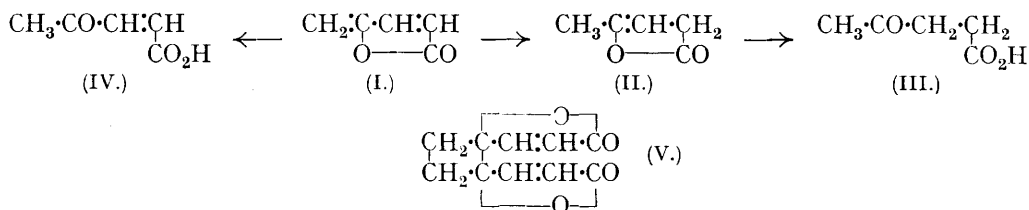


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270. The Lactone of γ -Hydroxyvinylacrylic Acid, Protoanemonin.

By FREDERIC B. KIPPING.

By steam-distillation of *Ranunculus japonicus* and subsequent extraction of the distillate with ether or chloroform an exceedingly vesicant oily substance can be isolated; this was investigated by Asahina (for references, see Asahina and Fujita, *Acta Phytochim.*, 1922, 1, 1; *Chem. Zentr.*, 1922, 3, 712), who showed that it polymerised to anemonin, and it was therefore designated protoanemonin. Asahina (*loc. cit.*, p. 19) has also shown that when protoanemonin in methyl-alcoholic solution is reduced with sodium amalgam and acetic acid it gives a neutral liquid (II), b. p. 190°, which by treatment with alkali, yields lævulic acid (III); from this fact and from the relationship of protoanemonin to anemonin, the constitution of which had been determined (V), it was concluded that the former is (I).



This structure was subsequently assigned to a totally different substance by Muskat, Becker, and Lowenstein (*J. Amer. Chem. Soc.*, 1930, 52, 326, 812), who found that vinylacrylic acid dibromide ($\gamma\delta$ -dibromo- Δ^{α} -pentenoic acid) and the corresponding dichloride decomposed on distillation under reduced pressure, yielding a lower-boiling fraction from which, after standing, a solid, m. p. 143° (solidifying again at 162°), was readily isolated. The analytical data and molecular-weight determinations in boiling acetone for this substance (called, for convenience, Muskat's lactone) agreed with the formula $\text{C}_5\text{H}_4\text{O}_2$: it dissolved slowly in alkali, showing an equivalent weight of 96, and the product of hydrolysis gave a hydrazone, m. p. 160° (decomp.), which was assumed to be that of β -acetylacrylic acid (IV). On the basis of these results, the authors assigned the structure (I) to Muskat's lactone without apparently being aware of Asahina's work on protoanemonin. The physical properties of protoanemonin and of Muskat's lactone show at once that they are different compounds and cannot both be represented by formula (I).

First, therefore, protoanemonin was reinvestigated, and as it is such an exceedingly disagreeable compound which polymerises readily, all experiments were carried out on the crude material. It was easily reduced by hydrogen in the presence of platinum, yielding mainly *n*-valeric acid with some γ -valerolactone, the volume of hydrogen absorbed corresponding roughly with that required for the reduction of (I) to valeric acid (3 mols.). Proto-

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anemonin showed the slow neutralisation with alkali characteristic of lactones, but it could be titrated in aqueous-acetone solution, the results being in rough agreement with formula (I). From the resulting liquid, β -acetylacrylic acid was isolated, and its hydrazone prepared; the identity of this acid was further proved by reducing it catalytically to lævulic acid, identified by means of the hydrazone and semicarbazone.

These results show conclusively that protoanemonin is correctly represented by (I). Muskat's lactone was therefore prepared; the solid obtained from vinylacrylic acid dibromide showed a m. p. slightly higher than that recorded by Muskat, and did not depress the m. p. of anemonin. Molecular-weight determinations in boiling acetone gave values of 215, and not 86 as found by Muskat. With hydriodic acid, dilævulic acid was formed (*loc. cit.*, p. 27), identical with that obtained from anemonin and with a synthetic sample (Diels and Alder, *Annalen*, 1931, **486**, 218): the various samples of this acid all gave identical semicarbazones.

There can be little doubt, therefore, that Muskat's lactone was, in fact, anemonin, as it seems certain that the substance dealt with here is identical with that obtained by him.

EXPERIMENTAL.

Two species of ranunculus were examined, *ranunculus hirsutus* and *r. bulbosus*, the former being treated in November and the latter in May and June; the results were the same in each case, except that the yields of protoanemonin were higher in the summer months. The plants were steam-distilled in lots of about 10 lbs., 2 l. of distillate being collected. This was saturated with salt, extracted with ether, the extract dried (sodium sulphate), and the ether removed, the last portion under reduced pressure; protoanemonin was thus obtained as a colourless, exceedingly vesicant and lachrymatory oil.

Reduction of Protoanemonin.—The residual oil was dissolved in alcohol and reduced with hydrogen and platinum ("Organic Syntheses," Vol. 8, 92): in a typical experiment the oil from about 30 lbs. of *r. bulbosus* with 0.5 g. platinum oxide absorbed 16 l. of hydrogen during 1½ hrs. The platinum was removed, and the liquid fractionated in a vacuum; after the alcohol had distilled, nearly the whole of the residue boiled at 90—91°/21 mm., 184°/756 mm., and weighed 24 g., corresponding with 34 g. per g.-mol. of hydrogen absorbed [Found, in various samples: equiv., 120—130 (by titration); 101 (by Ag salt); *M* (Victor Meyer), 98. Calc. for valeric acid: equiv. and *M*, 102]. In some cases, reduction ceased before the requisite amount of hydrogen had been absorbed, presumably owing to poisoning of the platinum, but was completed by addition of more catalyst.

The anilide crystallised from light petroleum (b. p. 60—80°) in needles, m. p. and mixed m. p. with *n*-valerianilide 61—62°; the *p*-toluidide was similarly obtained in plates, m. p. and mixed m. p. with *n*-valero-*p*-toluidide, 72—73°. 48 G. of the liquid reduction product were dissolved in excess of sodium carbonate, and the solution extracted exhaustively with ether; the recovered valeric acid had equiv. 105 (by titration). From the dried ethereal extract, a neutral substance (5 g.), b. p. 200—203°, was isolated [Found: C, 59.6; H, 8.0; equiv., 98.5 (by back titration). Calc. for C₅H₈O₂: C, 60.0; H, 8.0%]. These figures agree with those required by γ -valerolactone, and the presence of this substance probably accounts for the high equivalent of the valeric acid when determined by direct titration, as the lactone is not affected by alkali under the conditions used.

In some experiments, a residue remained after the distillation of the crude valeric acid; this crystallised easily from alcohol, m. p. and mixed m. p. with tetrahydroanemonin prepared by catalytic reduction of anemonin (*ibid.*, p. 35), 156°. This is doubtless formed by polymerisation of the protoanemonin to anemonin before reduction.

In order to make certain that no changes take place during the steam distillation, the expressed juice of *r. hirsutus* was extracted with ether; the extract was apparently the same as before.

Hydrolysis of Protoanemonin.—The crude protoanemonin was dissolved in a little acetone, and water added; titration with *N*-sodium hydroxide could then be carried out fairly rapidly at about 60° with a relatively sharp end-point; there was practically no free acid present. The quantity of protoanemonin present as thus determined agreed to within 2—4% with that calculated by the hydrogen absorbed in the catalytic reduction. After removal of the acetone from the product, the solution was extracted with ether to remove neutral impurities, acidified, saturated with salt, and exhaustively extracted with ether; the product on evaporation of the

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ether crystallised from benzene in needles, m. p. 125—126°; phenylhydrazone, m. p. 165° (β -acetylacrylic acid has m. p. 125°; phenylhydrazone, m. p. 169°). It was easily reduced by hydrogen and platinum in alcoholic solution, giving a liquid product which yielded a phenylhydrazone, m. p. 108°, and a semicarbazone, m. p. 189—190°, the m. p.'s of which were not depressed by admixture with the authentic derivatives of lævulic acid.

Muskat's Lactone.—Vinylacrylic acid was prepared and brominated according to Muskat's method; small quantities of the dibromide appeared to distil unchanged under reduced pressure, but when the product from 13.5 g. of vinylacrylic acid was distilled at 5 mm., a low-boiling first fraction was obtained, which deposited crystals after two days. After being washed with ether, this substance had m. p. 147—149°, and after crystallising from alcohol (needles or prisms), m. p. 151—152°, resolidifying at *ca.* 175—185° (*M*, in boiling acetone, 229, 203, 204, 230. Calc. for anemonin : 192). Three different mixtures with anemonin showed no depression of m. p.

Dilævulic acid ($\gamma\gamma'$ -diketosebacic acid) was prepared from this substance and from anemonin by means of hydriodic acid (Asahina, *loc. cit.*, p. 27) : m. p. and mixed m. p. *ca.* 150°; disemicarbazone, m. p. 183—184°. It was also prepared from pyrrole and maleic anhydride; m. p. 152—158°; disemicarbazone, m. p. 183—184°. Mixtures of any two of the three specimens of semicarbazones showed no depression of m. p. The low m. p. of the dilævulic acid from anemonin may possibly be accounted for by contamination with unchanged anemonin. The anemonin used in this work was very kindly given by Mr. Shearer : it had m. p. 151—152°, resolidification 175—185° (*M*, in boiling acetone, 192, 187).

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