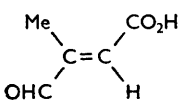
119. *Oxidation of 3-Methylbut-2-enolide to* cis-β-*Formylcrotonic Acid.*

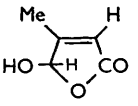
By W. J. Conradie, C. F. Garbers, and P. S. Steyn.

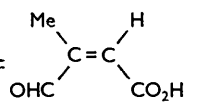
Ethyl γ-acetoxy-β-hydroxy-β-methylbutyrate has been converted into 3-methylbut-2-enolide which on treatment with *N*-bromosuccinimide and subsequent hydrolysis afforded pure, crystalline *cis*-β-formylcrotonic acid.

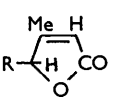
β-Formylcrotonic acid and its esters could form intermediates in the synthesis of dimers of vitamin A. For *trans*-β-formylcrotonic acid (I) [1] and its esters,[2,3] efficient syntheses have been elaborated, but for *cis*-β-formylcrotonic acid (II) an efficient synthesis is still lacking. *trans*-β-Formylcrotonates, on acid hydrolysis,[3,4] yield the *cis*-acid (II), but the latter has not yet been isolated in a pure form. We have investigated the oxidation of 3-methylbut-2 enolide and the acid hydrolysis of methyl *trans*-β-formylcrotonate as possible methods for the synthesis of *cis*-β-formylcrotonic acid.

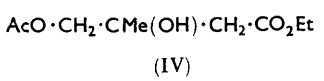
Synthesis of 3-methylbut-2-enolide has been attempted before, but no analysis of the product has been published.[5,6] We have synthesised the butenolide (IIIa) from ethyl γ-acetoxy-β-hydroxy-β-methylbutyrate (IV).[7] Saponification of the ester (IV) gave a mixture of the butenolide (IIIa) and the 3-hydroxy-3-methylbutanolide (Va) in various yields. Treatment of the crude saponified product with hydrogen bromide in acetic acid [8] gave the butenolide (IIIa) in poor yield. Better yields were obtained when the butenolide (IIIa) and butanolide (Va) were separated by fractional distillation, the latter being subsequently heated with pyridine and acetic anhydride. Treatment of the saponified product with a mixture of pyridine and acetic anhydride [6] at room temperature yielded both the acetoxy-butanolide (Vb) and the butenolide (IIIa), and the former was converted in high yield into the butenolide (IIIa) by heating it with pyridine.

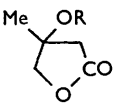

(I)

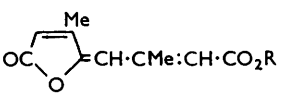

(IIa)


(IIb)


(IIIa: R = H)
(IIIb: R = Br)


(IV)


(Va: R = H)
(Vb: R = Ac)


(VIa: R = H)
(VIb: R = Me)

The butenolide (IIIa) with *N*-bromosuccinimide yielded smoothly 4-bromo-3-methylbut-2-enolide (IIIb) but this could not be separated from the unchanged butenolide (IIIa) by fractional distillation, and prolonged heating caused decomposition of the product. The bromination mixture was therefore hydrolysed to give a mixture consisting mainly of *cis*-β-formylcrotonic acid (II) and the unchanged butenolide (IIIa). Attempted separation of these two products, by conversion of the acid (II) with sodium hydrogen carbonate into its sodium salt and extraction of the non-acidic substances, failed. A condensation

[1] Pommer and Sarnecki, G.P. 1,068,709.
[2] Pommer, *Angew. Chem.*, 1960, **72**, 811.
[3] Sisido, Kondô, Nozaki, Tuda, and Udô, *J. Amer. Chem. Soc.*, 1960, **82**, 2286.
[4] Wiley and Weaver, *J. Amer. Chem. Soc.*, 1955, **77**, 3422; 1956, **78**, 808.
[5] Smith and Jones, *Canad. J. Chem.*, 1959, **37**, 2092.
[6] Kuschinsky, Lange, Scholtissek, and Turba, *Biochem. Z.*, 1955, **327**, 314.
[7] Stewart and Woolley, *J. Amer. Chem. Soc.*, 1959, **81**, 4951.
[8] Rubin, Paist, and Elderfield, *J. Org. Chem.*, 1941, **6**, 260.

product (VIa) of the butenolide (IIIa) with the formylcrotonic acid (IIb) was isolated instead. This product had an absorption maximum at 320·5 mμ,and its infrared spectrum showed two bands in the C=O stretching range ($\nu_{max.}$ 1773 and 1755 cm.$^{-1}$) of the but-2-enolide ring. This splitting of the carbonyl stretching frequency has been established as a general property of 3-substituted and 3,4-disubstituted but-2-enolides.[9] Further proof of structure (VIa) was obtained from the presence of two *C*-CH_3 groups and from the nuclear magnetic resonance spectrum of the methyl ester (VIb). Apart from the three-proton singlet at τ 6·23, due to the methoxyl group, the nuclear magnetic resonance spectrum showed two three-proton doublets at τ 7·65 and 7·71 (J ~1·5 c./sec.) ascribed to the two methyl groups on the double bonds, and two one-proton unresolved multiplets at τ 3·92 and 4·15 due to the two α-hydrogen atoms. An unresolved triplet at τ 2·46 is ascribed to the remaining γ-hydrogen. The same acid (VIa) was also obtained by condensation of the formylcrotonic acid (II) with the butenolide (IIIa).

The components of the hydrolysed bromination products were effectively separated by counter-current distribution. Thus, *cis*-β-formylcrotonic acid was isolated as crystals and was identical with the crystalline *cis*-β-formylcrotonic acid obtained in high yield from methyl *trans*-β-formylcrotonate by acid hydrolysis. Its ultraviolet and infrared spectra showed it to have the cyclic structure (IIa), and this was confirmed by the properties of the γ-anilino-derivative.[10] The formylcrotonic acid (IIb) reacted with 2,4-dinitrophenylhydrazine in acid medium to give a hydrazone derivative which was identical with the product previously prepared.[4]

Experimental

Ultraviolet and infrared spectra were determined on a Zeiss model 4MQ11 and a Perkin-Elmer model 21 spectrophotometer, respectively. Light petroleum refers to the fraction of b. p. 40—60°.

3-*Methylbut*-2-*enolide* (IIIa).—The starting material, ethyl γ-acetoxy-β-hydroxy-β-methylbutyrate (IV), was prepared from acetoxyacetone and ethyl bromoacetate.[7] This acetoxy-ester (IV) was saponified according to procedure A of Stewart and Woolley,[7] to give a mixture of butenolide (IIIa) and hydroxy-butanolide (Va). The butenolide (IIIa) was obtained in several ways from the saponified material, as follows:

(*a*) *Dehydration with pyridine and acetic anhydride.* The saponified material was fractionally distilled through a Vigreaux column to give the butenolide (IIIa), b. p. 70°/0·1 mm., in 31% yield, and the hydroxy-butanolide (Va), b. p. 123—127°/0·1 mm., in 21% yield (lit.,[7] b. p. 90°/0·001 mm.). The hydroxy-butanolide (Va) (9 g.) was heated under reflux for 20 min. with pyridine (12 ml.) and acetic anhydride (12 ml.). The excess of pyridine and anhydride was removed *in vacuo*, the residue dissolved in 6N-hydrochloric acid, and the resulting solution continuously extracted with ether. The ether solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was distilled to yield the butenolide (IIIa) (4·3 g.), b. p. 68·5—70°/0·1 mm. The butenolide fractions were combined and redistilled to give 3-methylbut-2-enolide (IIIa), b. p. 70°/0·1 mm., n_D^{25} 1·6735 (Found: C, 61·3; H, 6·1. $C_5H_6O_2$ requires C, 61·25; H, 6·1%), $\lambda_{max.}$ 211·5 mμ (ε 13,090; concn. 0·5105 × 10^{-4} mole/l. in water), $\nu_{max.}$ (film) 1778 and 1744 cm.$^{-1}$ (C=O).

(*b*) *Reaction with pyridine in cold acetic anhydride.*[6] The saponified material was distilled and the distillate, b. p. 105—126°/0·3 mm., (37 g.) was mixed with pyridine (120 ml.) and acetic anhydride (120 ml.) and left at room temperature for 18 hr. The excess of reagents was removed *in vacuo* and the residue adsorbed on alumina. The product was eluted with ether–ethyl acetate (1 : 1), the solvent removed *in vacuo*, and the residue distilled to yield a distillate (39·3 g.), b. p. 93—130°/0·8 mm., which was still contaminated with pyridine derivatives. This distillate was consequently dissolved in 6N-hydrochloric acid and worked up as described in (*a*). Distillation of the residue though a Vigreaux column yielded a mixture (23·2 g.), b. p. 97—105°/0·8 mm., of the acetoxy-butanolide (Vb) and the butenolide (IIIa). Crystallisation of this

[9] Jones, Angell, Ito, and Smith, *Canad. J. Chem.*, 1959, **37**, 2007; Castaner and Pascual, *J.*, 1958, 3962; Belil, Castella, Mestres, Pascual, and Serratosa, *Anales real Soc. espan. Fis. Quim.*, 1961, **57**, *B*, 617.

[10] Wheeler, Young, and Erley, *J. Org. Chem.*, 1957, **22**, 547.

mixture from ether–light petroleum, gave 3-*acetoxy*-3-*methylbutanolide* (Vb) (20 g.), m. p. 56° (Found: C, 53·4; H, 6·4; Ac, 26·5. $C_7H_{10}O_4$ requires C, 53·2; H, 6·4; Ac, 27·2%), $\nu_{max.}$ (in $CHCl_3$) 1785 and 1740 cm.$^{-1}$. 3-Methylbut-2-enolide (IIIa), b. p. 70°/0·1 mm., was isolated from the mother-liquors.

The acetoxy-butanolide (Vb) (3 g.) was refluxed with pyridine (1·46 g.) and worked up as described to give the butenolide (IIIa) (1·65 g.), b. p. 70/0·1 mm.

Treatment of the acetoxy-butanolide (Vb) with sodium t-butoxide in tetrahydrofuran or with an excess of boiling pyridine led to decreased yields of the butenolide.

(*c*) *Dehydration by acetic acid saturated with hydrogen bromide.*[8] The crude saponified material (21·3 g.) was dissolved in a saturated solution of hydrogen bromide in acetic acid (80 ml.) and was refluxed for 50 min. The dark mixture was cooled and poured into ice–water (200 ml.), the acids were neutralised by the addition of potassium carbonate, and the solution was continuously extracted with ether. The ether extract was worked up as in (*a*), and fractionation of the residue, after removal of the ether, gave the butenolide (IIIa) (4·5 g.), b. p. 66—70°/0·1 mm.

cis-β-*Formylcrotonic acid* (IIb).—3-Methylbut-2-enolide (7 g.) in carbon tetrachloride (20 ml.) was refluxed with N-bromosuccinimide (13·1 g.) for 35 min., reaction being then complete. The mixture was cooled, filtered from succinimide, and evaporated *in vacuo*. The residue was distilled through a Vigreaux column to give fractions (1) (8·12 g.), b. p. 72—74°/0·04 mm., and (2) (0·46 g.), b. p. 85—113°/0·1 mm. Treatment of these fractions with 2,4-dinitrophenylhydrazine reagent gave the same 2,4-dinitrophenylhydrazone, m. p. 248° (from ethyl acetate) (lit.,[4] 250°) (Found: C, 44·7; H, 3·5; N, 18·4. Calc. for $C_{11}H_{10}N_4O_6$: C, 44·9; H, 3·4; N, 19·05%), $\lambda_{max.}$ 372 mμ (ε 31,500 in 96% EtOH). The bromination product from fraction (1) (5·97 g.) was heated under reflux with water (50 ml.) for 1 hr. and the homogeneous aqueous solution subsequently continuously extracted with ether. The ether extract was dried ($MgSO_4$), and the ether removed *in vacuo*, to yield the crude formylcrotonic acid (IIa) (4 g.) as an oil. Part of this crude product (3·3 g.) was further purified by a 36-tube counter-current distribution (phase capacity 50 ml.) in 1 : 1 ether–water at 25°. The contents of the tubes were determined spectrophotometrically and the solutions were pooled and worked up as follows:

(*a*) Tubes 1—17 (max. concn. at tube 8) contained formylcrotonic acid (IIb). The ether layers were combined and the aqueous layers extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue (3·1 g.) distilled practically completely at 110° (air-bath temp.)/0·01 mm., to yield the cis-β-*formylcrotonic acid* which crystallised. Recrystallised from ether–light petroleum, it had m. p. 45—46° (Found: C, 52·95; H, 5·5. $C_5H_6O_3$ requires C, 52·65; H, 5·3%), $\lambda_{max.}$ 211 mμ (ε 13,700; concn. $0·5105 \times 10^{-4}$ mole/l. in H_2O), $\nu_{max.}$ (film) 3455 (OH) and 1774, 1745 cm.$^{-1}$ (weak splitting of CO frequency).

4-*Anilino*-3-*methylbut*-2-*enolide*.—This lactone was prepared[10] by heating a solution of *cis*-β-formylcrotonic acid (0·25 g.) in acetone (0·5 ml.) to the b. p. and adding a solution of aniline (0·208 g.) in acetone (0·5 ml.). Refluxing was continued for 5 min. The crystals formed were collected and thrice recrystallised from ethyl acetate, to yield the *anilino-butenolide* (100 mg.), m. p. 149° (Found: C, 69·6; H, 5·8. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·8%), $\lambda_{max.}$ 207, 237, and 280 mμ (ε 16,600, 13,450, and 2700, respectively, in 96% EtOH).

(*b*) Tubes 18—30 (max. concn. at tube 25). The material (0·112 g.) was isolated as described under (*a*) and distilled [b. p. 80—90° (air-bath temp.)/0·01 mm.]. The distillate contained bromine and did not yield a 2,4-dinitrophenylhydrazone and was not investigated further. It had $\nu_{max.}$ (film) 1746 cm.$^{-1}$.

(*c*) Tubes 31—36 (max. concn. at tube 35) contained very little bromine-free material (0·06 g.).

Addition of azoisobutyronitrile[11] to the butenolide and *N*-bromosuccinimide in carbon tetrachloride reduced the time required for reduction of the *N*-bromosuccinimide, but did not affect the constitution of the brominated reaction mixture.

Acid Hydrolysis of Methyl trans-β-*Formylcrotonate* (with J. P. VAN DER MERWE).[4]—Methyl *trans*-β-formylcrotonate (10 g.) was refluxed with 6N-hydrochloric acid (35 ml.) for 3 hr. Every 45 min. ~2 ml. were distilled from the reaction mixture to remove the methanol formed. The reaction mixture was concentrated *in vacuo*, water (20 ml.) added, and the latter again removed

[11] Horner and Winkelmann, *Angew. Chem.*, 1959, **71**, 349.

in vacuo. This was repeated five more times and the residue (8·2 g.) was distilled *in vacuo*, to give *cis*-β-formylcrotonic acid (7·6 g.), b. p. 130°/0·5 mm., m. p. 45—46° (Found: C, 52·65; H, 5·7%). The infrared spectrum of a chloroform solution was identical with that of the *cis*-β-formylcrotonic acid prepared from the butenolide (IIIa).

4-(3-*Carboxy*-2-*methylallylidene*)-3-*methylbut*-2-*enolide* (VIa).—A mixture of 3-methylbut-2-enolide (0·5 g.) and β-formylcrotonic acid (IIb) (0·586 g.) was heated for 5 min. with water (10 ml.) and sodium hydrogen carbonate (1·9 g.) on a boiling-water bath, then cooled, extracted with ether, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The latter extracts were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*, to give a crystalline residue (680 mg.) which was recrystallised from ethyl acetate to yield the *butenolide* (VIa) (265 mg.), m. p. 209° (Found: C, 62·2; H, 5·2; *C*-CH_3, 15·15. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·15; 2*C*-CH_3, 15·2%), $\lambda_{max.}$ 320·5 mμ (ε 25,800 in 96% EtOH), $\nu_{max.}$ (in saturated chloroform solution) 1773 and 1755 $cm.^{-1}$ (weak splitting of butenolide C=O frequency).

The same product (VIa) (m. p. and mixed m. p. 209°) was obtained when the bromination mixture (4 g.) was heated on a water bath with water (20 ml.) and sodium hydrogen carbonate (3·8 g.) and the reaction mixture worked up as above.

The butenolide (VIa) was treated with diazomethane and gave the *ester* (VIb), m. p. 116° (Found: C, 63·7; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

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Department of Chemistry, University of Stellenbosch,
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