

564. Bromination of But-2-enolides with N-Bromosuccinimide

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Butenolides (VI, a—e) were synthesised and brominated with *N*-bromosuccinimide to give the γ -bromobutenolides.

OXIDATION of 3-methylbut-2-enolide with *N*-bromosuccinimide and hydrolysis of the bromination product gave the lactol tautomer (I) of cis- β -formylcrotonic acid (II), required for synthetic work in the vitamin A field.¹ This oxidation has now also been performed with other but-2-enolides.

Butenolides (VIa)² and (VI d)³ were prepared as described. The hydroxy-ester (Vb), required for the synthesis of 3-ethylbut-2-enolide, was synthesised from 1-acetoxybutan-2-one (prepared from propionyl bromide and diazomethane *via* the diazoketone)⁴ and ethyl bromoacetate in a Reformatski reaction.⁵ Saponification of the ester (Vb) gave a mixture of the butenolide (VIb) and the hydroxybutanolide (VIIb) which on treatment with hydrogen bromide in acetic acid³ gave the butenolide (VIb) in poor yield. Better results were obtained by reaction of the mixture with acetic anhydride, separation of the butenolide (VIb) from the acetoxybutanolide (VIII), and conversion of the latter into the butenolide (VIb) by heating it with pyridine.¹ Similarly the butenolides (VIc) and (VIe) were synthesised by saponification of the corresponding hydroxy-esters (Vc) and (Ve); any hydroxybutanolide present was dehydrated to the butenolide.

The results from a large number of *N*-bromosuccinimide brominations have indicated that allylic hydrogens are substituted preferentially to ethylenic hydrogens⁶ and that increased acidity of the hydrogens does not necessarily lead to a decrease in the ease of substitution.⁷ In agreement therewith, 3-methylbut-2-enolide was readily converted into 4-bromo-3-methylbut-2-enolide.¹ Similar results were obtained with 3-ethylbut-2-enolide, and but-2-enolide. The bromobutenolides (IX; R = R' = H, R'' = Br) and (IX;

¹ W. J. Conradie, C. F. Garbers, and P. S. Steyn, *J.*, 1964, 594.

² R. J. D. Smith and R. N. Jones, *Canad. J. Chem.*, 1959, **37**, 2092.

³ M. Rubin, W. D. Paist, and R. C. Elderfield, *J. Org. Chem.*, 1941, **6**, 260.

⁴ B. Eistert in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, 1948, p. 513.

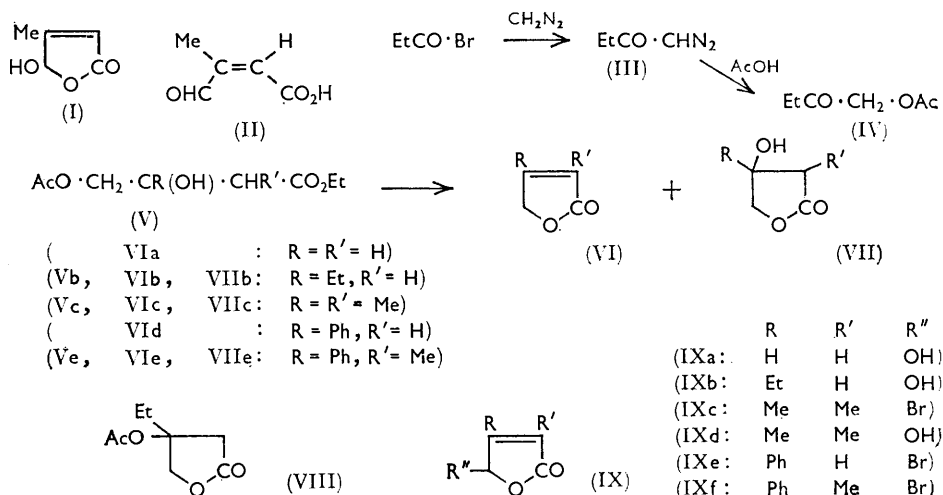
⁵ J. M. Stewart and D. W. Woolley, *J. Amer. Chem. Soc.*, 1959, **81**, 4951.

⁶ R. E. Pearson and J. C. Martin, *J. Amer. Chem. Soc.*, 1963, **85**, 354, 3142; P. S. Skell, D. L. Tuleen, and P. D. Radio, *ibid.*, p. 2850; C. Walling, A. L. Rieger, and D. D. Tanner, *ibid.*, p. 3129; C. Walling and A. L. Rieger, *ibid.*, p. 3134; G. A. Russell and C. DeBoer, *ibid.*, p. 3136; G. A. Russell and K. M. Desmond, *ibid.*, p. 3139.

⁷ L. Horner and E. Winkelmann, *Angew. Chem.*, 1959, **71**, 349.

R = Et, R' = H, R'' = Br) were not isolated in pure form, but on hydrolysis the hydroxybutenolides (IXa) and (IXb) could be separated from the respective unchanged butenolides. In both instances products which still contained bromine were isolated from the hydrolysed mixture, but they were not investigated. The hydroxybutenolides (IXa) and (IXb) readily gave the 2,4-dinitro- and 4-nitro-phenylhydrazones of the corresponding tautomeric cis- β -formylacrylic acids.

2,3-Dimethylbut-2-enolide reacted with *N*-bromosuccinimide to give a bromo-derivative (IXc) which did not yield a dinitrophenylhydrazone, even after prolonged boiling with the



reagent. Attempted purification of the bromobutenolide by chromatography on alumina led to hydrolysis *in situ* to give the lactol (IXd). The bromobutenolide was effectively purified by chromatography on silica gel. Its infrared spectrum showed an absorption band at 1775 cm^{-1} , which is displaced by 25 cm^{-1} if compared with the carbonyl absorption band of the dimethylbutenolide (VIc). Such displacements have been observed in γ -lactones with electronegative substituents in the γ -position.⁸ Although the structure would be mechanistically unlikely, the bromobutenolide (IXc) was at first thought to be 2-bromomethyl-3-methylbut-2-enolide, but the nuclear magnetic resonance spectra clearly indicated the presence of two three-proton multiplets in both the hydroxybutenolide (IXd) and the bromobutenolide (IXc) (see Table). The reluctance of the hydroxy-lactone (IXd) to yield a hydrazone shows it to be entirely in the lactol form, which is compatible with the observation that dimethylmaleic acid spontaneously forms an anhydride.

3-Phenyl- and 2-methyl-3-phenyl-but-2-enolide have, in addition to the 4-methylene group, the α -carbon or the α -methyl group as possible positions of attack by the *N*-bromosuccinimide, since the intermediate radicals will be stabilised by resonance by the phenyl and substituted styryl groups respectively; *e.g.*, α -methylstyrene gives allylic and vinylic substitution.⁹ Both butenolides however gave the 4-bromobutenolides, as indicated by their nuclear magnetic resonance spectra (see Table). The bromobutenolides (IXe) and (IXf) both showed carbonyl absorption bands displaced by approximately 30 cm^{-1} to higher frequencies if compared with the band at approximately 1750 cm^{-1} for the

⁸ *E.g.*, W. Brügel, G. Stengel, F. Reicheneder, and H. Suter, *Angew. Chem.*, 1956, **68**, 441; R. E. Lutz, C. T. Clark, and J. P. Feifer, *J. Org. Chem.*, 1960, **25**, 346; R. D. H. Murray, W. Parker, and R. A. Raphael, *Tetrahedron*, 1961, **16**, 74; G. W. Perold and K. Pachler, *Proc. Chem. Soc.*, 1964, 62.

⁹ H. Pines, H. Alul, and M. Kolobielski, *J. Org. Chem.*, 1957, **22**, 1113.

butenolides.^{10,11} The ultraviolet spectra of the bromo-derivatives (IXe) and (IXf) showed bathochromic shifts if compared with the spectra of the butenolides (IVd) and (VIe) respectively.

It therefore appears that the simple butenolides are attacked preferentially at the

Spectral data of butenolides

Compound (IX)			Infrared		Nuclear magnetic resonance †	
R	R'	R''	Solvent	$\nu(\text{CO})$ (cm. ⁻¹)	Chemical shift (τ scale)	Assignment
Et	H	H	Film	1781 1746		
Et	H	OH	CHCl ₃	1762		
Me	Me	H	Film	1750 *	7.96, 8.17	two Me
					5.34	CH ₂
Me	Me	OH	CHCl ₃	1756	8.01, 8.21	two Me
					4.08	CH(C-4)
					4.54	OH
Me	Me	Br	Film	1775	7.87, 8.10	two Me
					3.27	CH(C-4)
Ph	H	Br	CHCl ₃	1784	3.49	α -H(s)
					2.67	γ -H(s)
Ph	Me	H	CHCl ₃	1748		
Ph	Me	Br	CHCl ₃	1778	2.76	γ -H(q)
					7.86	Me(d)

* Cf. ref. 5. † Unless otherwise indicated, values refer to multiplet absorptions; s = singlet, d = doublet, q = quadruplet.

4-methylene group by *N*-bromosuccinimide. A similar observation was recently made in the bromination of 2-acetoxy-3-methylbut-2-enolide,¹² but it is interesting that certain cardenolides gave the 17-bromo-derivatives on bromination with *N*-bromosuccinimide.¹³

EXPERIMENTAL

Ultraviolet and infrared spectra were determined on a Zeiss model 4 MQ11 and a Perkin-Elmer model 21 Spectrophotometer, respectively. N.m.r. spectra were recorded on a Varian A-60 spectrometer, dilute deuterio-chloroform solutions being used with tetramethylsilane as internal reference (τ 10.0).

Analyses were done by F. Pascher, Bonn, and by the Micro-analytical Section, S.A.C.S.I.R., Pretoria.

Synthesis of Butenolides.—*But-2-enolide* (VIa). This was prepared from propargyl alcohol according to the method of Smith and Jones;² it had b. p. 87—90°/12 mm., n_D^{25} 1.634 (lit.,² b. p. 86—87°/12 mm., n_D^{25} 1.4670).

3-Ethylbut-2-enolide (VIb). Propionyl bromide (50 g.) was added gradually to a stirred and cooled solution (0°) of diazomethane (prepared from 159 g. of nitrosomethylurea) in ether (1540 ml.). The mixture was left in the refrigerator overnight, then the ether was removed *in vacuo* and the crude diazoketone was treated with acetic acid (300 ml.) and heated until gas evolution stopped; potassium acetate was added, and the mixture was refluxed for 2 hr.⁴ When cooled it was diluted with ether (1500 ml.) and neutralised with potassium carbonate. The solids were collected at the pump and washed with ether. The ether was evaporated from the combined filtrates and the residue distilled through a Vigreux column to yield 1-acetoxybutan-2-one (IV) (68%), b. p. 83—85°/18 mm., n_D^{25} 1.416 (Found: C, 55.9; H, 7.8. C₆H₁₀O₃ requires C, 55.4; H, 7.7%).

¹⁰ R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Canad. J. Chem.*, 1959, **37**, 2007; J. Castaner and J. Pascual, *J.*, 1958, 3962; G. Belil, J. Castella, R. Mestres, J. Pascual, and F. Serratos, *Anales real Soc. españ. Fis. Quim.*, 1961, **57**, B, 617.

¹¹ L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 2nd edn., 1958, p. 186.

¹² D. M. Green, A. G. Long, P. J. May, and A. F. Turner, *J.*, 1964, 766.

¹³ L. Ruzicka, P. A. Plattner, and H. Heusser, *Helv. Chim. Acta*, 1946, **29**, 473.

Ethyl β -acetoxyethyl- β -hydroxyvalerate (Vb) (31.1 g.) b. p. 85—90°/0.7 mm., was synthesised in 60% yield from the acetoxybutanone (IV) (31 g.), ethyl bromoacetate (41 g.), and zinc (30 g.) in ether (113 ml.), and saponified according to procedure A of Stewart and Woolley⁵ to give a mixture of 3-ethylbut-2-enolide (VIb) and 3-ethyl-3-hydroxybutanolide (VIIb). The butenolide (VIb) was obtained from this saponification mixture in various ways.

(i) Saponified material (18 g.) was mixed with pyridine (15 ml.) and acetic anhydride (15 ml.) and set aside for 18 hr. The mixture was concentrated *in vacuo*, and a solution of the residue in 6*N*-hydrochloric acid was continuously extracted with ether to give a product which was distilled to yield a mixture (8.4 g.); this was fractionally crystallised from light petroleum to yield 3-acetoxy-3-ethylbutanolide (VIII) (2 g.), m. p. 36° (Found: C, 55.4; H, 6.3. $C_8H_{12}O_4$ requires C, 55.8; H, 7.0%), and 3-ethylbut-2-enolide (VIb) (6 g.), b. p. 74°/0.1 mm., m. p. 33°, λ_{\max} . 212.5 μ (ϵ 8050 in water) (Found: C, 64.0; H, 7.35. $C_6H_8O_2$ requires C, 64.3; H, 7.2%).

The acetoxybutanolide (VIII) (1 g.) was refluxed with pyridine¹ for 10 min. and worked up as described to yield butenolide (VIb) (0.57 g.), b. p. 74°/0.1 mm.

(ii) Alternatively, the saponified product could be fractionally distilled to yield the ethylbutenolide (VIb) (24%), b. p. 74—76°/0.1 mm., and hydroxybutanolide (VIIb) (23%), b. p. 132—138°/0.12 mm. The latter (2 g.) was dehydrated by refluxing for 20 min. with pyridine-acetic anhydride (1 : 1; 4.9 ml.). The butenolide (VIb) (0.93 g.), b. p. 78—80°/0.15 mm. was isolated as described in (i).

2,3-Dimethylbut-2-enolide (VIc). Ethyl γ -acetoxy- β -hydroxy- $\alpha\beta$ -dimethylbutyrate (Vc) was saponified according to procedure A of Stewart and Woolley⁵ to give 2,3-dimethylbut-2-enolide (VIc) (45%) and the hydroxybutanolide (VIIc); the latter (VIIc) was converted into the butenolide (VIc) in 50% yield by treatment with hydrogen bromide in acetic acid.³ Recrystallisation of the combined product gave the butenolide (VIc), m. p. 34—36° (lit.,⁵ m. p. 36—38°).

3-Phenylbut-2-enolide (VIId) prepared as described³ had m. p. 92°.

2-Methyl-3-phenylbut-2-enolide (VIe). Methyl γ -acetoxy- β -hydroxy- α -methyl- β -phenylbutyrate (Ve) was prepared¹⁴ from ω -acetoxyacetophenone (80 g.), methyl α -bromopropionate (80 g.), zinc (33 g.), and benzene (350 ml.). The crude acetoxybutyrate (Ve) was saponified and the butenolide (VIe) was obtained from the saponification mixture as follows:

(i) The mixture (24 g.) was left with pyridine-acetic anhydride (1 : 1; 29.2 ml.) for 18 hr. and worked up as in (i) above. The crude butenolide was thrice recrystallised from benzene to yield 2-methyl-3-phenylbut-2-enolide (8.6 g.), m. p. 121—122°, λ_{\max} . 212 and 260 μ (ϵ 13,200 and 16,000, respectively, in cyclohexane), ν_{\max} . 1750 cm^{-1} (C=O) (Found: C, 75.8; H, 5.8. $C_{11}H_{10}O_2$ requires C, 75.9; H, 5.75%).

(ii) The saponified material (15 g.) was refluxed for 1 hr. with a saturated solution of hydrogen bromide in acetic acid (50 ml.) and worked up as described³ to give the butenolide (VIe) (3.3 g.), m. p. (from benzene) and mixed m. p. 121—122°.

Reaction of Butenolides with N-Bromosuccinimide.—Bromination of but-2-enolide. The butenolide (2.9 g.) in carbon tetrachloride (9 ml.) was refluxed with *N*-bromosuccinimide (6.32 g.) and azoisobutyronitrile (0.06 g.). After 5 min. the mixture was cooled, and the succinimide was filtered off and washed with cold carbon tetrachloride. The filtrate was evaporated *in vacuo* to give a dark residue (5.68 g.) (which gave a precipitate with 2,4-dinitrophenylhydrazine reagent). This (5.6 g.) was refluxed for 45 min. with water (56 ml.) and the solution was then continuously extracted with ether to give a product (2.85 g.), which still contained bromine. It was purified by a 36-tube countercurrent distribution (phase capacity 50 ml.) in 1 : 1 ether-water at 25°. The contents of the tubes were examined spectrophotometrically and the solutions were pooled and worked up as follows:

(i) Tubes 1—16 (max. concentration at tube 8) contained the *cis*- β -formylacrylic acid. The ether layers were combined and the aqueous layers extracted with ether. The combined extracts gave a residue (1.6 g.) which could only be distilled partly; the distillate, b. p. 80—85° (air-bath)/0.05 mm. (Found: C, 47.2; H, 4.35. Calc. for $C_4H_4O_3$: C, 48.0; H, 4.0%) (lit.,¹⁵ m. p. 60°) gave a 4-nitrophenylhydrazone, m. p. 234° (lit.,¹⁶ m. p. 230°) and a 2,4-dinitrophenylhydrazone, m. p. 261°, λ_{\max} . 374.5 μ (ϵ 29,900 in 96% EtOH) (Found: C, 42.4; H, 3.0; N, 19.2. $C_{10}H_8N_4O_6$ requires C, 42.9; H, 2.9; N, 20.0%).

(ii) Tubes 17—31 (max. concentration at tube 22) gave material (0.78 g.), isolated as in (i),

¹⁴ L. N. Owen and M. U. S. Sultanbawa, *J.*, 1949, 3103.

¹⁵ G. O. Schenck and R. Appel, *Naturwiss.*, 1946, 33, 122.

¹⁶ G. O. Schenck, *Annalen*, 1953, 584, 156.

b. p. 70—80° (air-bath temp.)/0.01 mm., which contained bromine and showed a single C=O band at 1761 cm.⁻¹; it was not investigated further.

(iii) Tubes 32—36 (max. concentration at tube 35) gave unchanged butenolide (0.1 g.).

In another experiment a sample of the crude bromination product was distilled (b. p. 70—80°/0.006 mm.) (Found: C, 28.4; H, 2.9; Br, 45.3. C₄H₇O₂Br requires C, 29.4; H, 1.8; Br, 49.1%).

Bromination of 3-ethylbut-2-enolide. The butenolide (VIb) (4 g.) in carbon tetrachloride (7 ml.) was refluxed with *N*-bromosuccinimide (6.54 g.) for 20 min., when the reaction was complete. The mixture was worked up as before to give the crude product (6.80 g.) which on distillation gave a large residue and a distillate (3.6 g.), b. p. 106—123°/0.05 mm. (Found: Br, 32.4. Calc. for C₆H₇O₂Br: Br, 41.9%). The distillate (3.2 g.) was refluxed with water (30 ml.) for 50 min. and worked up as above to give a product (2.25 g.) which was separated by similar counter-current distribution in 1:1 ether (containing 10% light petroleum)—water at 25°. The material (1.5 g.) isolated from tubes 1—21 was distilled and the distillate, b. p. 140° (air-bath temp.)/0.01 mm., was recrystallised from ether to give *3-ethyl-4-hydroxybut-2-enolide* (IXb) m. p. 79—80° (Found: C, 56.1; H, 6.40. C₆H₈O₃ requires C, 56.25; H, 6.25%). The hydroxybutenolide (IXb) gave a *4-nitrophenylhydrazone*, m. p. 215—216° (Found: C, 55.0; H, 5.05, N, 15.8. C₁₂H₁₃N₃O₄ requires C, 54.75; H, 4.9; N, 16.0%) and a *2,4-dinitrophenylhydrazone*, m. p. 252° (Found: C, 46.9; H, 4.2; N, 17.3. C₁₂H₁₂O₆N₄ requires C, 46.8; H, 3.9; N, 18.2%).

Tubes 22—36 contained little material; this was not investigated further.

Bromination of 2,3-dimethylbut-2-enolide. The butenolide (4 g.) in carbon tetrachloride (8 ml.) was refluxed with *N*-bromosuccinimide (6.54 g.) for 20 min., when the reaction was complete. The crude product (6.8 g.) was isolated as usual and it yielded no precipitate with 2,4-dinitrophenylhydrazine. Purification by fractional distillation was unsuccessful, and prolonged heating caused decomposition, but by chromatography on silica gel the bromination product was separated from unchanged butenolide (VIc), and distillation then gave *4-bromo-2,3-dimethylbut-2-enolide* (IXc) b. p. 85—90° (air-bath)/0.1 mm., *n*_D²⁵ 1.5222 (Found: C, 37.8; H, 3.9; Br, 40.8. C₆H₇O₂Br requires C, 37.7; H, 3.75; Br, 41.9%).

Reaction of the bromo compound (IXc) (0.6 g.) with silver 3,5-dinitrobenzoate (1 g.) in boiling benzene (5 ml.) for 7 hr. gave *2,3-dimethyl-4-(3',5'-dinitrobenzoyloxy)but-2-enolide*, which when recrystallised from chloroform—light petroleum had m. p. 164° (Found: C, 48.0; H, 3.1. C₁₃H₁₆N₂O₈ requires C, 48.4; H, 3.1%).

The bromobutenolide (297 mg.) in benzene was filtered through alumina (10 g.) and the hydrolysed product eluted with ethyl acetate—methanol. Evaporation of the solvent gave a solid (172 mg.) which was recrystallised from ether and the crystals (140 mg.) distilled to yield *4-hydroxy-2,3-dimethylbut-2-enolide*, b. p. 90° (air-bath)/0.01 mm., m. p. 79° (Found: C, 56.2; H, 6.3. C₆H₈O₃ requires C, 56.25; H, 6.25%).

Bromination of 3-phenylbut-2-enolide. The butenolide (2 g.) in carbon tetrachloride (14 ml.) was refluxed for 20 min. with *N*-bromosuccinimide (2.3 g.) and azoisobutyronitrile (0.023 g.), when the reaction was complete. The product (2.72 g.), isolated as before and recrystallised from benzene, was *4-bromo-3-phenylbut-2-enolide* (1.82 g.), m. p. 99—100°, *λ*_{max.} 219 and 281 mμ (ε 13,600 and 16,200, respectively, in cyclohexane) (Found: C, 49.75; H, 3.2; Br, 33.9. C₁₀H₇O₂Br requires C, 50.2; H, 2.9; Br, 33.45%).

Bromination of 2-methyl-3-phenylbut-2-enolide. The butenolide (VIe) (5 g.) was dissolved in carbon tetrachloride (50 ml.), *N*-bromosuccinimide (5.4 g.) was added, and the mixture was refluxed for 1 hr. The product was recrystallised from benzene to give *4-bromo-2-methyl-3-phenylbut-2-enolide* (5.1 g.), m. p. 80—81°, *λ*_{max.} 213 and 273 mμ (ε 13,100 and 11,800, respectively, in cyclohexane) (Found: C, 52.0; H, 3.6. C₁₁H₉BrO₂ requires C, 52.2; H, 3.6%).

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