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A NOVEL METHOD OF THE SYNTHESIS OF SUBSTITUTED FURANS WITH THE USE OF ACETYLENIC ALKOXY β-KETOESTERS

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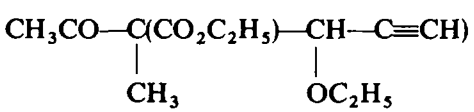
Abstract—The action of organic acids on acetylenic alkoxy β-keto-esters of type I and the corresponding vinylacetylenic β-keto-esters (II) gives rise to trisubstituted furans, shown to possess structure III.

OUR PREVIOUS studies concerning the reactivity of acetals showed that on treatment with boron trifluoride etherate they condense readily with various β-dicarbonyl compounds to give the corresponding C-alkylated products.[1] This observation was extended to the acetals of acetylenic aldehydes.[2,3] The latter react with ethyl acetoacetate to give in high yield acetylenic alkoxy β-keto-esters (I), a new type of unsaturated β-dicarbonyl compound.[4] In this communication we report on specific features of their reactivity.

When treated with organic acids, all acetylenic alkoxy β-keto-esters undergo a characteristic cyclization, which leads to the substituted furan derivatives of general type III, the substituent at C_2 being either an acyloxymethylenic group (IIIa, b) or a group resulting from its subsequent modification (IIIc, d). We also found that in all cases the furanization is accompanied by a parallel reaction which, upon the loss of an alcohol molecule, leads to the corresponding vinylacetylenic keto-esters (II). We prepared these compounds, reported for the first time, by Knoevenagel condensation of ethyl acetoacetate with the corresponding acetylic aldehydes and showed that they are capable of undergoing the same furanization on treatment with organic acids as in the case of the related alkoxy keto-esters (I). In cases where the formation of a vinylacetylenic system is impossible (e.g. in the case of



$$CH_3CO{-}\underset{CH_3}{\underset{|}{C}}(CO_2C_2H_5){-}\underset{OC_2H_5}{\underset{|}{C}H}{-}C{\equiv}CH)$$

the furanization does not occur. This fact implies that the vinylacetylenic β-keto-esters of type II serve as intermediates in the mechanism of furanization of acetylenic alkoxy β-keto-esters (I).

The course of furanization in each case (Ia–d) and the structure of the corresponding products is discussed below.

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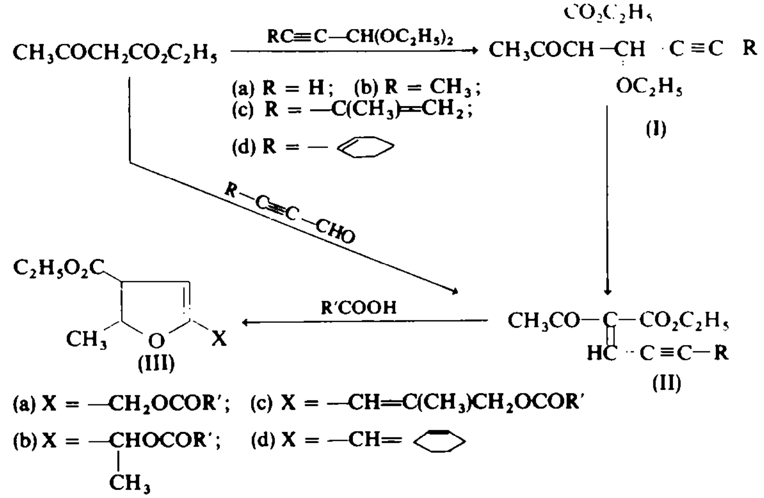
[1] S. S. Yufit and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otdel Khim. Nauk*, 1658 (1960).

[2] Zh. A. Krasnaya and V. F. Kucherov, *Akad. Nauk SSSR, Otdel Khim. Nauk* 1070 (1965).

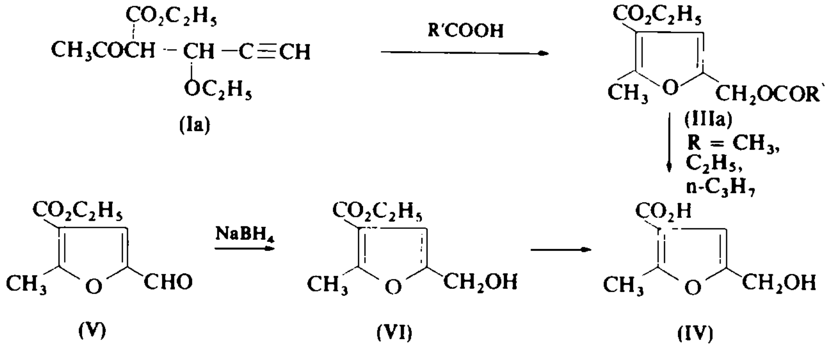
[3] Zh. A. Krasnaya, S. S. Yufit and V. F. Kucherov, *Akad. Nauk SSSR, Otdel Khim. Nauk*, in press.

[4] S. S. Yufit, Zh. A. Krasnaya, T. S. Levchenko and V. F. Kucherov, *Akad. Nauk SSSR, Otdel Khim. Nauk*, 132 (1967).



Our experiments showed that 3-carbethoxy-4-ethoxy-5-hexyn-2-one (Ia) on heating with acetic, propionic or butyric acid gives the corresponding 4-carbethoxy-2-acyloxymethyl-5-methylfurans (IIIa) as main products. Hydrolysis of these products leads to the same hydroxymethylenic acid IV. The latter was shown to be 4-carboxy-2-hydroxymethyl-5-methylfuran since it was prepared by sodium borohydride reduction of the known 4-carbethoxy-2-formyl-5-methylfuran (V)[5] followed by hydrolysis of the 4-carbethoxy-2-hydromethyl-5-methylfuran (VI) thus obtained.

We also prepared compound VI according to Payne's procedure,[6] i.e. by condensation of epoxyacrolein with acetoacetic ester and then hydrolysed it to IV. All three samples of IV proved to be identical.



The structure of the furanization product was also corroborated by the NMR spectrum of methyl ester of IV (see Fig. 1). The NMR spectrum of this compound[7] displays two singlets with δ 2·45 and 3·70 ppm accounting for two CH_3-groups (at C_5 and in the ester function), a signal with δ 4·33 ppm (methylenic protons in the

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[5] J. K. N. Jones, *J. Chem. Soc.* 116 (1945).

[6] P. H. Williams, G. B. Payne, W. J. Sullivan and P. R. Van Ess, *J. Am. Chem. Soc.* **82**, 4883 (1960).

[7] A. V. Kessenikh and E. P. Prokofiev, *Zh Strukt. Khim.* in press.

hydroxymethylenic group at C_2) and signals with δ 4·02 and 6·28 ppm corresponding to a hydroxylic proton and to the C_3-proton in the furan ring.

When we attempted to bring about the furanization of Ia by action of acetic acid–sodium acetate buffer we obtained the expected product IIIa (R′ = CH_3), only in minor quantities. The main product of this reaction was a high-melting compound $C_{18}H_{20}O_6$ which contained neither carbonyl nor acetylenic group and displayed strong absorbancy at 327 and 344 mμ. The analysis of its NMR spectrum (see Fig. 2) led to the conclusion[7] that this compound might possess the structure of 1,2-di(4′-carbethoxy-5′-methyl-2′-furyl)ethylene (VII). Our guess was justified by the following transformations. Compound $C_{18}H_{20}O_6$ was hydrolysed to a dicarboxylic acid (VIII) which was then decarboxylated to give 1,2-di(5′-methyl-2′-furyl)ethylene (IX).

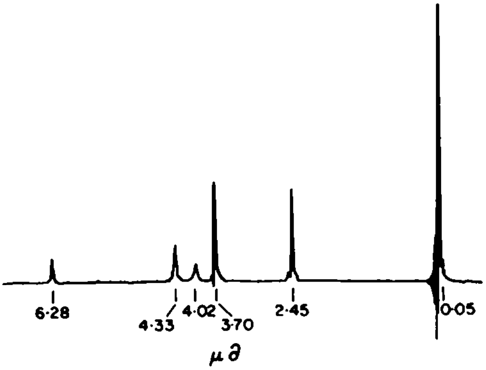

FIG. 1. NMR-spectrum of 4-carbomethoxy-2-hydroxymethyl-5-methylfuran.

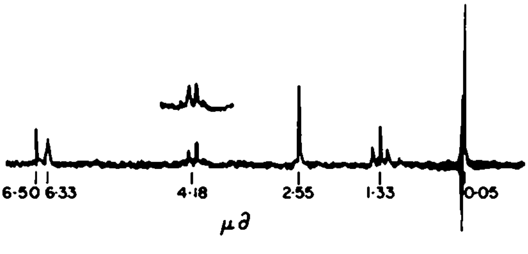

FIG. 2 NMR spectrum of 1,2-di(4′-carbethoxy-5′-methyl-2′-furyl)ethylene (VII).

The latter was identical in all respects with a sample prepared from 2-formyl-5-methylfuran according to the procedure described earlier for the synthesis of 1,2-di(2′-furyl)ethylene.[8]

In contrast to the cyclodimerization of Ia the heating of 3-carbethoxy-4-ethoxy-5-heptyn-2-one (Ib) with the buffer leads only to a mixture of IIb with methyl-2-(4-carbethoxy-5-methyl)furyl carbinol acetate (IIIb). The structure of IIIb follows from the closest similarity of its UV and IR spectra with those of the above-mentioned IIIa.

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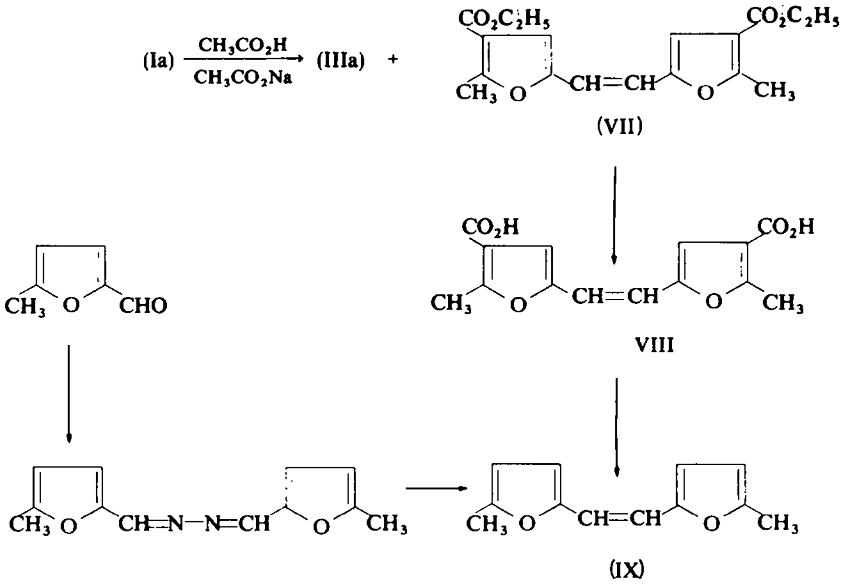
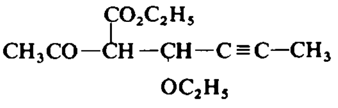
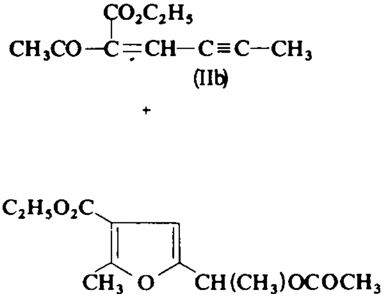
[8] N. J. Shulkin, M. V. Yushkevich and G. S. Belikova, *Sbornik statei Obshch Khim.* **2**, 1112 (1953).





(Ib)

$$CH_3CO-\underset{}{\overset{CO_2C_2H_5}{CH}}-\underset{OC_2H_5}{CH}-C\equiv C-CH_3$$



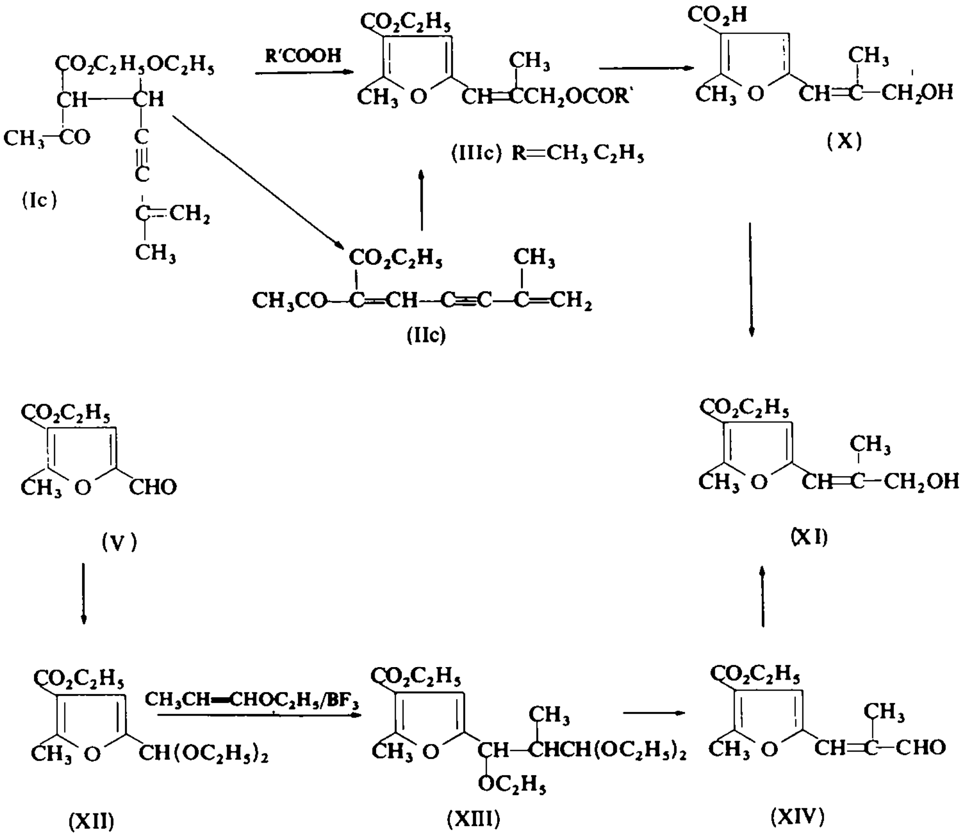
$$CH_3CO-\overset{CO_2C_2H_5}{C}=CH-C\equiv C-CH_3$$

(IIIb)

The cyclization of 3-carbethoxy-4-ethoxy-7-methyl-7-octen-5-yn-2-one (Ic), induced by acetic or propionic acid, is accompanied by allylic isomerization and results in the furanization products of structure IIIc. Saponification of these gives unsaturated hydroxy acid X. One of furanization products (IIIc, R' = CH_3) was also prepared by action of hot acetic acid on 3-carbethoxy-7-methyl-3,7-octadien-5-yn-2-one (IIc); the latter, in its turn, can be obtained in considerable amounts on treating Ic with acetic acid–sodium acetate buffer under mild conditions.

The structure of acid X was confirmed by the synthesis of its ethyl ester XI from 4-carbethoxy-2-formyl-5-methylfuran (V) by sequence XII → XIII → XIV → XI as well as by NMR data.[7]

Finally, the acid-induced cyclization of Id, which contains a cyclohexenyl substituent in conjugation with a triple bond, proceeded in a more complex way due to the easy elimination of the elements of organic acid from the initial furanization product.



In this case both heating with acetic or propionic acid and treatment with the buffer gave rise to only one product which possesses structure IIId and gives on hydrolysis a monocarboxylic acid XV. The same product was obtained on furanization of the related dienyne (IId). The "normal" furanization product (XVI) was isolated from its mixture with IIId only when alkoxy β-keto-ester (Id) was heated with n-butyric acid.

The structure of IIId was confirmed by its transformation to 5-methyl-2(cyclohexyl)methylfuran (XVIII) after hydrogenation and decarboxylation. This product was prepared from 2-formyl-5-methylfuran by the sequence XIX → XX → XVIII.

The results obtained in all four cases show that this intermolecular cyclization, typical of acetylenic alkoxy β-keto-esters and the corresponding vinylacetylenic keto-esters, differs considerably from the known examples of furanization of acetylenic ketones[9-11] both by reaction conditions and by structure of reaction products. The application of acetylenic β-keto-esters to the synthesis of furans and the mechanism of the furanization will be the subject of our further studies.

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[9] L. Crombie and K. Mackenzie, *J. Chem. Soc.* 4417 (1958).

[10] K. E. Sehulte, J. Reisch and A. Mock, *Archiv der Pharmazie*, **295**, 627 (1962).

[11] Zh. A. Krasnaya, S. L. Portnova and V. F. Kucherov, *Khim. Heterocycl. Soedin.* in press.

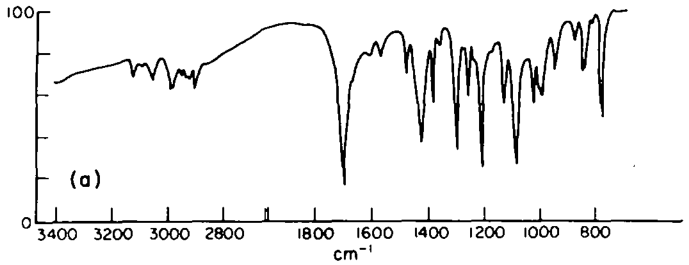

FIG 3a IR-spectrum of 1,2-di(4'-carbethoxy-5'-methyl-2'-furyl)ethylene (VII).

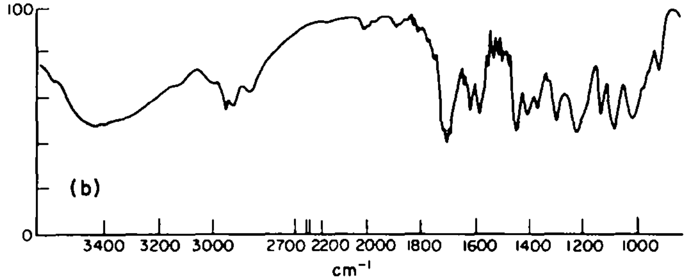

FIG. 3b IR-spectrum of 4-carbomethoxy-2-hydroxymethyl-5-methylfuran.

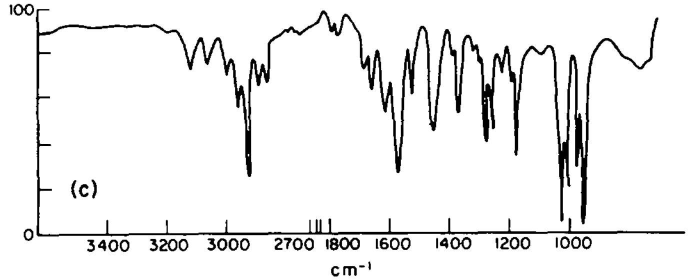

FIG. 3c IR-spectrum of 1,2-di(5'-methyl-2'-furyl)ethylene (IX).

EXPERIMENTAL

Ultra-violet spectra were determined in ethanol solution using a SF-4 spectrophotometer. Infra-red spectra were taken with an IKS-14 or an UR-10 spectrometer. NMR spectra were recorded with a RS-60 spectrometer operating at 60 Mc/s in carbon tetrachloride (hexamethyldisiloxane as internal reference).[7]

All compounds were GLC-analysed using an instrument with flame ionization detection (column length 2 m, hydrogen as carrier, 1 per cent polymethylsiloxane on NaCl).[12] The data will be published elsewhere in a special communication.

1. *Condensation of Acetoacetic Ester with Acetylenic Aldehydes*

(*a*) A mixture of propargylic aldehyde (2 g), acetoacetic ester (4·8 g), acetic acid (0·75 ml) and β-alanine (0·065 g) in 95% ethanol (5·9 g) was allowed to stand at room temperature for 48 hr. The mixture was then diluted with ether, washed with aqueous sodium bicarbonate and water and dried ($MgSO_4$). Evaporation of the solvent gave a product which, according to GLC-data, contained 67% of 3-carbethoxy-3-hexen-5-yn-2-one (IIa) and 33% of acetoacetic ester. The latter could not be completely removed by fractional distillation.

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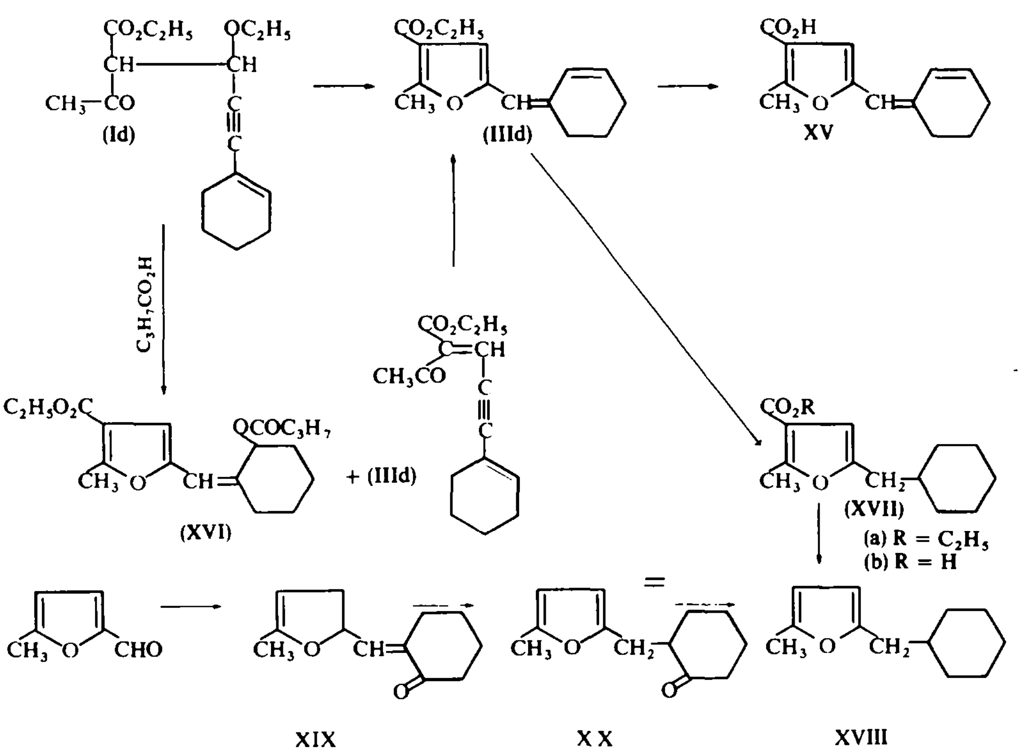
[12] B. A. Rudenko and V. F. Kucherov, *Dokl. Akad. Nauk SSSR* **145**, 577 (1962).



(*b*) A mixture of 4-methyl-4-penten-2-ynal diethyl acetal[13] (6·4 g) and conc. H_2SO_4 (2·2 ml) in water (31 ml) was heated at 70–75° for 20 min. Then ether was added and the organic layer was extracted with aqueous sodium bicarbonate, washed with water and dried ($MgSO_4$). Subsequent vacuum distillation gave 4-methyl-4-penten-2-ynal (1·2 g) as an unstable liquid, b.p. 65–67°/50 mm n_D^{20} 1·4920, λ_{max} 230 mμ (ε 5600). This aldehyde was treated with acetoacetic ester (21 ml) and one drop of piperidine and the mixture was allowed to stand at 0° for 5 days. Then it was diluted with ether, washed with 1% H_2SO_4 and water and dried ($MgSO_4$). Vacuum distillation gave 3-carbethoxy-7-methyl-3,7-octadien-5-yn-2-one (II; 0·9 g), b.p. 92–95°/0·11 mm, n_D^{20} 1·5280. (Found: C, 69·66; H, 7·25. $C_{12}H_{14}O_3$ requires: C, 69·88; H, 6·84%.) λ_{max} 296 mμ (ε 11,700).

(*c*) A stirred mixture of β-cyclohexenylpropargylic aldehyde diethyl acetal[13] (10 g) and conc. H_2SO_4 (3·3 ml) in water (46 ml) was heated at 90–95° for 0·5 hr. The procedure described above gave β-cyclohexenylpropargylic aldehyde (3·6 g), b.p. 72–75°/2 mm, n_D^{20} 1·5490. The latter was mixed with acetoacetic ester (3 g) and piperidine (0·2 g) and the mixture was kept at 0° for 2 days. After the usual working up (IId) was obtained, yield 3·2 g, b.p. 118–120°/0·09 mm, n_D^{20} 1·5640. (Found: C, 73·38; H, 7·59. $C_{15}H_{18}O_3$ requires: C, 73·14; H, 7·37%.)

2. *Transformations of* 3-*Carbethoxy-4-ethoxy-5-hexyn-2-one* (1a)

(*a*) *In acetic acid–sodium acetate buffer*

(*i*) A stirred mixture of 3-carbethoxy-4-ethoxy-5-hexyn-2-one (1a; 12, 2 g), sodium acetate (11 g) and acetic acid (66 ml), was heated at 60–65° for 2 hr. After cooling a yellow crystalline product was filtered and thoroughly washed with water, giving 1,2-di(4'-carbethoxy-5'-methyl-2'-furyl) ethylene (VIII; 3·6 g), which crystallized from acetone, m.p. 142–146°. (Found: C, 64·92; H, 6·00%; mass-spectrum: M 332. $C_{18}H_{20}O_6$ requires: C, 65·05; H, 6·07%; M 332·3); λ_{max} 327, 344 mμ (ε 41,700, 33,600); IR spectrum—see Fig. 3(a); R_f 0·6 (alumina grade II, hexane–acetone 9:1).

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[13] V. B. Mochalin and N. G. Ivanova, *Zh. Obshch. Khim.* 31, 3896 (1961).

The mother liquor after isolation of VII was concentrated and then vacuum-distilled to give an oily product (1·8 g), b.p. 90–105°/0·25 mm, n_D^{20} 1·4780, which solidified on cooling and gave 4-carbethoxy-2-acetoxymethyl-5-methylfurane (IIIa, R′ = CH_3), m.p. 38–39° (from hexane). (Found: C, 58·43; H, 6·13. $C_{11}H_{14}O_5$ requires: C, 58·40; H, 6·24%); λ_{max} 220·5 and 243 mμ (ε 7550 and 4600), $\nu_{max}^{CCl_4}$ 1582, 1621, 1715, 1746, 3125, 3409, 3468 cm^{-1}; R_f 0·54 (alumina grade II, hexane–acetone 9:1). In addition to this product, the mother liquor contained also 3-carbethoxy-3-hexen-5-yn-2-one (IIa), which was detected by GLC. A sample of (IIa), prepared in a separate experiment (0·8 g), was heated with acetic acid (5·5 g) and sodium acetate (0·9 g) at 60° for 2 hr. Working up as above gave 0·2 g of (VII), m.p. 141–143°, and 0·1 g of (IIIa, R′ = CH_3), m.p. 37–39°.

(*ii*) A mixture of acetate (IIIa. R′ = CH_3; 0·4 g), 20% ethanolic potassium hydroxide (7 ml) and ethanol (4 ml) was refluxed for 2 hr. Vacuum-evaporation of the mixture gave a residue, which was dissolved in water. The solution was acidified and extracted with ether. Evaporation of ether gave 4-carboxy-2-hydroxymethyl-5-methylfuran (IV; 0·25 g), m.p. 156–157° (from acetone). (Found: C, 53·80; H, 5·22%, equiv., 150·0. $C_7H_8O_4$ requires: C, 53·84; H, 5·16%; M, 156, 13.) λ_{max} 220 and 246 mμ (ε 5300 and 4070); ν_{max} 1583, 1610, 1685, 3102, 3266, 3335 cm^{-1} (in Nujol mulls). When methanolic solution of (IV) was treated with diazomethane 4-carbomethoxy-2-hydroxymethyl-5-methylfuran was obtained, b.p. 112/114°/3 mm, n_D^{18} 1·5050. (Found: C, 56·26; H, 6·15. $C_8H_{10}O_4$ requires C, 56·46; H, 5·92%.) λ_{max} 247 mμ (ε 3880); IR spectrum—see Fig. 3(b). Ethanolic solution of (IV) on treatment with diazoethane gave 4-carbethoxy-2-hydroxymethyl-5-methylfurane (VI), b.p. 124–126°/2 mm, n_D^{20} 1·4940, λ_{max} 249 mμ (ε 5130).

(*b*) *In organic acid media*

(*i*) A mixture of 3-carbethoxy-4-ethoxy-5-hexyn-2-one (Ia; 1·5 g), acetic acid (8·2 ml) and water (0·5 ml) was heated at 70–80° for 8 hr, then diluted with ether, washed with water, dried and evaporated. GLC-analysis of the residue showed the presence of 4-carbethoxy-2-acetoxymethyl-5-methylfuran (IIIa, R′ = CH_3) as well as 3-carbethoxy-3-hexen-5-yn-2-one (IIa) and starting alkoxy β-keto ester (Ia). The proportion IIIa : IIa : Ia was about 70 : 18 : 12.

(*ii*) Ten g of (Ia), 57 ml of propionic acid and 3·3 ml of water were heated at 75–80° for 7 hr and the reaction mixture was worked up as above, giving 4-carbethoxy-2-propionoxymethyl-5-methylfuran (IIIa, R′ = C_2H_5 6·2 g), m.p. 55–57° (from abs. ethanol). (Found: C, 60·14; H, 6·42. $C_{12}H_{16}O_5$ requires: C, 59·99; H, 6·71%.) λ_{max} 243 mμ (ε 5400); $\nu_{max}^{CCl_4}$: 1542, 1573, 1623, 1726, 1753 cm^{-1}. On saponification with alcoholic alkali this product gave 4-carboxy-2-hydroxymethyl-5-methylfuran (IV), m.p. 156–158°.

(*iii*) Five g (Ia) and 28 ml of butyric acid were heated at 80–90° for 6 hr and worked up as above to give 1·3 g of an oily product (b.p. 112–118°/0·5 mm, n_D^{20} 1·4750) from which pure butyrate (IIIa, R′ = n-C_3H_7) was isolated as yellowish crystals, m.p. 27–28° (from methanol). (Found: C, 61·44; H, 7·25. $C_{13}H_{18}O_5$ requires C, 61·40; H, 7·14%.) λ_{max} 247 mμ (ε 5400). On treatment with alcoholic alkali it gave acid (IV), m.p. 155–157°, in good yield.

(*c*) *Synthesis of* 4-*carboxy*-2-*hydroxymethyl*-5-*methylfuran* (IV)

Four-carbethoxy-2-formyl-5-methylfuran (V), prepared according to[3], had m.p. 55° and λ_{max} 276 mμ (ε 16,600). To a stirred solution of 5·5 g of (V) in 39 ml of ethanol sodium borohydride (0·81 g) was added at 15° and the mixture was allowed to stand overnight. The excess of borohydride was destroyed with acetic acid and the volatile products were removed by evaporation. Dilution with water, extraction with ether and evaporation of the ether solution gave 4-carbethoxy-2-hydroxymethyl-5-methylfuran (VI; 3·1 g) as a colourless oil (n_D^{20} 1·4980) which was saponified with 10% ethanolic potassium hydroxide without further purification. Working up as usual gave 4-carboxy-2-hydroxymethyl-5-methylfuran (IV; 2·2 g), m.p. 154–156°, identical with the sample described above.

(*d*) *Synthesis of* 1,2-*di*(5′-*methyl*-2′-*furyl*)*ethylene* (IX)

(*i*) A mixture of 1,2-di(4′-carbethoxy-5′-methyl-2′-furyl)ethylene (VII; 1·6 g) and 10% ethanolic potassium hydroxide (45 ml) was refluxed for 1·5 hr and worked up as usual to give 1·3 g of dicarboxylic acid (VIII) as brownish crystalline powder. The latter did not melt up to 300° and was almost insoluble in acetone and ethanol. It could be crystallized only from a large volume of dioxane. The acid (5 g) was heated with quinoline (12 ml) and copper chromite catalyst (1·2 g) at 220° for 15 min, producing theoretical amount of carbon dioxide (195 ml). The volatile products were removed (130°/3 mm) and the residue was extracted with ether. The ether solution was combined with the primary distillate and washed with hydrochloric acid (1 : 1), aqueous sodium bicarbonate and water. Evaporation of ether gave a dark crystalline residue, which was dissolved in hexane and filtered through an alumina column. The filtrate was evaporated to give 1,2-di(5'-methyl-2'-furyl)ethylene (IX; 2·65 g), m.p. 60–62° (from ethanol). (Found: C, 76·59; H, 6·73. $C_{12}H_{12}O_2$ requires: C, 76·57; H, 6·43%.) λ_{max} 234, 331 and 350 mμ (ε 6850, 37,500 and 32,000); IR spectrum—see Fig. 3(c); R_f 0·65 (alumina grade II, hexane–acetone 9:1).

(*ii*) Freshly distilled 2-formyl-5-methylfuran (16 g) was gradually added at 0° to a stirred and cooled solution of hydrazine hydrate hydrochloride (5 g) in water (22 ml). After one hour of stirring a solution of sodium hydroxide was added to the formed suspension and the medium was made alkaline. The precipitate was recrystallized twice from ethanol to give the azine, m.p. 112–114° (7 g) which was dissolved in benzene (33 ml) and passed in a stream of nitrogen through a catalytic tube with 70 ml of grounded quartz glass (435°, 15 min). Benzene was evaporated and the residue (2·5 g) was sublimed at 110–120°/7 mm. Crystallization from ethanol gave 1,2-di(5'-methyl-2'-furyl)ethylene (IX; 1·5 g), m.p. 59–61°, identical with the previous sample.

3. *Transformations of* 3-*Carbethoxy-4-ethoxy-5-heptyn-2-one*(Ib)

(*a*) A solution of 3-carbethoxy-4-ethoxy-5-heptyn-2-one (Ib; 1·6 g) in acetic acid (8·5 ml) was heated at 85–90° for 15 hr. Acetic acid was removed in vacuum, the residue dissolved in ether and washed with aqueous sodium bicarbonate and water. Vacuum distillation gave 2-(4-carbethoxy-5-methyl)-furylmethylcarbinol acetate (IIIb; 0·7 g), b.p. 79–82°/0·1 mm, n_D^{15} 1·4800. (Found: C, 60·21; H, 7·15. $C_{12}H_{16}O_5$ requires C, 59·99; H, 6·71%.) λ_{max} 246 mμ (ε 3000), $\nu_{max}^{CCl_4}$ 1542, 1573, 1623, 1726, 1753 cm^{-1}.

(*b*) A mixture of 2 g of (Ib), 15 ml of acetic acid and 2·5 g of sodium acetate was heated at 60° for 2 hr and then at 110° for 5 hr. Working up as above gave an oily product (1·2 g) which, according to GLC-data, contained 38·4% of (IIIb), 45·4% of (Ib) and 16·2% of 3-carbethoxy-3-hepten-5-yn-2-one (IIb).

4. *Transformations of* 3-*Carbethoxy-4-ethoxy-7-methyl-7-octen-5-yn-2-one* (Ic)

(*a*) *In organic acid media*

(*i*) The keto ester (Ic, 15 g) was mixed with acetic acid (82 ml) and water (5 ml) and heated at 90° for 3 hr. The reaction mixture was diluted with ether, washed with aqueous sodium bicarbonate and water and dried ($MgSO_4$), Vacuum distillation gave 8·5 g of acetate (IIIc, R' = CH_3), b.p. 111–114°/0·08 mm, n_D^{20} 1·5160. (Found: C, 62·83; H, 6·89. $C_{14}H_{18}O_5$ requires: C, 63·14; H, 6·81%.) λ_{max} 266 mμ (ε 20,500), $\nu_{max}^{CCl_4}$ 1539, 1607, 1724, 1752, 2923, 2956, 3106, 3436, 3598 cm^{-1}.

Saponification with ethanolic potassium hydroxide gave the corresponding hydroxy acid (X), m.p. 173–174° (from acetone). (Found: C, 61·23; H, 6·34. $C_{10}H_{12}O_4$ requires: C, 61·21; H, 6·17%); λ_{max}264 mμ (ε 22,600). ν_{max} 1583, 1612, 1695, 1799, 3207, 3292 cm^{-1} (in Nujol mulls). A solution of (X) in ethanol was treated with diazoethane to yield ethyl ester (XI) m.p. 57–58° (from hexane–acetone). (Found: C, 63·95; H, 7·40. $C_{12}H_{16}O_4$ requires: C, 64·27; H, 7·19%.) λ_{max} 264 mμ (ε 21,300).

(*ii*) A mixture of (Ic) (4 g), propionic acid (22·8 ml) and water (1·3 ml) was heated at 80–85° for 6·5 hr. Usual working up and vacuum distillation gave 2·6 g of propionate (IIIc, R' = C_2H_5), b.p. 130–132°/0·3 mm, n_D^{20} 1·5090. (Found: C, 64·24; H, 7·46. $C_{15}H_{20}O_5$ requires: C, 64·27; H, 7·19%.)

Saponification with alcoholic alkali produced the same hydroxy acid (X), m.p. 173–175°.

(*b*) *In acetic acid–sodium acetate buffer*

(*i*) A mixture of the keto ester (Ic) (16·5 g), acetic acid (77 ml) and sodium acetate (13·8 g) was stirred and heated at 80–85° for 3 hr. Usual working up gave acetate (IIIc, R' = CH_3) (10·6 g), b.p. 122–125°/0·35 mm, n_D^{20} 1·5160, identical in all respects with the previous sample of (IIIc, R' = CH_3) and giving on saponification hydroxy acid (X).

(*ii*) 8·6 g of (Ic) in 40 ml of acetic acid and 7·1 g of sodium acetate were heated at 60° for 2 hr and then at 80° for next 1·5 hr and the reaction mixture was working up as above. Fractional distillation gave two products: (*i*) b.p. 90–95°/0·25 mm, n_D^{20} 1·5270; λ_{max} 300 mμ (ε 12,400), identified as 3-carbethoxy-7-methyl-3,7-octadien-5-yn-2-one (IIb) described earlier (3·1 g) and (*ii*) b.p. 115–120°/0·2 mm, n_D^{20} 1·5170, identified as acetate (IIIc, R' = CH_3) (2·5 g). On heating with the buffer at 80° for 5 hr (IIb) transforms completely into acetate (IIIc, R' = CH_3).

(*c*) *Synthesis of the hydroxy ester* (XI)

A mixture of 4-carbethoxy-2-formyl-5-methylfuran (V, 5 g), orthoformic ester (6 ml), abs. ethanol (2·3 ml) and p-toluenesulphonic acid (a few crystals) was allowed to stand at room temperature for 12 days.

The mixture was diluted with ether, washed with aqueous sodium bicarbonate and dried. Fractional distillation gave 4-carbethoxy-2-diethoxymethyl-5-methylfuran (XII; 5·6 g), b.p. 102–104°/2 mm, n_D^{15} 1·4665. The latter was treated with boron trifluoride etherate (0·2 g) and then with propenylethyl ether (1·9 g) at 40–50°. After 1 hr of stirring at that temperature the mixture was treated with aqueous sodium acetate, dried and distilled to give ethoxy acetal (XIII) (3·7 g), b.p. 129–131°/mm, n_D^{17} 1·4685. A mixture of 1·5 g of (XIII), 7 ml of acetic acid and 1·15 g of sodium acetate was heated at 95° in a stream of nitrogen for 1·5 hr and then worked up as usual. Ethoxy aldehyde (XIV) was obtained (1·05) as yellowish crystals, m.p. 79–80° (from hexane). (Found: C, 65·02; H, 6·16. $C_{12}H_{14}O_4$ requires: C, 64·90; H, 6·31%.) To a solution of 0·5 g of (XIV) in 8 ml of ethanol sodium borohydride (0·14 g) was gradually added and the reaction was worked up as usual to give 0·3 g of crystalline product with m.p. 56–57° (from hexane–acetone). This product was shown to be identical in all respects with the sample of hydroxy ester (XI) described earlier.

5. *3-Carbethoxy-4-ethoxy-6-($\Delta^{1'}$-cyclohexenyl)-5-hexyn-2-one* (Id) *and its Transformations*

(*a*) Keto ester (Id) was obtained, in 70% yield, by condensation of β-cyclohexenylpropargylic aldehyde with acetoacetic ester in the presence of boron trifluoride etherate according to an earlier procedure.[4] B.p. 124–127°/0·25 mm, n_D^{20} 1·4940. (Found: C, 69·84; H, 8·32. $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%.)

(*i*) The keto ester (10 g), sodium acetate (6·8 g) and acetic acid (45 ml) were heated at 95–100° for 4 hr. The reaction mixture was worked up as usual to give after vacuum distillation 4-carbethoxy-5-methyl-2-($\Delta^{2'}$-cyclohexenylidene)-methylfuran (IIId, 6 g), b.p. 108–111°/0·06 mm, n_D^{20} 1·5880. (Found: C, 72·81; H, 7·55. $C_{15}H_{18}O_3$ requires: C, 73·14; H, 7·37%); λ_{max} 302 mμ (ε 24,100); R_f 0·65 (alumina grade II, hexane–acetone 17:3).

The same product was obtained in good yield when the keto ester (Id) was heated with acetic or propionic acid (100°, 5 hr). On saponification it gave 4-carboxy-5-methyl-2-($\Delta^{2'}$-cyclohexenylidene)methylfurane (XV) in quantitative yield; m.p. 142–144° (from benzene). (Found: C, 71·72; H, 6·45. $C_{13}H_{14}O_3$ requires: C, 71·60; H, 6·42%.)

(*ii*) A mixture of 5 g of keto ester (Id) and 25 ml of butyric acid was heated at 100° for 6 hr and worked up as usual. Fractional vacuum distillation gave two products: (*i*) b.p. 125–127°/0·4 mm, identified as (IIId), yield 1·7 g and (*ii*) butyrate (XVI), b.p. 158–160°/0·4 mm, n_D^{20} 1·5280. (Found: C, 68·03; H, 7·57. $C_{19}H_{26}O_5$ requires: C, 68·24; H, 7·84%.) λ_{max} 268 mμ (ε 18,100).

(*iii*) A mixture of (IId) (1 g), acetic acid (4 ml) and sodium acetate (0·5 g) was heated at 80° for 5 hr. After usual working up the residue represented, according to GLC and TLC data, 4-carbethoxy-2($\Delta^{2'}$-cyclohexenylidene)methyl-5-methylfuran (IIId).

(*b*) *Transformations of* (IIId)

Ethyl ester (IIId) (1·1 g) in abs. ethanol (10 ml) was hydrogenated over 5% palladium on calcium carbonate (0·02 g) until uptake ceased (190 ml at NTP, about 2 mole). Usual working up and distillation gave 4-carbethoxy-5-methyl-2-(cyclohexyl)methylfuran (XVIIa; 0·8 g), b.p. 95–97°/0·1 mm, n_D^{26} 1·4880. (Found: C, 71·89; H, 8·93. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%.) λ_{max} 255 mμ (ε 4750). Its saponification with 10% alcoholic alkali gave, in quantative yield, the corresponding acid (XVIIb), m.p. 124–125° (from methanol). (Found: C, 70·14; H, 8·30. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%.) λ_{max} 246 mμ (ε 3500). This acid (2·1 g) was heated at 200–210° with quinoline (6 ml) and copper chromite catalyst (0·6 g) until gas evolution ceased. The volatile products were removed at 118–120°/25 mm, the distillate was diluted with ether and washed with hydrochloric acid (1:1), aqueous sodium bicarbonate and water. Fractional distillation gave 5-methyl-2(cyclohexyl)methylfuran (XVIII; 1·4 g), b.p. 68–69°/3 mm, n_D^{18} 1·4880. (Found: C, 80·90; H, 10·29. $C_{12}H_{18}O_3$ requires: C, 80·85; H, 10·18%.) λ_{max} 223 mμ (ε 14,700); R_f 0·69 (alumina grade II, hexane).

(*c*) *Synthesis of 5-methyl-2(cyclohexyl)methylfurane* (XVIII)

A mixture of 2-formyl-5-methylfuran (5·4 g), cyclohexanone (10·8 g) and 1% aqueous sodium hydroxide was vigorously stirred at room temperature for 3·5 hr and then neutralized with diluted hydrochloric acid and extracted with benzene. The organic layer was washed with water, dried and distilled to give 2-(5′-methylfurfurilidene)-cyclohexanone (XIX; 7·3 g), b.p. 130–132°/2 mm, n_D^{20} 1·5760, which became completely crystalline on cooling, m.p. 65–67°. Hydrogenation of (XIX) in ethanol over 10% palladium on calcium carbonate gave, in quantative yield, dihydro compound (XX) as a viscous yellow oil, n_D^{26} 1·5000. The latter was subjected to Kishner–Huang–Minlon reduction in tri-ethylene glycol to give 5-methyl-2(cyclohexyl)methylfuran (XVIII), b.p. 72–74°/3·5 mm, n_D^{20} 1·4870, identified with the previous sample on the basis of GLC and TLG data.