304. *Unsaturated Lactones. Part II. (Researches on Acetylenic Compounds. Part XIX.) Reactions of the Esters of αβ-Acetylenic Hydroxy-acids with Nucleophilic Reagents.*

By E. R. H. Jones and M. C. Whiting.

With esters of both γ- and δ-hydroxy-αβ-acetylenic acids (*e.g.*, I and IV) amines give β-substituted γ- and δ-lactones (*e.g.*, II, III, and V). It is suggested that the initial reaction in these cases is *cis*-addition of the nucleophilic reagent to the triple bond. The addition of alcohols, catalysed by alkoxides or boron trifluoride–mercuric oxide, similarly leads to β-alkoxy-lactones (*e.g.*, II, III, and VII). With phenol and benzylthiol mixtures of lactones and (presumably) *trans*-hydroxy-esters are obtained.

The β-substituted γ-lactones exhibit anomalous light absorption properties and are unusually resistant to acid or alkaline hydrolysis. These abnormalities are explained in terms of enhanced stabilisation of dipolar resonance forms by an inductive effect through the ring system.

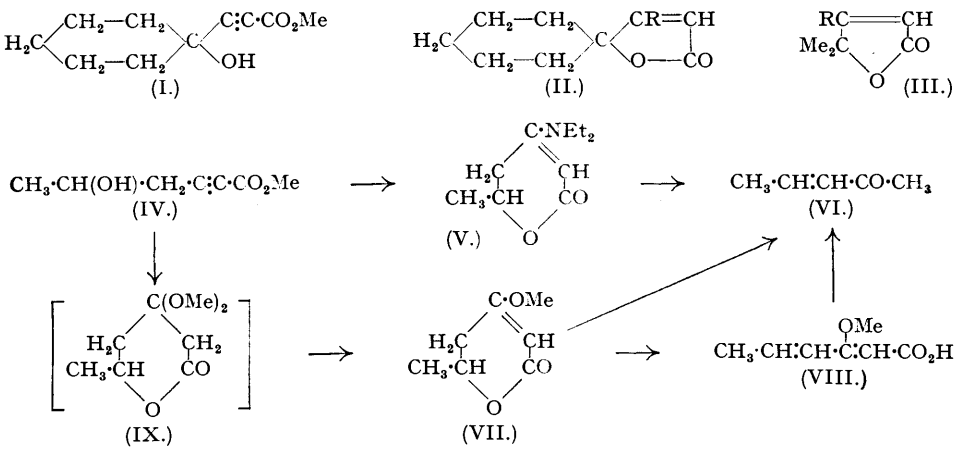
The addition of amines to the esters of αβ-acetylenic acids has been studied by Ruhemann *et al.* (*J.*, 1898, **73**, 723; 1894, **75**, 954), Moureu and Lazennac (*Compt. rend.*, 1906, **143**, 596; *Bull. Soc. chim.*, 1906, **35**, 1190), and Strauss and Voss (*Ber.*, 1926, **59**, 1740), all of whom obtained β-substituted mono-adducts ($NHR\cdot\overset{|}{C}{:}CH\cdot CO_2Et$), sometimes formulated as the imino-compounds ($NR{:}\overset{|}{C}\cdot CH_2\cdot CO_2Et$). The application of this and analogous reactions to the esters of the readily available αβ-acetylenic γ- and δ-hydroxy-acids (Haynes and Jones, *J.*, 1946, 503, 954) has now been examined. This research was initiated with the object of obtaining amino-substituted αβ-unsaturated lactones of possible biological interest and as part of a more extensive project on the synthesis of substances related to auxins-a and -b.

Exothermic reactions occurred when the αβ-acetylenic hydroxy-esters were treated with secondary aliphatic amines at room temperature; aniline was less reactive and in this case heating to 100° was necessary to initiate reaction. Analytical data indicated that the products in all cases were lactones, and their β-substituted nature was evident from their behaviour on hydrolysis (see below and preceding paper). Thus, the *ester* (I) gave with diethylamine, diethanolamine, and aniline crystalline *lactones* [II; R = NEt_2, $N(CH_2\cdot CH_2\cdot OH)_2$, and NHPh respectively) in yields ranging from 45 to 85%. The *methyl* ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid similarly gave crystalline *lactones* (III; R = $C_5H_{10}N$ and NHPh) with piperidine and aniline (65% yield in each case), and the methyl ester of the homologous hex-1-yn-3-ol-1-carboxylic acid, derived from a secondary carbinol, gave with diethylamine a liquid *lactone* in 75% yield. The *methyl* ester of the δ-hydroxy-acid, pent-1-yn-4-ol-1-carboxylic acid (IV), and diethylamine gave with equal facility the δ-lactone (V), which is formally related to the naturally occurring $\delta\text{-}\Delta^{\alpha\beta}$-hexenolactone (cf. Haynes and Jones, *loc. cit.*). Hydrolysis of the amino-lactone (V) with 20% sulphuric acid was accompanied by decarboxylation giving ethylideneacetone (VI).

In spite of a careful study in several cases, no products other than the amino-lactones could be isolated from these addition reactions. This fact appears to support the hypothesis that the initial reaction of primary and secondary amines is *cis*-addition to the acetylenic linkage, followed by lactone formation by the elimination of alcohol from the activated molecule. It is possible, however, that equilibrium between the products of *trans*- and *cis*-addition might

be facilitated by the diminution in double-bond character of the ethylenic linkage in $R_2N-C=C-C=O$, due to resonance with a form of the type $R_2\overset{+}{N}=C-C=C-\overset{-}{O}$, the stabilisation of the *cis*-adduct by lactonisation resulting in the latter being the sole product. There is some evidence of facile interconversion between the two isomers of β-anilinoacrylic ester (Strauss and Voss, *loc. cit.*) and in the case of some of the amine adducts obtained from ethynyl ketones (Bowden and Jones, *J.*, 1946, 45). It seems probable that further studies now in progress will make some contribution towards the elucidation of the mechanism of the addition of nucleophilic reagents to acetylenic linkages.

The addition of alcohols to the esters of αβ-acetylenic carboxylic acids in the presence of alkali alkoxides has been described by Michael and Bucher (*Ber.*, 1895, **28**, 2512; 1896, **29**, 1792) and Moureu (*Bull. Soc. chim.*, 1904, **31**, 293), both mono- and di-adducts being obtained, the latter, however, only under comparatively vigorous conditions. The addition of alcohols to acetylenic bonds, not necessarily conjugated to carbonyl or similar groups, in the presence of a mercuric oxide–boron trifluoride catalyst has been extensively investigated. It was applied to the esters of αβ-acetylenic acids by Hennion and Zoss (*J. Amer. Chem. Soc.*, 1941, **63**, 1151). Recently, it was employed by Raphael (*J.*, 1947, 805) in the case of the ester of a γ-hydroxy-αβ-acetylenic acid, a β-methoxy-αβ-ethylenic γ-lactone being obtained in good yield.



The ester (I) and the methyl ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid reacted vigorously with methanol containing sodium methoxide (30—50 mols. %) to give 60% yields of crystalline *lactones* (II and III, respectively; R = OMe). With the methyl ester of hex-1-yn-3-ol-1-carboxylic acid, derived from a secondary carbinol, the addition of methanol was less smooth; to avoid a very vigorous reaction leading to the formation of gummy acidic material it was essential to conduct the reaction below room temperature; even so, the yield of the liquid *methoxy-lactone* was only 20%. With the mercuric oxide–boron trifluoride catalyst, however, a 65% yield of the same product was obtained.

When (IV), a δ-hydroxy-ester, was treated with methanolic sodium methoxide at 0° it gave a mixture of a neutral product, m. p. 69°, with lactonic properties, and an acid, m. p. 152° (decomp.). Both were isomeric with the starting material and both were hydrolysed rapidly by hot 2N-sulphuric acid to ethylideneacetone (VI) (isolated as its 2 : 4-*dinitrophenylhydrazone*). There was therefore little doubt that these substances were respectively β-*methoxy*-δ-$\Delta^{\alpha\beta}$-*hexeno-lactone* (VII) and β-*methoxysorbic* acid (VIII), respectively, and this conclusion was confirmed by their light-absorption properties (see below). The variations in the yields of the two products with time of reaction and methoxide concentration are tabulated in the Experimental portion. The yield of acid increased at the expense of that of lactone with increasing methoxide concentration and, as was expected, it was found that (VIII) was formed by the action of sodium methoxide on (VII) (cf. Hofmann, *Annalen*, 1859, **110**, 129). It may be noted that δ-hydroxy-αβ-ethylenic esters are similarly unstable, readily undergoing dehydration under alkaline conditions (Jones, O'Sullivan, and Whiting, this vol., p. 1415).

This method thus seemed to be unsatisfactory for preparing the lactone (VII), and the effect of employing the boron trifluoride–mercuric oxide catalyst was therefore examined. On mixing the reactants and the catalyst a vigorous exothermic reaction took place; isolation of the

product shortly after this had subsided gave a non-homogeneous oil, b. p. *ca.* 80°/0·1 mm., which contained *ca.* 35% of (VII), estimated by light-absorption data, and no other light-absorbing substance and none of the starting material (shown by the absence of an exothermic reaction with piperidine). On standing for 24 hours at room temperature with a methanolic solution of boron trifluoride or of sulphuric acid, it was converted into crystalline (VII), which was also obtained, in 65% yield, when the original reaction mixture was allowed to stand for 24 hours or more before isolation of the product. The first-formed oil gave, on treatment with methanolic 2 : 4-dinitrophenylhydrazine sulphate solution, the derivative of 4-hydroxy-6-methyl-5 : 6-dihydro-2-pyrone (see the preceding paper) in good yield; this was not obtained under the same conditions from (VII). It is accordingly considered that the liquid product consists largely of the dimethoxy-lactone (IX), a view which gains support from the fact that the simple acetylenic esters give di-adducts with the boron trifluoride–mercuric oxide catalyst, which lose one molecule of methanol on vigorous acid treatment (Hennion and Zoss, *loc. cit.*). The β-substituted δ-lactones of type (VII) are thus, as in many other respects (see below), intermediate in behaviour between the γ-lactones and the analogous open-chain compounds. By the same procedure the methyl ester of but-1-yn-4-ol-1-carboxylic acid gave the corresponding *lactone*, m. p. 78°, in similar yield.

The ester (I) on treatment with ethylene glycol in which a small quantity of sodium had been dissolved gave the *lactone* (II; R = $O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$) in 45% yield. The ethyl ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid gave a 20% yield of the corresponding *ethoxy-lactone* with ethanolic sodium ethoxide. The addition of primary alcohols to the esters of αβ-acetylenic hydroxy-acids, under the influence of alkoxide or boron trifluoride–mercuric oxide catalysts, and leading to β-substituted αβ-ethylenic γ- and δ-lactones, thus appears to be a general reaction. Attempts to utilise secondary alcohols, *e.g.*, *iso*propyl alcohol and *cyclo*hexanol, with alkoxide catalysis were uniformly unsuccessful, this paralleling the experience of Bowden and Jones (unpublished results) in attempts to add similar alcohols to ethynyl ketones.

The addition of phenols to the esters of αβ-acetylenic acids in the presence of the appropriate alkali phenoxides was examined by Ruhemann and Beddow (*J.*, 1900, **77**, 984), employing the esters of phenylpropiolic and acetylenedicarboxylic acids. They obtained β-substituted mono-adducts, probably formed by *trans*-addition.

When the ester (I) was treated with phenol and sodium phenoxide at *ca.* 80°, an exothermic reaction took place and two crystalline compounds, m. p.s 103° and 69·5°, readily separated by fractional crystallisation, were isolated from the neutral portion of the product (total yield, 70%). The former product proved to be the *hydroxy*-ester $[CH_2]_5 > C(OH){\cdot}C(OPh){:}CH{\cdot}CO_2Me$, hydrolysed by cold alkali to the *hydroxy-acid*, which showed no tendency to cyclise to a lactone even when heated above its melting point. It seems reasonable to assume that in the ester the carbomethoxyl and the 1-hydroxy*cyclo*hexyl group have a *trans*-configuration about the double bond. The second compound, m. p. 69·5°, is the *lactone* (II; R = OPh). No evidence of the formation of the latter from the hydroxy-ester could be obtained by treatment with potassium phenoxide and phenol even under conditions much more vigorous than those appertaining in the addition reaction, and it is concluded that the hydroxy-ester and the lactone are formed independently by simultaneous *trans*- or *cis*-additions, or by exclusive *cis*-addition followed by either isomerisation or cyclisation of an unstable *cis*-adduct.

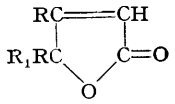
The addition of thiophenols to αβ-acetylenic esters was studied by Ruhemann *et al.* (*J.*, 1900, **77**, 1179), who used the corresponding sodium salt as catalyst, and obtained mainly β-substituted mono-adducts. Secondary and tertiary amines have been used to catalyse analogous addition reactions to αβ-acetylenic and -ethylenic carbonyl compounds. The ester (I) reacted exothermically with benzylthiol in the presence of a little triethylamine. When the product, an uncrystallisable syrup, was hydrolysed with cold potassium hydroxide solution, the *lactone* (II; R = $Ph{\cdot}CH_2{\cdot}S$) and the corresponding *hydroxy-acid* (presumably *trans*) were readily isolated from the neutral and the acidic fraction, respectively, in a total yield of about 80%.

When the light absorption properties of the lactones and hydroxy-acids described in this paper are compared with those of corresponding acyclic analogues some interesting anomalies are observed (see Table). Whereas the data for δ-lactones of type B show little variation from those of the simple β-substituted crotonic acid derivatives the γ-lactones (type A) absorb at much shorter wave-lengths. The effect is particularly marked in the β-dialkylamino-series, where the differences average about 200 A. These light-absorption anomalies are almost certainly related to the remarkable chemical stability which these γ-lactones exhibit. Acid hydrolysis to tetronic acids (preceding paper) takes place only under drastic conditions, whereas acyclic analogues, *e.g.*, β-diethylamino-αβ-ethylenic esters, undergo rapid hydrolysis even with organic

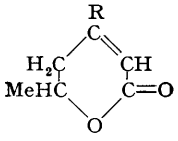
acids (Moureu and Lazennac, *loc. cit.*). The non-formation of di-adducts in alkoxide-catalysed alcohol addition reactions, the almost complete absence of basic properties in the amino-lactones and the impossibility of preparing methiodides from the latter, are further examples. Abnormal stability is also observed on attempted hydrolytic fission of the 5-membered lactone ring; after standing in 10% potassium hydroxide in methanol for some days the lactone (II; R = OMe) was recovered in 75% yield on dilution and ether extraction. The δ-lactones, which do not exhibit any light-absorption anomalies, are much more normal in their chemical properties.

In β-substituted αβ-unsaturated esters and carbonyl compounds in which the substituent carries a free electron-pair, resonance with dipolar forms results in characteristic variochromic effects (Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45). The parallelism between the auxochromic effects of such substituents and their tautomeric effects on chemical reactivity is well known (see, *inter alia*, Bowden, Braude, and Jones, *J.*, 1946, 984). The chemical and optical

Light absorption data for β-substituted αβ-unsaturated lactones and the corresponding hydroxy-acids (in alcoholic solutions).



Type A (5-membered ring).



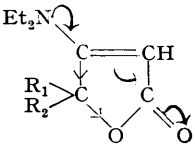
Type B (6-membered ring).

Type.			$\lambda_{max.}$, A.	$\varepsilon_{max.}$
A	R = NEt_2	$R_1R_2 = (CH_2)_5$	2680	29,000
A	R = $N(CH_2{\cdot}CH_2{\cdot}OH)_2$	$R_1R_2 = (CH_2)_5$	2680	29,000
A	R = N<[CH_2]$_5$	$R_1 = R_2$ = Me	2670	33,000
A	R = NEt_2	$R_1 = R_2$ = Me	2670	30,000
A	R = NEt_2	R_1 = Pr; R_2 = H	2650	28,000
B	R = NEt_2		2910	28,000
B	R = N<[CH_2]$_5$		2910	23,500
	cf. $Et_2N{\cdot}CMe{:}CH{\cdot}CO_2Et$ [1]		2850 2880	30,500 30,500
A	R = NHPh	$R_1R_2 = (CH_2)_5$	2810 2880	27,000 24,000
A	R = NHPh	$R_1 = R_2$ = Me	2810	24,000
	cf. $NHPh{\cdot}CMe{:}CH{\cdot}CO_2Et$ [2]		2940	11,500
A	R = OMe	$R_1R_2 = (CH_2)_5$	2210	15,500
A	R = $O{\cdot}CH_2{\cdot}CH_2OH$	$R_1R_2 = (CH_2)_5$	2210	16,000
A	R = OMe	$R_1 = R_2$ = Me	2180	17,000
A	R = OEt	$R_1 = R_2$ = Me	2190	19,000
A	R = OMe	R_1 = Pr; R_2 = H	2210	13,500
B	R = OMe		2340	17,000
B	R = OMe	without Me substituent	2330	13,500
	cf. $MeO{\cdot}CMe{:}CH{\cdot}CO_2H$ [3]		2340	13,500
A	R = OPh	$R_1R_2 = (CH_2)_5$	2230 2370 *	13,000 11,000
	[CH_2]$_5$>$C(OH){\cdot}C(OPh){:}CH{\cdot}CO_2Me$		2180 2560	21,500 3,500
	[CH_2]$_5$>$C(OH){\cdot}C(OPh){:}CH{\cdot}CO_2H$		2200 2540	16,000 3,500
	cf. $PhO{\cdot}CMe{:}CH{\cdot}CO_2H$		2360	11,000
A	R = $S{\cdot}CH_2Ph$	$R_1R_2 = (CH_2)_5$	2650	16,000
	[CH_2]$_5$>$C(OH){\cdot}C(S{\cdot}CH_2Ph){:}CH{\cdot}CO_2H$		2160 † 3000	16,000 3,500
	cf. $Ph{\cdot}CH_2{\cdot}S{\cdot}CH{:}CH{\cdot}CO_2H$ [4]	*trans*	2810	16,000
		,, *cis*	2730	20,000
	cf. β-Methoxysorbic acid		2650	15,000
	Sorbic acid		2540	25,000

* Inflexion. † No maximum.

[1] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45.
[2] Dr. E. A. Braude, private communication.
[3] Owen, *J.*, 1945, 385.
[4] Dr. L. N. Owen and M. Sultanbawa, private communication.

peculiarities of the β-substituted 5-membered-ring lactones, as compared with those of their acyclic analogues, can be ascribed to increased dipolar character arising from the proximity of the electropositive substituent R and the electronegative carboxyl residue. This results in the electron drift due to the tautomeric effect being supplemented by an inductive effect operating along the alternative path around the ring (see inset). Such increased dipolar character would clearly lead to a diminished tendency towards proton addition at the nitrogen or similar atom—hence the resistance both to acid hydrolysis and to quaternary-salt formation and to reduced reactivity of the potential carboxyl group towards hydroxyl ions. As would be expected the effects are less marked in systems with β-substituents (*e.g.*, NHPh, OMe) containing less mobile electron pairs, and they largely disappear when the possibility of transmission of inductive effects is greatly reduced, in the 6-membered rings, by the introduction of a further methylene group.



The differences between the absorption spectra (Table) of the *trans*-hydroxy-acids and their esters, and those of their simple analogues are presumably due to steric inhibition of resonance, evidence in support of which has been accumulating rapidly in recent years. The effects observed (greatly reduced intensities of absorption and displacements towards longer wavelengths) are similar to those found in cases (*e.g.*, β-ionone) where substitution tends to prevent the adoption of coplanar structures in which maximum resonance is possible (see, *inter alia*, Braude, Jones, Koch, Richardson, and Sondheimer, this vol., p. 607). In the present instances the possibility of interference with the coplanarity of the Ph·CH_2·S·C=C·C=O and PhO·C=C·C=O chromophores by the bulky hydroxy*cyclo*hexyl group is readily apparent.

The availability of data for both stereoisomers of β-benzylthioacrylic acid demonstrates that the anomalies discussed are not due merely to *cis–trans*-isomerism.

Experimental.

Acetylenic Hydroxy-acids.—These were prepared essentially by the method of Haynes and Jones (*loc. cit.*) except that the solution of the Grignard complex, obtained by adding the acetylenic carbinol to the cooled solution of ethylmagnesium bromide, was not heated under reflux. The formation of the complex appears to be completed in the cold when the reaction is effected on a moderately large scale, notwithstanding the evidence of Zerewitinoff determinations (Jones and McCombie, *J.*, 1942, 733) which were carried out in di*iso*amyl ether. In this way better yields of purer products were obtained and the procedure was expedited. It was also found possible to prepare the acid derived from 1-ethynyl*cyclo*hexanol by pouring the solution of the Grignard complex in a mixture of ether and benzene (1 : 1) on to a large excess of carbon dioxide with manual stirring. The use of high-pressure equipment was thereby avoided, the conversion falling only from 70% to 50%. Ether, benzene, and toluene separately were less satisfactory solvents in this case. Propylethynylcarbinol was similarly carboxylated (30% conversion) using benzene as solvent and without stirring.

Esterifications.—The appropriate acids, the preparation of which has been described by Haynes and Jones (*loc. cit.*), were esterified in the usual manner with methanol and sulphuric acid. The *methyl* ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (I) formed needles, m. p. 59—60°, after crystallisation from benzene–light petroleum (b. p. 40—60°) (Found: C, 66·1; H, 7·85. $C_9H_{14}O_3$ requires C, 65·9; H, 7·75%). The *methyl* ester of pent-1-yn-4-ol-1-carboxylic acid (IV) had b. p. 86°/0·1 mm., $n_D^{19°}$ 1·4678 (Found: C, 59·45; H, 7·1. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%). The *methyl* ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid had b. p. 70°/0·2 mm., $n_D^{22°}$ 1·4555 (Found: C, 59·35; H, 6·95. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%). The methyl ester of pent-1-yn-4-ol-1-carboxylic acid was also prepared, with the same physical constants, by treating the product of the high-pressure carboxylation with a solution of excess of sulphuric acid in methanol (cooling), filtering from magnesium sulphate, refluxing, isolating with ether, and separating the methyl ester from the pent-1-yn-4-ol by distillation.

*Lactone of β-Diethylamino-β-(1-hydroxy*cyclo*hexyl)acrylic Acid* (II; R=NEt_2).—Diethylamine (2 g.) was added to a solution of the methyl ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (3 g.) in ether (15 c.c.). After 24 hours' standing at 20°, more diethylamine (2 g.) was added, the ether was slowly distilled off, and the residue was heated for 30 minutes on the steam-bath. On cooling, the residual oil solidified, and trituration with light petroleum (b. p. 60—80°) gave a product (3·4 g.), m. p. 108—110°. After crystallisation from benzene–light petroleum, the *lactone* formed leaflets (3·1 g.), m. p. 112° (Found: C, 70·0; H, 9·5. $C_{13}H_{21}O_2N$ requires C, 69·9; H, 9·5%).

*Lactone of β-Bis-2-hydroxyethylamino-β-(1-hydroxy*cyclo*hexyl)acrylic Acid* [II; R = $N(C_2H_4·OH)_2$].—Diethanolamine (1·3 g.) was added to a solution of the methyl ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (2·1 g.) in acetone (4 c.c.). After standing for 18 hours at 20°, the separated crystals were collected and recrystallised from ethyl acetate to give the *lactone* (1·7 g.) as needles, m. p. 129° (Found: C, 61·05; H, 8·2. $C_{13}H_{21}O_4N$ requires C, 61·15; H, 8·3%).

*Lactone of β-Anilino-β-(1-hydroxy*cyclo*hexyl)acrylic Acid* (II; R = NHPh).—Aniline (0·8 g.) was added to the methyl ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (1·0 g.) and the mixture was heated for 24 hours on the steam-bath, a mass of crystals being obtained. Digestion with boiling methyl cellosolve gave the *lactone* (1·0 g.) as plates, m. p. 306°, unchanged on crystallisation from pyridine or ethyl acetoacetate (Found: C, 74·1; H, 6·95; N, 6·15. $C_{15}H_{17}O_2N$ requires C, 74·0; H, 7·05; N, 5·75%).

Lactone of 2-Piperidino-3-methylbut-1-en-3-ol-1-carboxylic Acid (III; R = NC_5H_{10}).—Piperidine (3 g.) was added to a solution of the methyl ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid (3 g.) in ether (15 c.c.). A vigorous exothermic reaction took place, some of the ether evaporating. After 24 hours' standing at 20°, more piperidine (2 g.) was added, the ether was slowly distilled off, and the residue was heated for 1 hour on the steam-bath. The resultant oil solidified on cooling; crystallisation from benzene–light petroleum (b. p. 60—80°) or water gave the *lactone* (3·1 g.) as long needles, m. p. 111° (Found: C, 67·9; H, 8·55. $C_{11}H_{17}O_2N$ requires C, 67·65; H, 8·75%).

Lactone of 2-Anilino-3-methylbut-1-en-3-ol-1-carboxylic Acid (III; R = NHPh).—Aniline (2·5 g.) was added to the methyl ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid (2·5 g.), and the mixture was heated on the steam-bath for 24 hours, a crystalline mass being obtained. Methanol (5 c.c.) was added, and the insoluble *lactone* (2·75 g.) was filtered off; m. p. 256° with slight decomposition, unchanged by recrystallisation from ethanol (Found: C, 71·2; H, 6·3. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·45%).

Lactone of 2-Diethylaminohex-1-en-3-ol-1-carboxylic Acid.—Diethylamine (4 g.) was added to a solution of the methyl ester of hex-1-yn-3-ol-1-carboxylic acid (4 g.) (Haynes and Jones, *loc. cit.*) in dry ether (8 c.c.). An exothermic reaction took place; after 24 hours' at 20°, more diethylamine (2 g.) was added and the mixture was heated on the steam-bath for 30 minutes. After the removal of the more volatile material, distillation at 100° (bath temp.)/10^{-4} mm. gave the *lactone* (4·4 g.) as a yellow, viscous liquid, $n_D^{18°}$ 1·5168 (Found: C, 66·8; H, 9·45. $C_{11}H_{19}O_2N$ requires C, 66·95; H, 9·7%).

Lactone of 2-Diethylaminopent-1-en-4-ol-1-carboxylic Acid (V).—Diethylamine (7 g.) was added to a solution of the methyl ester of pent-1-yn-4-ol-1-carboxylic acid (6·6 g.) in dry ether (10 c.c.). An exothermic reaction took place; after standing at 20° for 24 hours the mixture was heated on the steam-bath for 30 minutes. Removal of the more volatile material and distillation at 80° (bath temp.)/10^{-4} mm. gave the *lactone* (8·8 g.), $n_D^{18°}$ 1·5230 (Found: C, 65·3; H, 9·7. $C_{10}H_{17}O_2N$ requires C, 65·55; H, 9·35%).

Hydrolysis. The lactone (30 mg.) was heated under reflux for 15 minutes with 20% sulphuric acid; water (15 c.c.) was added, and the solution was distilled. The distillate (10 c.c.) was treated with an aqueous solution of 2 : 4-dinitrophenylhydrazine hydrochloride; a precipitate was formed which became crystalline on addition of methanol and heating. Crystallisation from ethyl acetate–methanol gave the *ethylideneacetone* 2 : 4-*dinitrophenylhydrazone* as spherical aggregates of small needles, m. p. 158—159°, undepressed on admixture with an authentic specimen. The latter was prepared in the usual way from ethylideneacetone and alcoholic 2 : 4-dinitrophenylhydrazine sulphate solution; after crystallisation from ethyl acetate it had m. p. 158—159° (Found: C, 50·1; H, 4·4. $C_{11}H_{12}O_4N_4$ requires C, 50·0; H, 4·6%). Light absorption: Maxima, 2450, 2510, 2580, 2900, and 3800 A.; ε = 17,000, 17,000, 17,000, 9,500, and 26,500, respectively; inflexion, 2810 A.; ε = 12,000.

Lactone of β-Methoxy-β-(1-hydroxycyclohexyl)acrylic Acid (II; R = OMe).—The methyl ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (2 g.) was added to a solution of sodium methoxide (from 0·1 g. of sodium) in dry methanol (3 c.c.), and the solution was heated under reflux for 45 minutes. On cooling and adding water (7 c.c.) the product crystallised; recrystallisation from aqueous methanol gave the *lactone* (1·0 g.) as laths, m. p. 108° (Found: C, 65·85; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%).

Lactone of β-2-Hydroxyethyl-β-(1-hydroxycyclohexyl)acrylic Acid (II; R = $O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$).—Sodium (0·1 g.) was dissolved in warm ethylene glycol (3 c.c.); to the cooled solution the methyl ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (2 g.) was added, and the mixture was heated on the steam-bath for 1½ hours. On cooling and dilution with water (5 c.c.), the product separated; recrystallisation from ethyl acetate–benzene gave the *lactone* (1·13 g.) as needles, m. p. 126° (Found: C, 62·6; H, 7·5. $C_{11}H_{14}O_4$ requires C, 62·25; H, 7·6%).

Lactone of 2-Methoxy-3-methylbut-1-en-3-ol-1-carboxylic Acid (III; R = OMe).—The methyl ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid (3 g.) was added to a solution of sodium methoxide (from 0·3 g. of sodium) in dry methanol (6 c.c.). After the initial vigorous reaction had subsided the mixture was heated under reflux for 45 minutes, diluted with water (30 c.c.), and extracted thoroughly with ether. Evaporation of the dried extract gave an oil which solidified on cooling and was crystallised from a small quantity of water to give the *lactone* (1·8 g.), m. p. 73—74°, which after recrystallisation from benzene–light petroleum formed prisms, m. p. 74° (Found: C, 59·35; H, 7·2. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%).

The corresponding *ethoxy-lactone* was obtained in the same way from the ethyl ester of 3-methylbut-1-yn-3-ol-1-carboxylic acid (Haynes and Jones, *loc. cit.*) (6 g.), sodium ethoxide, and ethanol, as an oil, b. p. 72°/0·01 mm., which after distillation solidified and was crystallised from light petroleum, giving prisms (1·3 g.), m. p. 40° (Found: C, 61·65; H, 7·55. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%).

Lactone of 2-Methoxyhex-1-en-3-ol-1-carboxylic Acid.—(*a*) The methyl ester of hex-1-yn-3-ol-1-carboxylic acid (6 g.) (Haynes and Jones, *loc. cit.*) was added to a cooled solution of sodium methoxide (from 0·7 g. of sodium) in dry methanol (30 c.c.). The mixture was kept at 0° for 6 hours and then at 20° for 18 hours. A solution of potassium hydroxide (3 g.) in water (7 c.c.) was then added, and the mixture kept for a further 24 hours at 20° to hydrolyse any unchanged ester. After addition of water (100 c.c.), the solution was extracted with ether; the dried extract was evaporated and the residual oil was distilled, giving the *lactone* (1·3 g.), b. p. 83°/10^{-2} mm., $n_D^{20°}$ 1·4724 (Found: C, 61·9; H, 7·8. $C_8H_{12}O_3$ requires C, 61·5; H, 7·75%).

(*b*) Boron trifluoride–ether complex (0·3 g.), trichloroacetic acid (0·1 g.), and mercuric oxide (0·3 g.) were added to dry methanol (6 c.c.). The mixture was heated to 65°, then cooled to 30°, and the methyl ester of hex-1-yn-3-ol-1-carboxylic acid (4·5 g.) was added. After standing at 20° for 24 hours the solution was filtered without using pressure, poured into water, and extracted with ether. The dried extract was evaporated, and the residue distilled, giving the lactone (2·9 g.), b. p. 87°/0·1 mm., $n_D^{18°}$ 1·4717.

Lactone of 2-Methoxypent-1-en-4-ol-1-carboxylic Acid (VII) *and β-Methoxysorbic Acid* (VIII).—(*a*) The methyl ester of pent-1-yn-4-ol-1-carboxylic acid (3 g.) was added to a cooled solution of sodium methoxide (from 0·3 g. of sodium) in dry methanol (10 c.c.). The solution was kept for 6 hours at 0°, then for 18 hours at 20°; water was added and the solution was saturated with sodium chloride and thoroughly extracted with ether. Evaporation of the dried extract gave an oil which solidified on

cooling and was crystallised from light petroleum to give the *lactone* (510 mg.) which after recrystallisation from *cyclo*hexene formed prisms, m. p. 69° (Found: C, 59·2; H, 7·0. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%).

Acidification of the aqueous layer, after the ether extraction, gave a crystalline precipitate of *β-methoxysorbic acid* (230 mg.), m. p. 150° (decomp.). The acid decomposed on warming with water, but was recrystallised either by dissolving it in cold methanol and adding water or in the usual way from benzene; it then formed prisms, m. p. *ca.* 152° (decomp.) (Found: C, 58·8; H, 6·95. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%).

When the proportion of sodium methoxide used was increased, the yield of β-methoxysorbic acid was greatly increased, as shown:

NaOMe, mols. %	20	60	100	100	200	400	600
Time (hours)	72	24	0·75	24	96	48	18
Lactone yield, %	—	17	10	5	—	—	—
Acid yield, %	—	7	—	25	44	60	38

The ester (3 g.) was added, in portions, to a solution of sodium methoxide (from 2 g. of sodium) in dry methanol (25 c.c.) with careful cooling. The solution was kept at 0° for 6 hours, then at 20° for 42 hours, the sodium salt of the acid separating as long needles. Water (70 c.c.) was added, the solution was cooled to −10° and acidified with concentrated hydrochloric acid, and the precipitated acid (1·8 g.) was collected.

β-Methoxysorbic acid was also obtained by adding the lactone (300 mg.) to a solution of sodium methoxide (from 0·3 g. of sodium) in methanol (12 c.c.); after standing overnight, the methanol was removed under reduced pressure and the residue dissolved in water. Acidification gave β-methoxysorbic acid (180 mg.) as a crystalline precipitate, m. p. 150° (decomp.). The lactone was prepared in better yield by using the boron trifluoride–mercuric oxide catalyst (method *b*).

(*b*) Boron trifluoride–ether complex (0·3 g.) and mercuric oxide (0·06 g.) were added to dry methanol (4 c.c.). The mixture was heated to 65°, then cooled to 30°. When the ester (2 g.) was added, an exothermic reaction took place, the temperature being kept below 55° by external cooling. The mixture was set aside at 20° for 18 hours, then at 0° for 4 days. The gelatinous precipitate was filtered off and washed with methanol, chloroform (12 c.c.) was added, and the solution was shaken with a saturated solution of potassium hydrogen carbonate (1 c.c.). The dried extract was evaporated under reduced pressure; the residue solidified partly, and was recrystallised from ether. Several crops were obtained; those which had an unsatisfactory m. p. were again recrystallised. The total yield of lactone (m. p. 64—66°) was 1·25 g. The m. p. was not depressed by admixture with a specimen prepared by method (*a*).

Hydrolysis. The lactone (200 mg.) was hydrolysed to ethylideneacetone by heating it under reflux with 20% sulphuric acid, as described for the corresponding diethylamino-compound. Because of the larger scale of the experiment the evolution of carbon dioxide was observed and confirmed by means of barium hydroxide solution.

β-Methoxysorbic acid (100 mg.) was hydrolysed in the same way, except that the reaction was almost instantaneous. In both cases the ketone was isolated as its 2 : 4-dinitrophenylhydrazone, which after crystallisation from ethyl acetate–methanol had m. p. 158—159°, undepressed on admixture with an authentic specimen.

Lactone of 2-Methoxybut-1-en-4-ol-1-carboxylic Acid.—The methyl ester of but-1-yn-4-ol-1-carboxylic acid (2·8 g.) was added to a solution of mercuric oxide (0·05 g.) and boron trifluoride–ether complex (0·3 g.) in dry methanol (6 c.c.). The mixture was warmed to 40° and an exothermic reaction took place; the temperature was then kept below 55°. After cooling and 3 days' standing, isolation of the product with chloroform in the usual way (care being taken to avoid losses due to water-solubility) gave an oil which solidified readily and was pressed on a porous tile at 0° to give crude lactone (1·6 g.), m. p. 66—70°. Digestion with ether, followed by crystallisation from carbon tetrachloride–light petroleum, gave the *lactone* as needles, m. p. 78° (Found: C, 55·95; H, 6·25. $C_6H_8O_3$ requires C, 56·25; H, 6·3%).

Lactone of β-Phenoxy-β-(1-hydroxycyclohexyl)acrylic Acid (II; R = OPh) *and* trans-*β-Phenoxy-β-(1-hydroxycyclohexyl)acrylic Acid and its Methyl Ester.*—The methyl ester of β-(1-hydroxy*cyclo*hexyl)-propiolic acid (4 g.) was added to a suspension of sodium phenoxide (from 0·2 g. of sodium) in phenol (8 g.), and the mixture was heated to 90°; an exothermic reaction took place, the temperature rising to 125°. After cooling and 2 hours' standing at 15°, ether was added and the solution was shaken with 4N-sodium hydroxide solution until free from phenol. The ethereal solution was dried, and the ether evaporated; the residual oil was dissolved in 50% more than the necessary minimum quantity of boiling light petroleum (b. p. 40—60°), seeded with material from a preliminary preparation, and cooled to 15°; the *methyl* ester of the *trans*-acid (2·7 g.) separated in prisms, m. p. 103°, unchanged by recrystallisation from the same solvent (Found: C, 69·55; H, 7·4. $C_{16}H_{20}O_4$ requires C, 69·55; H, 7·3%).

The filtrate was evaporated, and the residual oil was dissolved in methanol (15 c.c.). After removal of a small quantity of flocculent material, water was added until a turbidity just formed; on seeding and cooling to 0° the *lactone* (1·15 g.) separated as lustrous plates, m. p. 69·5°, unchanged on recrystallisation from the same solvent or from light petroleum (Found: C, 73·95; H, 6·4. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6%).

By extracting the filtrate with ether, drying, evaporating, and crystallising the residue from light petroleum, a further 0·25 g. of the *trans*-hydroxy-ester, m. p. 101—102°, was obtained.

In an exactly similar experiment in which all quantities were reduced to one-quarter of those stated, the yields of hydroxy-ester and lactone were 0·92 g. and 0·09 g., respectively. No explanation of this anomaly can be offered.

A solution of potassium hydroxide (0·5 g.) in water (1·5 c.c.) was added to a solution of the hydroxy-ester (0·8 g.) in methanol (3·5 c.c.). After standing at 20° for 3 days the mixture was acidified and diluted with water; crystallisation of the precipitate from aqueous methanol gave the trans-*hydroxy-*

acid (0·7 g.) as plates, m. p. 192° (decomp.) (Found : C, 68·65; H, 6·9. $C_{15}H_{18}O_4$ requires C, 68·65; H, 6·95%).

Lactone of β-Benzylthio-β-(1-hydroxycyclohexyl)acrylic Acid (II; R = Ph·CH_2·S) *and* trans-*β-Benzylthio-β-(1-hydroxycyclohexyl)acrylic Acid.*—The methyl ester of β-(1-hydroxy*cyclo*hexyl)propiolic acid (1 g.) was added to benzylthiol (1 g.) and triethylamine (0·1 g.); an exothermic reaction took place, the temperature rising to 95°. After the mixtures had stood for 1 hour at 20°, a solution of potassium hydroxide (1 g.) in aqueous methanol (20 c.c.) was added. The mixture was kept for 48 hours at 20° and then extracted with ether after dilution with water. The dried extract gave on evaporation an oil which solidified on cooling; crystallisation from light petroleum (b. p. 60—80°) gave the *lactone* (0·29 g.) as needles, m. p. 94° (Found : C, 69·9; H, 6·3. $C_{16}H_{18}O_2S$ requires C, 70·0; H, 6·6%).

The alkaline solution was acidified and extracted with ether, and the extract thoroughly washed with sodium hydrogen carbonate solution; on acidification of the washings, the trans-*hydroxy-acid* (0·98 g.) separated. Crystallisation from aqueous methanol gave plates, m. p. 151—152° (decomp.) (Found : C, 65·75; H, 7·1. $C_{16}H_{20}O_3S$ requires C, 65·7; H, 6·9%).

Repetition of this experiment on a small scale, using 300 mg. of the ester, yielded 190 mg. of the lactone and 163 mg. of the acid. The reaction temperature was rather lower (*ca.* 65°) in this case.

β-Phenoxycrotonic Acid.—Methyl tetrolate (0·5 g.) was added to a suspension of sodium phenoxide (from 0·05 g. of sodium) in phenol (3 g.) at 80°. No reaction took place, and the mixture was therefore warmed to 120°, whereupon an exothermic reaction began, the temperature rising to 160°. After cooling, water was added and the neutral fraction was isolated by extraction with ether, washing the extract well with sodium hydroxide solution, and drying and evaporating it. The crude methyl ester thus obtained was hydrolysed by adding a solution of potassium hydroxide (1 g.) in methanol (6 c.c.) and water (2 c.c.) and keeping it for 18 hours at 20°. The acidic fraction of the mixture was isolated in the usual way, giving the acid (180 mg.; 17%), m. p. 148—150° (decomp.). After crystallisation from benzene–light petroleum (b. p. 80—100°), *β-phenoxycrotonic acid* formed needles, m. p. 151—153° (slight decomp.) (Found : C, 67·35; H, 5·25. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·65%). The yield could probably have been improved if precautions had been taken to minimise the rapid hydrolysis of the product in acid solution.

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Imperial College of Science and Technology,
London, S.W.7.
The University, Manchester, 13.

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