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INTRAMOLECULAR CYCLIZATION OF ALKYL-PROPARGYLIDENEMALONIC ACIDS

CATALYTIC AND DIRECTING EFFECT OF SILVER ION*

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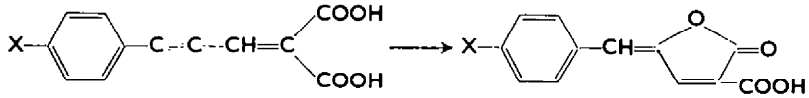
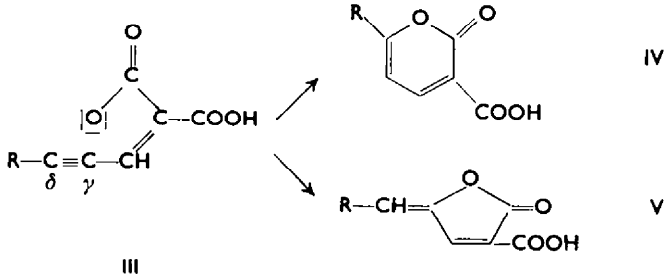
Abstract—Unlike phenylpropargylidenemalonic acids which always give butenolides by an intramolecular nucleophilic cyclization, the alkyl analogues give either butenolides or α-pyrones, or a mixture of both lactones, depending upon the experimental conditions; namely, the presence or absence of silver ions.

IN A previous communication,[1] the cyclization of phenylpropargylidenemalonic acids (I) with different substituents in the *para*-position (X = H, CH_3, OCH_3, Cl, NO_2) to γ-lactones (II) was reported. On the basis of UV and IR spectral data the α-pyrone (δ-lactone) structure was assigned to the product resulting from the thermal isomerization of n-butylpropargylidenemalonic acid, the only alkyl analogue studied.



I II

In principle, considering just the steric configuration of these acids (III), the cyclization to either γ- or δ-lactones, i.e. butenolides (V) or α-pyrones (IV) is equally possible. Actually, the results reported in the present communication show that both the course and the ease of cyclization are sensitive not only to the nature of the substituent attached to the triple bond, but also depend on the reaction conditions, namely, the presence or absence of silver ions.



III IV V

* Presented before the XIXth International Congress of Pure and Applied Chemistry, held in London, 10–17 July 1963.

[1] C. Belil, J. Castellá, J. Castells, R. Mestres, J. Pascual and F. Serratosa, *Anales real soc. españ. fís. y quím., Madrid* **57B**, 617 (1961).

Effect of the substituent. It is clear that the greatest tendency to cyclization—leading to butenolide—is exhibited by the *p*-nitrophenyl derivative (I, X = NO_2), which even cyclizes at room temperature.[1] The strong electron-attracting effect of the nitro group promotes a higher π electronic density on the δ carbon atom and, therefore, cyclization to the butenolide ring by a nucleophilic attack of the carboxyl group to the triple bond takes place. On the other hand, the inductive effect of the n-butyl group (III, R = n-C_4H_9)—contrary to the mesomeric effect of the *p*-nitrophenyl—promotes a higher π electronic density on the γ carbon atom, and the nucleophilic attack is directed towards the δ carbon atom.

Unfortunately, there is no data concerning this tendency in the simplest propargylidenemalonic acid (III, R = H), with no substituent. The spontaneous cyclization of *cis*-pent-4-yn-2-enoic acid (*cis*-propargylideneacetic acid)[2] to butenolide (protoanemonin) is not strictly comparable, since the presence of a second carboxyl group

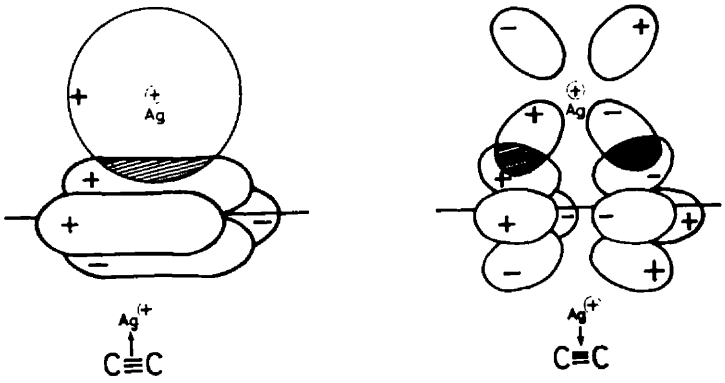


FIG. 1

in the malonic acid series must have a notable effect on the ease and the course of cyclization.[3] However, the next homologue—the methyl derivative (III, R = CH_3)—on heating affords the α-pyrone (IV, R = CH_3).

The IR spectra of the crude cyclization products of both n-butyl and methyl derivatives show the presence of minute amounts of butenolides (V).

Catalytic and directing effect of silver ions. In the previous communication,[1] the catalytic effect of silver ions on the cyclization of phenylpropargylidenemalonic acids[3] was reported. The catalytic effect was explained by means of a transient silver salt-coordination complex which, according to the molecular orbital theory, may be represented as in Fig. 1. This is similar to the description given by Dewar[4] for the coordination of the silver ion with olefins, but has the advantage that the axial symmetry of the triple bond allows a maximum overlap between the silver ion and the triple bond no matter the nature of the attack and accounts for the catalytic effect of silver ions in these reactions.

The effect of silver ions on alkyl-propargylidenemalonic acids is more complex

[1] I. Bell, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 1313 (1958).
[3] Cf. F. Serratosa, *Tetrahedron* **16**, 185 (1961).
[4] M. J. S. Dewar, *Bull. Soc. Chim. Fr* C 71 (1951).

since the cyclization is directed to the formation of butenolides (V) rather than α-pyrones (IV), or to a mixture of both lactones.

The effect of the silver ion is to bring the carboxyl group—which is electrostatically bound—very close to the triple bond. Therefore, in the phenyl series the presence of silver ions favours the formation of butenolides. In the alkyl analogs, the effect of silver ions is different since the geometry of the coordination complex (Fig. 2) probably only allows the carboxyl group to attack the γ carbon atom very near in space, and the attack on the δ carbon atom is "hindered" due to the screen effect of the bulky silver atom.

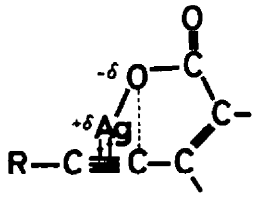


FIG. 2

The cyclization is, nevertheless, competitive and the ratio of δ- and γ-lactones varies from one experiment to another, even if the experimental conditions are, apparently, kept constant. Although in two experiments (catalytic conditions) the IR spectra of the crude cyclization products showed that butenolides were, by far, the predominant isomer, the results could not be reproduced later and usually a ~1:1 mixture of butenolide and α-pyrone is formed in the case of the n-butyl derivative, and a much higher proportion of α-pyrone is found in the case of the methyl derivative. Careful chromatographic separation on silica of the crude product from methyl-propargylidenemalonic acid affords the α-pyrone as the sole product. γ-Alkylidene-butenolides, like protoanemonin, are not stable and the ethylidenebutenolide (V, R = CH_3) has only been detected by IR and UV spectroscopy.

IR and UV spectra. Owing to the considerable amount of spectral data available in the field of unsaturated lactones, UV and IR spectra have proved very useful in the assignation of structures.

The IR spectra show that the α-pyrones have the lactone C=O st band at frequencies lower than 1755 cm^{-1}, whereas in the butenolides it is found at frequencies

TABLE 1. LACTONE C=O ST BAND IN BUTENOLIDES AND α-PYRONES[a]

Compound	cm^{-1}
6-Phenyl-α-pyrone	1730
6-Phenyl-3-carboethoxy-α-pyrone	1754
γ-Methylene-butenolide (protoanemonin)[b]	1786
Patulin[b]	1783–1745
γ-Benzylidene-butenolide	1786–1757
γ-Benzylidene-α-carboxy-butenolide	1786
Thermal cyclization product from III (R = n-C_4H_9)	1754
Catalytic cyclization product from III (R = n-C_4H_9)	1783
Thermal cyclization product from III (R = CH_3)	1754
Catalytic cyclization product from III (R = CH_3)[c]	1783

[a] Unless otherwise stated, IR spectra were measured in $CHCl_3$ soln.
[b] In CH_2Cl_2 soln. [c] Product not isolated in a pure state.

higher than 1780 cm^{-1} (Table 1).[1,3,5] Furthermore, the α-pyrones have a very strong and characteristic band at 1563 cm^{-1} very useful for the diagnosis.

Table 2 gives the UV absorption spectra of related butenolides and α-pyrones and shows that the main K band is bathochromically shifted in the α-pyrones and the ε is much lower (almost half) than that of the corresponding butenolides.

TABLE 2. UV SPECTRA OF BUTENOLIDES AND α-PYRONES[a]

Compound	$\lambda_{max}(m\mu)$	ε
6-Phenyl-α-pyrone[b]	334	13,930
6-Phenyl-3-carboethoxy-α-pyrone	363	19,820
γ-Methylene-butenolide (protoanemonin)	260	14,000
Patulin	276	16,000
γ-Benzylidene-butenolide	331	26,050
γ-Benzylidene-α-carboxy-butenolide	358	35,890
Thermal cyclization product from III (R = n-C_4H_9)	316	9,645
Catalytic cyclization product from III (R = n-C_4H_9)	287	19,460
Thermal cyclization product from III (R = CH_3)	317	8,535
Catalytic cyclization product from III (R = CH_3)	283	—[c]

[a] Unless otherwise stated, UV spectra were measured for ethanol solutions.
[b] In dioxane solution.
[c] Product not isolated in a pure state.

Preparation and cyclization of alkyl-propargylidenemalonic acids. The methyl- and n-butyl-propargylidenemalonic acids (III, R = CH_3, n-C_4H_9) were prepared as described previously.[1] The resulting methyl esters were hydrolysed to the free acids with aqueous potassium hydroxide, a monomethyl ester of methylpropargylidene-malonic acid being eventually obtained which fails to undergo cyclization and, therefore, a *trans*-configuration of the free carboxyl group to the triple bond[6] was assigned to it.

The 6-methyl- and 6-n-butyl-3-carboxy-α-pyrones (IV, R = CH_3, n-C_4H_9) were prepared by heating the corresponding acid in acetic acid solution; alternatively, 6-butyl-3-carboxy-α-pyrone has been prepared by condensation of 1-heptynal with malonic acid in hot acetic acid solution, as described previously.[1]

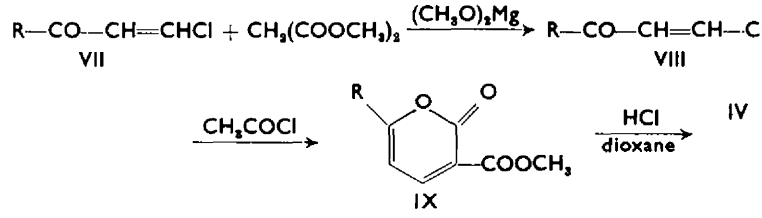
The catalytic isomerization was effected by dissolving the acid in methanol, adding two drops of 0·1N aqueous solution of silver nitrate and the mixture set aside for some hours. However, spectroscopic measurements show that the cyclization is practically complete after a few minutes.

Unequivocal synthesis of 6-alkyl-3-carboxy-α-pyrones. In order to obtain chemical evidence of the α-pyrone structure assigned to the thermal isomerization of methyl- and n-butyl-propargylidenemalonic acids, independent syntheses of these α-pyrones were undertaken.

6-Alkyl-3-carbomethoxy-α-pyrones (IX, R = CH_3, n-C_4H_9) were prepared according to the method by Kochetkov *et al.*[7] Hydrolysis of the methyl esters with HCl in dioxane give the corresponding 6-alkyl-3-carboxy-α-pyrones (IV) identical in all respects with the thermal cyclization products from alkyl-propargylidenemalonic acids.

[5] C. Belil, J. Pascual and F. Serratosa, *Anales real soc. españ. fís. y quím., Madrid* **59B**, 507 (1963).
[6] Cf. J. Castells and R. Mestres, *Anales real soc. españ. fís. y quím., Madrid* in preparation.
[7] N. K. Kochetkov, L. J. Kudryashov and B. P. Gottich, *Tetrahedron* **12**, 63 (1961).

The alternative methylation of 6-alkyl-3-carboxy-α-pyrones (IV) with diazomethane has not been affected since α-pyrones with a carboxyl group in the 3-position undergo a direct nuclear methylation when treated with excess diazomethane.[5]



EXPERIMENTAL

UV spectra were measured with a *Uvispek* Hilger Spectrophotometer and the IR spectra were recorded with a *Infracord* Perkin–Elmer, model 137. All m.ps were determined in a Kofler microscope and they are corrected.

n-Butylpropargylidenemalonic acid (III, R = n-C_4H_9). Improved conditions for the reported method[1] are as follows:

A mixture of hept-2-ynal[1] (4·9 g), methyl malonate (15·7 g) and acetic anhydride (7 g) was heated for 4 hr at 130°. The acetic anhydride and excess methyl malonate were removed *in vacuo* and the residue distilled at high vacuum to give dimethyl n-butylpropargylidenemalonate (7·1 g), b.p.$_{0.01}$ 79–82°; n_D^{25} 1·4922; λ_{max} 268 mμ; ε = 18·200 in EtOH. (Found: C, 64·24; H, 7·42; $C_{12}H_{16}O_4$ requires: C, 64·27; H, 7·20%).

The dimethylester (6·0 g) was shaken with 0·5N KOH aq (132 ml) until a homogeneous solution was obtained and then set aside for 24 hr. The solution was washed with ether, acidified with 2N H_2SO_4 and the free acid taken up with ether. The ether solution was washed and dried ($MgSO_4$).

Elimination of the ether *in vacuo* afforded the n-butylpropargylidenemalonic acid (4·5 g) as an oily product which eventually could be partially crystallized, m.p. 37–40°; λ_{max} 277 mμ; ε = 14·500 in EtOH. For the characterization of the crude acid see Ref. 1.

Catalytic cyclization of n-butylpropargylidenemalonic acid

γ-Pentylidene-α-carboxy-butenolide (V, R = n-C_4H_9). Crude n-butylpropargylidenemalonic acid (2·2 g) was dissolved in methanol (20 ml) and 3 drops 0·1N $AgNO_3$ aq was added. An exothermic reaction took place and the solution was set aside for 24 hr. Elimination of the methanol *in vacuo* gave a crystalline product which after recrystallization from benzene had m.p. 123·5–125·5° (2·0 g) and it was characterized as pure *γ-pentyliden-α-carboxy-butenolide*; λ_{max} 286 mμ; ε = 19·460 in EtOH. (Found: C, 60·95; H, 6·31; $C_{10}H_{12}O_4$ requires: C, 61·22; H, 6·17%). Acid equiv: 194·1. Calc. 196·2.

In another experiment a mixture of butenolide (0·63 g, m.p. 123·5–125·5°, IR spectrum = Fig. 3) and α-pyrone (0·54 g, m.p. 121–122°, IR spectrum = Fig. 4) was obtained from n-butylpropargylidenemalonic acid (1·9 g) in ice-cooled methanolic solution (20 ml), which were separated by fractional recrystallization from benzene and benzene–cyclohexane.

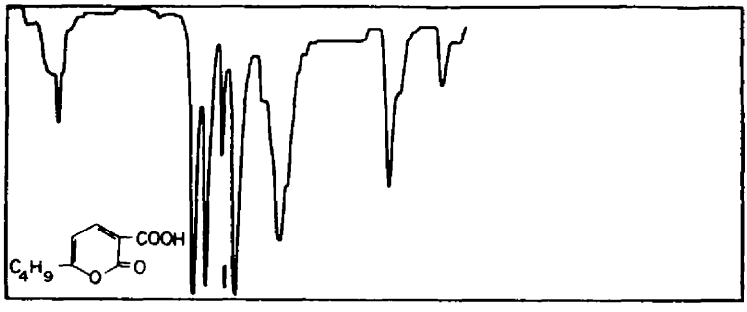


FIG. 3

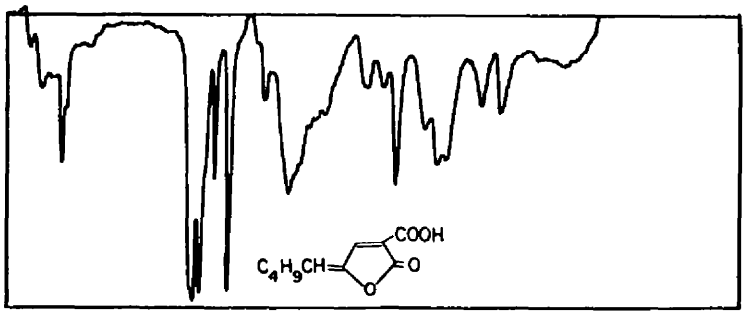


FIG. 4

Methylpropargylidenemalonic acid (III, R = CH_3). A mixture of tetrolic aldehyde (5·2 g), methyl malonate (14·0 g) and acetic anhydride (11·0 g) was heated, under an atm. of N_2, at 130° for 4 hr. The acetic anhydride and excess methyl malonate were removed *in vacuo* and the residue distilled at high vacuum to give *dimethylester* of *methylpropargylidenemalonic acid* (4·5 g), b.p.$_{0.4}$ 85°; $n_D^{22.5}$ 1·5023. (Found: C, 58·83; H, 5·89; $C_9H_{10}O_4$ requires: C, 59·33; H, 5·53%).

The dimethylester (3·6 g) was shaken with KOH aq (4·0 g in 170 ml) for 4 hr and then set aside for 24 hr at room temp. The resulting homogeneous solution was washed with ether, acidified with 2N H_2SO_4, the free acid taken up with ether, and the ether extracts dried ($MgSO_4$). Removal of the ether and recrystallization of the residue gave the *methylpropargylidenemalonic acid* (1·4 g), m.p. (on a preheated plate) 122·5–127·5° (some cyclization takes place); λ_{max} 273 mμ; ε = 11·610 in EtOH. (Found: C, 54·64; H, 4·26; $C_7H_6O_4$ requires: C, 54·55; H, 3·92%). Acid equiv: 71·6. Calc. 77·0

Hydrolysis of the dimethylester with one mole 0·1N KOH aq leads to a *monomethylester* (1·3 g from 2·4 g of dimethylester), m.p. 100–101°; λ_{max} 256 mμ; ε = 16·880 in EtOH. (Found: C, 56·87; H, 5·06; $C_8H_8O_4$ requires: C, 57·14; H, 4·80%). Acid equiv: 174·2. Calc. 168·15.

Thermal cyclization of methylpropargylidenemalonic acid

6-Methyl-3-carboxy-α-pyrone (IV, R = CH_3). Methylpropargylidenemalonic acid (0·3 g) was dissolved in glacial acetic acid (2 ml) and the solution was heated on the steam bath for 1 hr. The acetic acid was removed *in vacuo* (benzene was added to ensure the total elimination) and the residue (0·3 g) was chromatographed on silica-gel. The benzene–ether fractions (4:1) gave *6-methyl-3-carboxy-α-pyrone* (0·24 g), m.p. 171–172°; λ_{max} 317 mμ; ε = 8·535 in EtOH; IR spectrum = Fig. 5. (Found: C, 54·71; H, 4·66; $C_7H_6O_4$ requires: C, 54·55; H, 3·92%).

Catalytic cyclization of methylpropargylidenemalonic acid

γ-Ethylidene-α-carboxy-butenolide (V, R = CH_3). Methylpropargylidenemalonic acid (0·30 g) was dissolved in methanol (7 ml), the solution chilled with ice-water and 2 drops 0·1N $AgNO_3$ aq added. After 24 hr, the solution was filtered and the solvent removed *in vacuo* to give a mixture of α-pyrone and *γ-ethylidene-α-carboxy-butenolide*. Chromatography on silica-gel afforded pure α-pyrone (64 mg from 75 g of crude product), m.p. 171–172°.

In one experiment the IR spectrum (Fig. 6) of the crude cyclization product showed the almost exclusive formation of butenolide, but it could not be worked up without polymerization.

n-Butyl β-chlorovinyl ketone (VII, R = *n*-C_4H_9). A stream of dry acetylene was passed into a stirred, ice-cooled, solution of valeroyl chloride (60·3 g) in carbon tetrachloride (160 ml), containing a trace of $HgCl_2$, powdered $AlCl_3$ (73·4 g) being added in small fractions every 30 min. After this addition, the stream of acetylene was continued for a further 30 min and the black reaction mixture was then poured into ice-water. The lower organic layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed and dried ($MgSO_4$). The solvents were removed *in vacuo* and the residue distilled to give *n-butyl β-chlorovinyl ketone* (47·8 g), b.p.$_{20}$ 76°; n_D^{16} 1·4634. (Found: C, 57·26; H, 7·90; $C_7H_{11}C_{10}$ requires: C, 57·32; H, 7·56%).

Methyl (3-oxohept-1-enyl)malonate (VIII, R = n-C_4H_9). Dry magnesium methoxide (prepared

from 6·1 g Mg, 40 ml methanol and 1 ml CCl_4) was suspended in toluene (50 ml) and to the stirred suspension was added dropwise methyl malonate (33·0 g) and after the total addition the mixture was heated at 45° for 30 min. The reaction mixture was cooled with ice-salt and butyl β-chlorovinyl ketone (29·3 g) was added dropwise, the stirring being continued for 30 min and then set aside overnight. The reaction mixture was hydrolysed with HCl aq (13 ml in 100 ml of water) and worked up as usual[7] to give *methyl (3-oxohept-1-enyl)malonate* (19·3 g) as a colorless liquid, $b.p._{\cdot 01}$ 119° $n_D^{18\cdot 5}$ 1·4718. (Found: C, 59·52; H, 7·74; $C_{12}H_{18}O_5$ requires: C, 59·51; H, 7·49%)

6-Butyl-3-carbomethoxy-α-pyrone (IX, R = *n*-C_4H_9). A mixture of methyl (3-oxohept-1-enyl)malonate (15·8 g) and acetyl chloride (15 ml) was refluxed for 5 hr. The excess acetyl chloride was removed *in vacuo* and the residue distilled to give *6-butyl-3-carbomethoxy-α-pyrone* (7·1 g), as a liquid, $b.p._{\cdot 01}$ 117°, that solidified on standing, m.p. 26–27°; λ_{max} 321 mμ; ε = 12·740 in EtOH. (Found: C, 62·50; H, 6·89; $C_{11}H_{14}O_4$ requires: C, 62·84; H, 6·71%).

6-Butyl-3-carboxy-α-pyrone (IV, R = n-C_4H_9). To a solution of 6-butyl-3-carbomethoxy-α-pyrone (0·4 g) in dioxane (12 ml) was added conc. HCl (1 ml) and the solution heated on the steam bath for 1 hr. The dioxane was removed and the solid residue dissolved in ether. The ether solution was extracted with $NaHCO_3$ aq, the alkaline solution was washed with ether and then acidified with dil H_2SO_4, and the free acid taken up with ether. The combined ether extracts were dried and evaporated to give 6-butyl-3-carboxy-α-pyrone (0·23 g) which after recrystallization from ether–pet ether had m.p. 122–123°, and it was identical, in all respects, with the α-pyrone from the thermal cyclization of n-butylpropargylidenemalonic acid.

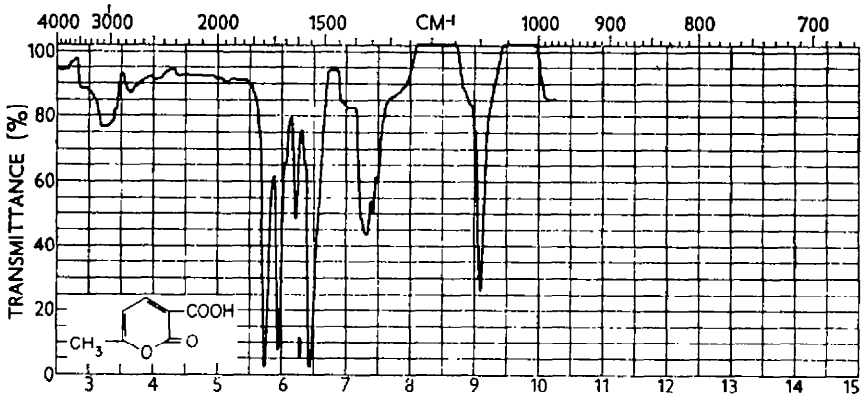


FIG. 5

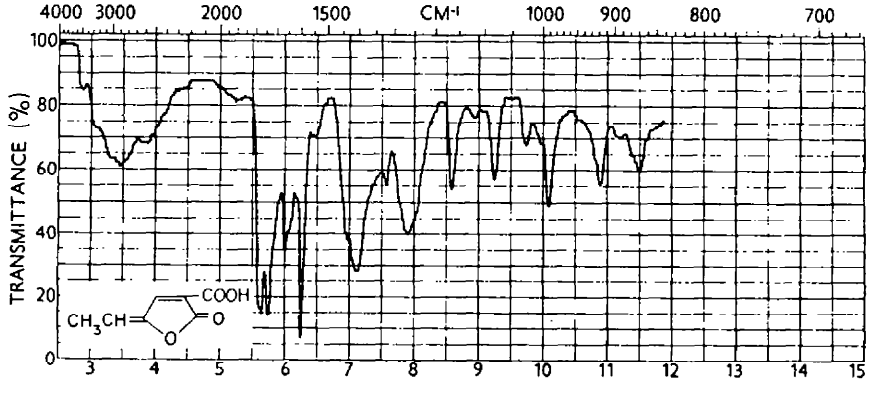


FIG. 6

Methyl (3-oxobut-1-enyl)malonate (VIII, R = CH_3). The product was obtained from methyl β-chlorovinyl ketone (7·6 g) according to the above described procedure, as a liquid (5·6 g), b.p.$_{1\cdot5}$ 120°, that did not analyze correctly, being only identified by its IR spectrum.

6-*Methyl*-3-*carbomethoxy*-α-*pyrone* (IX, R = CH_3). This, m.p. 90–91°, was obtained (0·4 g) from methyl (3-oxobut-1-enyl)malonate (1·0 g) and acetyl chloride (0·83 ml) as described for the butyl analog; λ_{max} 317 mμ; ε = 10·000 in EtOH. (Found: C, 57·25; H, 4·92; $C_8H_8O_4$ requires: C, 57·14; H, 4·80%).

6-*Methyl*-3-*carboxy*-α-*pyrone* (IV, R = CH_3). Hydrolysis of the methyl ester (0·40 g) with dioxane–HCl gave 6-methyl-3-carboxy-α-pyrone (0·22 g), m.p. 171–172°, identical, in all respects, with the α-pyrone from the cyclization of methylpropargylidenemalonic acid. The analysis of samples prepared according to this procedure give also high figures for H. (Found: C, 54·37; H, 4·52; $C_7H_6O_4$ requires: C, 54·55; H, 3·92%).

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