), identical with an authentic sample [9] was obtained.

Hydration of the methyl ester of β -(1-hydroxycyclohexyl)-propiolic acid (XXIX). A mixture of 5 g of the ester (XXIX) in 140 ml of a solution of mercury acetate in acetic acid (from 14 g of mercury oxide) was heated at 90-95° for 14 hours. The solution was filtered, the filtrate was evaporated to dryness in vacuum, and the residue was heated with 30 ml of concentrated hydrochloric acid. The reaction product was extracted with ether and the extract was dried with magnesium sulfate. A yield of 2.2 g of the lactone (XXX) with m.p. 196-198° (from ethyl acetate), identical with that described above, was obtained.

SUMMARY

1. The synthesis of a series of γ -hydroxyacetylenic and vinylacetylenic acids has been carried out from some acetylenic alcohols and vinylacetylene derivatives.

2. The addition of sodium phenoxide to the triple bond of some γ -hydroxyacetylenic and vinylacetylenic acids has been studied and a number of conversions of the β -phenoxy-substituted acrylic esters thus formed have been established.

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