SYNTHESIS AND TRANSFORMATIONS OF UNSATURATED CARBOXYLIC ACIDS

COMMUNICATION 2. A NEW METHOD OF SYNTHESIZING UNSATURATED γ-KETO ACIDS

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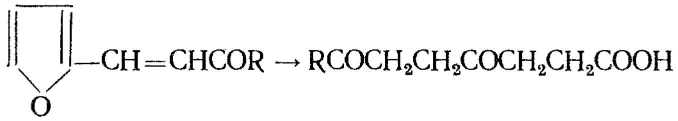
As a result of numerous investigations it has been established that long-chain unsaturated carboxylic acids are an essential part of several very important liquids of the animal organism [1], lipids of microbic cells [2], and of several classes of antibiotics [3]. The higher unsaturated acids and their functional derivatives are especially interesting as factors in vitamin action [4] and as substances possessing very valuable and interesting physiological properties [5, 6]. A search for a synthetic route to different types of higher unsaturated acids [7] is therefore of considerable interest, and the objective of the present study was the development of a new method of preparing γ -keto acids containing a system of conjugated double bonds.

It was shown previously that suitable starting materials for the synthesis of saturated γ -keto acids are found in various alkylfuryl-carbinols [8] and furfurylidene ketones [9], the opening of the furan ring which enables the carbon chain to be lengthened at once by five carbon atoms with good yields.



For the purpose of synthesizing unsaturated γ -keto acids we studied in detail the transformations of the acetylenic γ -glycol (I), which was prepared by reacting furfurol with a Mg-organic derivative of dimethylethinylcarbinol [10]. It was found that the acetylenic glycol (I) could be selectively hydrogenated with Pd/$CaCO_3$ to the corresponding ethylenic γ -glycol (II), which could be hydrogenated further to the saturated γ -glycol (III). As its structure suggests, the ethylenic glycol (II) can be readily dehydrated, and when it was heated with potassium bisulfate it gave a 70% yield of 2,2-dimethyl-5-furyl-2,5-dihydrofuran (IV). The ultraviolet spectrum of the dihydrofuran derivative (IV) showed the presence of a double bond not conjugated with the furan ring [11]. By catalytic hydrogenation with a Pd catalyst one mole of hydrogen added readily to this compound and formed the corresponding 2,2-dimethyl-5-furyltetrahydrofuran (V), which was also obtained by dehydration of the saturated γ -glycol (III).

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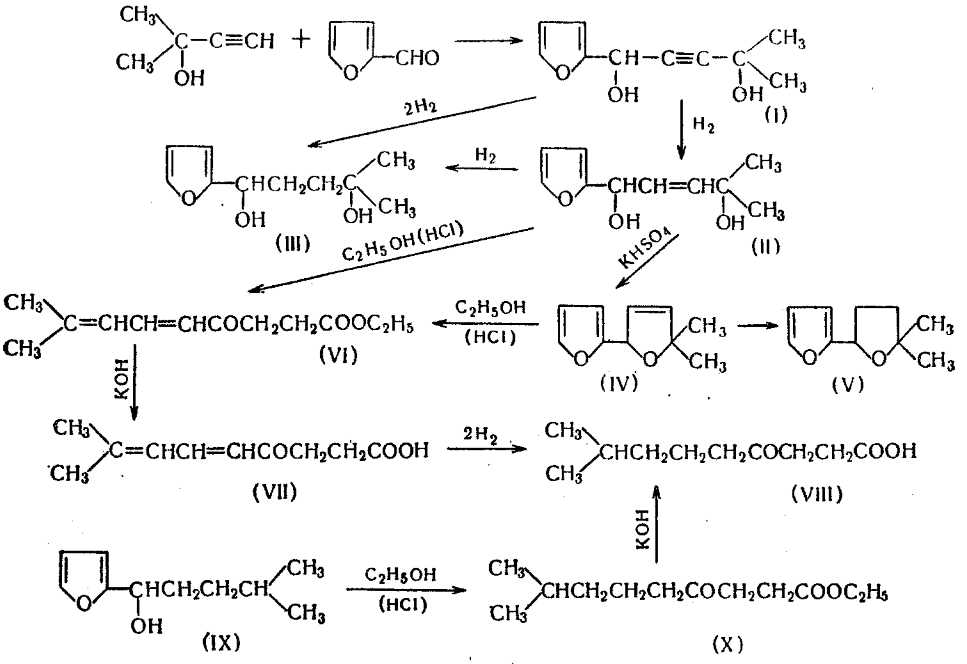
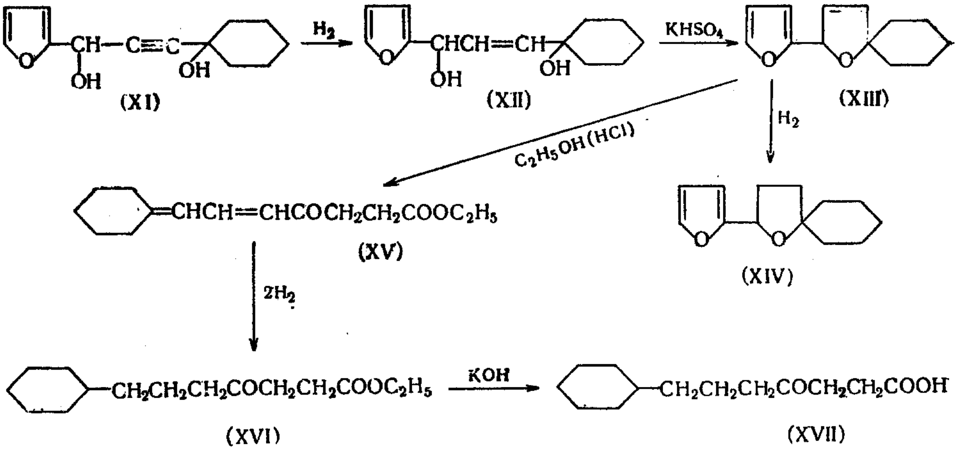
*For Communication 1 of this series see Izv. AN SSSR, Otd. Khim. Nauk, 1512 (1960).



The furylacetylenic γ -glycol (I) was found to be very sensitive to the action of alcoholic hydrogen chloride under conditions necessary to open the furan ring [12], and for this reason a mixture of products together with a large quantity of tar was obtained in the transformation. However, the opening of the furan ring of the ethylenic glycol (II) is an easier reaction, and in this case a yield of up to 25% was obtained of the ethyl ester of 4-keto-8-methylnonadien-5,7-oic acid (VI), which gave a good yield of the corresponding unsaturated γ-keto acid (VII) when it was saponified with a water-alcohol solution of alkali. The acidic isomerization of the furan ring was much better in the case of 2,2-dimethyl-5-furyl-2,5-dihydrofuran (IV), which gave a yield of up to 65% of the diene γ -keto ester (VI) when it was boiled for one hour in a solution of ethyl alcohol in the presence of catalytic quantities of hydrogen chloride. The ester (VI) absorbed two moles of hydrogen during catalytic hydrogenation, but it did not give an adduct with maleic anhydride, and according to the ultraviolet and infrared spectra (Figs. 1 and 2) it contained a keto group conjugated with a system of two conjugated double bonds [13]. In view of all this evidence there was not much doubt about the structure of the diene keto ester (VI). However, in order to confirm the presence in it of the γ-keto group a counter synthesis was carried out in which 4-keto-8-methylnonanoic acid (VIII) was formed by hydrogenation of the diene keto acid (VII). With the same end in view isoamylfurylcarbinol (IX) [14] was converted into the γ -keto ester (X), saponification of which resulted in the desired γ -keto acid (VIII), which did not give a depression with the sample prepared above.

We also used the above scheme for synthesizing diene γ -keto acids in the case of furylacetylenic γ -glycol (XI) obtained by reacting furfurol with the Mg-organic derivatives of cyclohexylethinylcarbinol. This



glycol, like the γ -glycol (I) described above, could be selectively hydrogenated over Pd/CaCO$_3$ in a solution of aqueous methanol to form the ethylenic glycol (XII), which was converted without being isolated into the corresponding derivative of dihydrofuran (XIII). This product contained a double bond not conjugated with the furan ring, and it added on one mole of hydrogen to form 2-furyloxa-1-spirodecane (XIV), which was also prepared by dehydrating the product obtained by adding two moles of hydrogen to the original γ -glycol (XI). Under conditions of acidic isomerization in a solution of ethyl alcohol the furan ring of the dihydrofuran (XIII) readily opened and gave the diene γ -keto ester (XV) in a yield of up to 50%, the infrared spectrum of which was found to be completely identical with that of the ester of 4-keto-8-methylnonadien-5,7-oic acid (VI) described above. When the unsaturated γ -keto ester (XV) was hydrogenated catalytically it added on two moles of hydrogen, and was converted into the saturated γ -keto ester (XVI), saponification of which gave 7-cyclohexyl-4-ketoheptanoic acid (XVII).

This method which we have developed for preparing unsaturated γ -keto acids is quite simple and convenient, and at the present time we are studying in detail the possibility of using it for synthesizing various unsaturated γ -keto acids is quite simple and convenient, and at the present time we are studying in detail the possibility of using it for synthesizing various unsaturated γ -keto acids with long and branched chains.

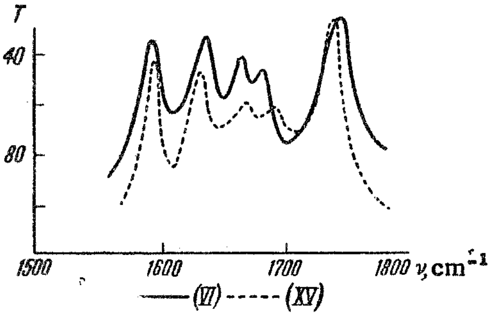


Fig. 1.

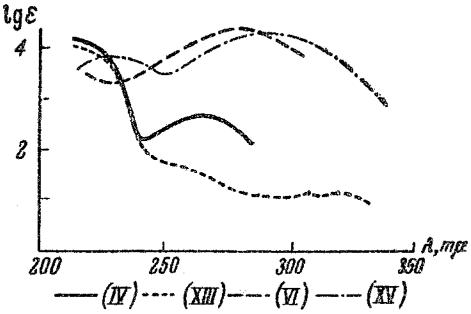


Fig. 2.

EXPERIMENTAL

Acetylenic γ -glycol (I). A solution of magnesium ethyl bromide was prepared from 24.3 g of Mg and 121 g of ethyl bromide in 250 ml of ether, and to it was added slowly (during one and one half hours) at a temperature not above 8°, a solution of 42 g of dimethylethinylcarbinol in 50 ml of benzene, after which the mixture was stirred at this temperature for one more hour. The ether was distilled off and was replaced by benzene after which the magnesium addition compound was reacted with a solution of 48 g of furfurol in 50 ml of benzene which was added over the course of two hours while stirring vigorously at a temperature of −2 to +2°. The mixture was then kept at 12-15° for two hours and decomposed with a saturated solution of ammonium chloride at 4-6°. The benzene layer was separated, the aqueous portion was carefully extracted with ether, and the combined benzene-ether solution was dried over potash. The solvent was distilled off, and the crystalline reaction product was carefully washed on a filter with petroleum ether. The yield of the acetylenic γ -glycol (I) was 53.6 g (60%), and after it was crystallized from a 1: 1 mixture of ether and petroleum ether it melted at 59.5-60.5°. Found: C 66.32; 66.24; H 6.83; 6.92%. $C_{10}H_{10}O_3$. Calculated: C 66.65; H 6.71%.

Hydrogenation of the acetylenic γ -glycol (I). A solution of 15 g of the acetylenic γ -glycol (I) in a mixture of 40 ml of methanol and 5 ml of water was hydrogenated over Pd/CaCO$_3$. After one mole of hydrogen had been absorbed the rate of hydrogenation decreased markedly and hydrogenation was discontinued. The catalyst was filtered off, and the solvent was distilled off under vacuum. Yield was 12.8 g (84.7%) of the ethylenic γ-glycol (II) with b.p. 103-104° (0.3 mm); $n^{20}D$ 1.5081. Found: C 65.76; 65.57; H 7.81; 7.80%. $C_{10}H_{14}O_3$. Calculated: C 65.91; H 7.74%.

Exhaustive hydrogenation of the acetylenic γ -glycol (I) over Pd/CaCO$_3$ resulted in the absorption of two moles of hydrogen, and after distillation a 69% yield was obtained of the saturated glycol (III), with b.p. 111-113° (0.37 mm); $n^{20}D$ 1.4952 Found: C 64.84; 65.00; H 8.69; 8.62. $C_{10}H_{16}O_3$. Calculated: C 65.19; H 8.75%

Dehydration of the ethylenic γ -glycol (II). A solution of 4.5 g of the ethylenic γ -glycol (II) in 40 ml of benzene was added drop by drop to 0.45 g of finely ground KHSO$_4$ heated to 120° with simultaneous distillation under vacuum (50 mm). The distilled mixture of water, benzene, and dehydration product was dried with potash, the benzene was distilled off, and the residue was distilled under vacuum. Yield of dihydrofuran derivative (IV) was 2.7 g (66.7%) with b.p. 72-73° (8 mm); $n^{20}D$ 1.4802; λ_{max} 216 mμ 10200. Found: C 72.80; H 7.30%. $C_{10}H_{12}O_2$. Calculated: C 73.14; H 7.37%.

When (IV) was catalytically hydrogenated over $Pd/CaCO_3$ in a solution of methanol one mole of hydrogen was absorbed, and after distillation a quantitative yield was obtained of 2,2-dimethyl-5-furyltetrahydrofuran (V) with b.p. 78-79° (8 mm); $n^{20}D$ 1.4747; Found: C 72.31; 72.16; H 8.27; 8.43%. $C_{10}H_{14}O_2$. Calculated: C 72.26; H 8.49%.

4-Keto-8-methylnonadien-5,7-oic acid (VII) and its ethyl ester (VI). To a solution of 4.4 g of (IV) in 50 ml of absolute ethyl alcohol was added 0.3 ml of a saturated alcoholic solution of hydrogen chloride, and the mixture was boiled for one hour. The alcohol was distilled off under vacuum, and the residue was treated with water and neutralized with sodium bicarbonate; the reaction product was extracted with ether and dried with magnesium sulfate. After the solvent was distilled off distillation of the residue under vacuum gave 3.4 g (60.4%) of the diene γ -keto ester (VI) with b.p. 98-99° (0.25 mm); $n^{20}D$ 1.5196. λ_{max} 235.5 mμ; lg ε 3.26; λ_{max} = 279 mμ; lg ε 4.412. The infrared spectrum had characteristic absorption bands at 1591, 1633, 1677, and 1738 cm^{-1}. Found: C 68.44; 68.21; H 8.70; 8.64%. $C_{12}H_{18}O_3$. Calculated: C 68.54; H 8.63%.

The 2,4-dinitrophenylhydrazone of the diene γ -keto ester (VI) melted at 137-138° (alcohol). Preparation of the same γ -keto ester from the ethylenic γ -glycol (II) using the method described above gave a yield of only 22.5%.

Saponification was carried out by boiling a mixture of 1.5 g of the unsaturated γ -keto ester (VI), 10 ml of methanol, 1 ml of water, and 0.5 g of potassium hydroxide for one hour; the alcohol was distilled off under vacuum, 10 ml of water was added to the residue, the neutral products were extracted with ether, and the aqueous layer was acidified with 20% sulfuric acid; the saponified product was extracted with ether and dried with magnesium sulfate. After the ether was distilled off the yield was 1.09 g (84%) of 4-keto-8-methylnonadien-5,7-oic acid (VII) with m.p. 97-5-98.5° (from petroleum ether). Found: C 66.30; 66.00; H 7.97; 7.89%. $C_{10}H_{14}O_3$. Calculated: C 65.91; H 7.74%.

When the acid (VII) was hydrogenated with $Pd/CaCO_3$ two moles of hydrogen was absorbed and a quantitative yield was obtained of 4-keto-8-methylnonanoic acid (VIII) with m.p. 61.9-62.5° (from hexane). Found: C 64.42; 64.64; H 9.67; 9.85%. $C_{10}H_{18}O_3$. Calculated: C 64.49; H 9.74%.

Isoamylfurylcarbinol (IX) and its transformation. Furfurol and magnesium i-amyl bromide were reacted using the method of [14], and a yield of 86.5% of i-amylfurylcarbinol (IX) was obtained with b.p. 110-111° (12 mm); $n^{20}D$ 1.4700.

i-Amylfurylcarbinol (IX) was isomerized by adding 0.5 ml of an alcoholic solution of hydrogen chloride to a solution containing 19 g of (IX) in 120 ml of absolute ethyl alcohol and boiling the mixture for one hour. After the usual treatment and distillation under vacuum we obtained;

a) 5 g of product with b.p. 106.5-107° (21 mm); $n^{20}D$ 1.4514 which according to its analysis corresponded to the ethyl ether of i-amylfurylcarbinol. Found: C 73.45; 73.66; H 10.20; 10.08%. $C_{12}H_{20}O_2$. Calculated: C 73.43; H 10.27 %.

b) 10.1 g (41.5%) of the ethyl ester of 4-keto-8-methylnonanoic acid (X) with b.p. 130-131° (6 mm); $n^{20}D$ 1.4374, which was saponified to the corresponding γ-keto acid (VIII) with m.p. 61-62°, and which did not give a depression with the sample described above.

Acetylenic γ -glycol (XI) and its transformations. Furfurol and cyclohexylethinylcarbinol when reacted according to the method described above gave a yield of 87% of the acetylenic γ -glycol (XI) with m.p. 89.5-90° (from hexane). Found: C 71.23; 71.26; H 7.48; 7.42%. $C_{13}H_{16}O_3$. Calculated: C 70.90; H 7.32%. When it was hydrogenated over $Pd/CaCO_3$ in an aqueous methanol solution, one mole of hydrogen was selectively absorbed, after which the hydrogenation slowed down markedly. The ethylenic γ -glycol (XII) in a viscous high-boiling liquid which can be readily dehydrated by heating it to 100°. Dehydration was carried out by adding a solution of 61 g of the unsaturated ethylenic γ -glycol (XII) in 250 ml of benzene slowly (over two hours) to anhydrous $KHSO_4$ heated to 120° with simultaneous vacuum distillation (50 mm). The azeotropic mixture of benzene and water was distilled off, and the residue was distilled under vacuum. 36 g (65) of the dehydration product (XIII) was obtained with b.p. 70-71° (0.22 mm); $n^{20}D$ 1.5105; λ_{max} 217 mμ ; ε 10650. Found: C 76.46; 76.20; H 8.24; 7.90%. $C_{13}H_{16}O_2$. Calculated: C 76.44H 7.90%.

When the dihydrofuran derivative (XIII) was hydrogenated over $Pd/CaCO_3$ one mole of hydrogen was absorbed and a good yield was obtained of 2-furyloxa-1-spirodecane (XIV) with b.p. 65-66° (0.09 mm); $n^{20}D$ 1.5062. Found: C 75.96; H 8.70. $C_{13}H_{18}O_2$. Calculated: C 75.69; H 8.80%.

Ethyl ester of the γ -keto acid (XV) and its transformations. An alcoholic solution of the dihydrofuran (XIII) was boiled in the presence of hydrogen chloride following the method described above and a yield of 46% was obtained of the diene γ -keto ester (XV) with b.p. 132-133° (0.08 mm); $n^{20}D$ 1.5308; λ_{max} 231 mμ ; lg ϵ 3,835; λ_{max} 292.5 mμ; lg ϵ 4.270. The infrared spectrum had characteristic absorption bands at 1592, 1632, 1685, and 1734 cm^{-1}. Found C 72.35; 72.15; H 8.50; 8.69%. $C_{15}H_{22}O_3$. Calculated: C 71.97; H 8.86%.

When the ester (XV) was catalytically hydrogenated it absorbed two moles of hydrogen and after distillation a quantitative yield was obtained of the saturated γ -keto ester (XVI) with b.p. 121-122° (0.22 mm); $n^{20}D$ 1.4638. Found: C 70.91; 71.04; H 10.31; 10.10%. $C_{15}H_{26}O_3$. Calculated: C 70.83; H 10.30%. Saponification with a water-alcohol solution of alkali resulted in a 90% yield of 4-keto-7-cyclohexylheptanoic acid (XVII) with m.p. 65-65.5° (from hexane). Found: C 69.19; 69.10; H 9.92; 9.79%. $C_{13}H_{22}O_3$. Calculated: C 68.99; H 9.80%.

SUMMARY

A new method was developed for synthesizing diene γ -keto acids and their esters based on available furylacetylenic γ -glycols.

LITERATURE CITED

1. G. Popjak and F. Le Breton, Biochemical Problems of Lipids (London, 1956).
2. R. J. Anderson, Chem. Red. 29, 225 (1911).
3. J. Patrick, R. Williams, and J. Webb, J. Amer. Chem. Soc. 80, 6689 (1958).
4. C. Nieman, Bacterial Rev. 18, 147 (1954).
5. A. Keys, J. T. Anderson, F. Fidanza, M. H. Keys, and B. Swahn, Clin. Chem. 1, 34 (1955).
6. H. O. Kunkel and J. N. Williams, J. Biol. Chem. 189, 755 (1951).
7. J. Nichols and E. Schipper, J. Amer. Chem. Soc. 80, 5705 (1958).
8. V. F. Kucherov, Zh. obshch. khimii 20, 1885 (1950).
9. R. Lukes and J. Strogni, Coll. czevholsov. chem. communicat. 24, 220 (1959).
10. Sh. Mikadze and I. Gverdtsiteli, Trudy Tbilissk. Inst. 62, 167 (1957).
11. E. Andrisano and A. Tundo, Atti Accad. Lincei 13, 158 (1952).
12. M. I. Ushakov and V. F. Kucherov, Zh. obshch. khimii 14, 1073 (1944).
13. L. Bellamy, Infrared Spectra of Molecules [Russian translation] (IL, Moscow, 1957).
14. V. Grignard, Ann. chimie (7), 24, 468 (1901).

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.
