

85. Compounds Related to Penicillic Acid. Part I. Ethyl β -Propionylacrylate and its Formylation Product.

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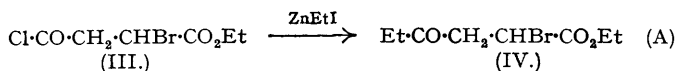
The synthesis of ethyl β -propionylacrylate by three different routes is described. Of these, the most satisfactory for preparative purposes was the esterification of β -propionylacrylic acid, obtained by the acid hydrolysis of ethyl propionyl-fumarate (or -maleate), which is the product of condensation between ethyl hydroxyethoxyacetate and ethyl propionylacetate. Formylation of ethyl β -propionylacrylate yielded a product which could not be purified but which, from its properties, and by analogy with the successful formylation of ethyl propionyl-fumarate (or -maleate) also described, would appear to consist essentially of ethyl 6-hydroxy-4-keto-5-methyl- $\Delta^{2:5}$ -hexadienoate. None of these compounds showed marked bacteriostatic activity.

THE antibacterial activity of the mould metabolic product, penicillic acid, to which formula (I) has been ascribed (Oxford, Raistrick, and Smith, *Chem. and Ind.*, 1942, 22), prompted an investigation of the possible antibacterial properties of a number of other compounds of similar structure. The preparation of ethyl 6-hydroxy-4-keto-5-methyl- $\Delta^{2:5}$ -hexadienoate (II) was undertaken because it contains a similar system of unsaturation to that postulated for (I) as well as the hydroxymethylene grouping which occurs in other compounds of biological significance. Colchicine, for example, as formulated by Windaus (*Annalen*, 1924, 439, 59) contains this grouping, while the mould metabolic product patulin (Raistrick *et al.*, *Lancet*, 1943, 625) appears to contain an anhydride ring formed from a carboxyl and a hydroxymethylene grouping.



Ethyl β -propionylacrylate, the obvious intermediate for the preparation of (II), is not mentioned in the literature, where the only β -acylacrylic acids described appear to be benzoyl- and acetyl-acrylic acids. Of the methods previously described for the synthesis of the latter, that which seemed most likely to be applicable to the preparation of homologues was the bromination of lævulic acid, or its ester, followed by removal of hydrogen bromide from the resulting β -bromo-derivative (Wolff, *Annalen*, 1891, 264, 246, 249). Bromination of ethyl β -propionylpropionate in ethereal solution yielded a product which appears to be mainly a mixture of monobromo-derivatives. On removal of hydrogen bromide with pyridine, this mixture gave ethyl β -propionylacrylate in 10% yield. The latter formed a crystalline 2 : 4-dinitrophenylhydrazone. As the bromination products of ethyl β -propionylpropionate have not been so far characterised, the structure of the unsaturated keto-ester thus obtained was considered ambiguous and its identity was established by its synthesis by the two methods given below.

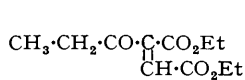
The first method involved the attempted preparation of ethyl α -bromo- β -propionylpropionate (IV) by the condensation of ethylzinc iodide with β -bromo- β -carbethoxypropionyl chloride (III). The Blaise reaction



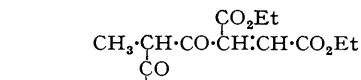
has been used by Müller and Feld (*Monatsh.*, 1931, 58, 22) to prepare ethyl propionylpropionate from β -carbethoxypropionyl chloride, and Wohlgemuth (*Compt. rend.*, 1914, 159, 80) describes a general method for the preparation of γ -chloro ketones from γ -chlorinated acid chlorides. On the other hand Blaise (*Compt. rend.*, 1912, 155, 46) found that the reaction of α -chlorinated acid chlorides with organozinc halides yielded mainly the esters of chlorinated acids with chlorinated alcohols. The use of this method to prepare α - or β -halogeno- γ -keto-esters or even simple β -halogeno-ketones is not reported in the literature. In the present work it was found that, while reaction (A) proceeded quite smoothly at -20° , the required bromoketo-ester (IV) could not be isolated in a pure condition from the reaction mixture. Decomposition with elimination of hydrogen bromide occurred on attempted distillation (<1 mm.), and the crude product was accordingly treated with quinoline to remove hydrogen bromide, when an unsaturated product, stable to distillation under reduced pressure, was obtained. The latter formed a 2 : 4-dinitrophenylhydrazone identical with that mentioned above, and had b. p. and refractive index similar to those of the ethyl β -propionylacrylate obtained by the previous method. However, analysis showed that it was not pure, and it was subsequently found to consist mainly of a mixture of ethyl β -propionylacrylate and fumarate (or maleate), the b. ps. of which are so close as to preclude ready fractionation.

The following method, which should be capable of general application to the synthesis of small quantities of β -acylacrylic acids, was found more satisfactory. Ethyl hydroxyethoxyacetate (Traube, *Ber.*, 1907, 40, 4944) was condensed with ethyl propionylacetate in presence of acetic anhydride to yield ethyl propionyl-fumarate (or -maleate) (V) which on hydrolysis and simultaneous decarboxylation with dilute hydrochloric acid gave β -propionylacrylic acid in 16% yield. The latter was converted into its ethyl ester by reaction of its silver salt with ethyl iodide. Formylation of ethyl β -propionylacrylate with ethyl formate in presence of sodium methoxide yielded a gum which resisted all attempts at purification. It gave a deep red colour with ferric

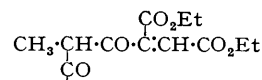
chloride, was precipitated as a copper salt on treatment with copper acetate solution, and gave analytical figures approaching those of the required formyl derivative (II).



(V.)



(VI.)



(VII.)

To ascertain whether a compound of the nature of (II) was in fact capable of existence, the formylation of the similarly constituted ethyl propionyl-fumarate (-maleate) (V) was studied. Reaction did not occur with sodium methoxide as condensing agent, but proceeded smoothly with powdered sodium. The product was a mixture of at least three components. The predominant one was an oil which distilled under high vacuum. It gave a deep red colouration with ferric chloride and analysed satisfactorily for the required *ethyl 6-hydroxy-4-keto-3-carbethoxy-5-methyl- $\Delta^{2:5}$ -hexadienoate*. A second component, m. p. 169—170° also gave a deep red colour with ferric chloride, was soluble in sodium bicarbonate solution, and analysed for the product of a Claisen condensation of two molecules of (V); it was presumably (VI) or (VII). The third constituent, a liquid which distilled under reduced pressure, gave no colour reaction with ferric chloride, and formed a crystalline 2 : 4-dinitrophenylhydrazone, has not been identified.

The minimum dilutions at which some of these compounds showed bacteriostatic activity when tested in broth were as follows :

	<i>S. aureus.</i>	M.E.D. <i>B. coli.</i>	<i>Ps. pyocyaneus.</i>
Ethyl 6-hydroxy-4-keto-3-carbethoxy-5-methyl- $\Delta^{2:5}$ -hexadienoate	1 : 4,000	1 : 4,000	1 : 4,000
Ethyl 6-hydroxy-4-keto-5-methyl- $\Delta^{2:5}$ -hexadienoate	1 : 2/4,000	1 : 2/4,000	1 : 4/8,000
Ethyl propionylacrylate	1 : 32/64,000	1 : 32/64,000	1 : 8/16,000
Propionylacrylic acid	1 : 2/4,000	1 : 2/4,000	<1 : 2,000

EXPERIMENTAL.

Ethyl β -Propionylpropionate.—The yield of 59% of this ester obtained by hydrolytic fission of the furan ring in 2-furylmethylcarbinol claimed by Tschitschibabin (*Chim. et Ind.*, 1932, 27, 563 (special)) could not be substantiated; under the conditions cited, we observed much resinification with low and inconsistent yields. The somewhat modified procedure adopted, which gave consistent yields of 20—23% of pure product over several runs, was as follows. To a solution of 2-furylmethylcarbinol (60 g.) (Tschitschibabin, *loc. cit.*) in ethanol (250 c.c.), hydrochloric acid (*d* 1.16; 15 c.c.) was added in portions with shaking whereby the mixture became deep apple-green. It was heated at 63—68° (internal temperature) for 1 hour, and then boiled gently under reflux on the steam-bath for 30 minutes. Most of the alcohol, etc., was removed at 40° under reduced pressure, and the residual black oil was diluted with ether (100 c.c.) and treated gradually, with shaking, with sodium bicarbonate solution until the aqueous layer was alkaline. The mixture was filtered, the resinous residue further extracted with ether, and after separation the ethereal layer was dried (CaCl₂). After removal of ether the residue was distilled, b. p. 97—104°/16 mm. (yield 27.5 g.). The combined distillates from 5 similar runs were fractionated under reduced pressure. The pure ester (yield 91 g.) had b. p. 102—104°/15 mm., n_D^{20} 1.4311.

Bromination of ethyl β -propionylpropionate. A solution of ethyl β -propionylpropionate (50 g.) in dry ether (100 c.c.) was cooled to 0°, and bromine (55 g.) was slowly added with vigorous stirring, during 75 minutes. Stirring with cooling at 0° was continued for 30 minutes, after which the mixture was diluted with ether (75 c.c.), washed several times with water, shaken with charcoal, and filtered. The ether was removed under reduced pressure and the residue distilled in a high vacuum. The distillate, b. p. 70—84°/0.3 mm. (63.5 g.), was refractionated and the following arbitrary fractions collected: (a) 4.0 g., b. p. 58—65°/0.1 mm., n_D^{20} 1.4862 (Found: Br, 35.5%); (b) 47.7 g., b. p. 62—77°/0.1 mm., n_D^{20} 1.4737 (Found: Br, 35.6%. Calc. for monobromopropionylpropionic ester, C₈H₁₃O₃Br; Br, 33.7%).

Ethyl β -Propionylacrylate.—The bromo-ester (fraction b; 31.5 g., fraction a may also be used) was mixed with dry pyridine (41 c.c.), the heat which was developed after a short time being moderated by occasional cooling. When the heat of reaction began to abate, the deep red mixture was heated on the steam-bath under reflux for 2 hours. After cooling it was poured into 2*N*-hydrochloric acid (200 c.c.) and extracted with ether. The ethereal extract was washed twice with water, dried (Na₂SO₄), and evaporated on the steam-bath. The residue was distilled under reduced pressure, the product (2.77 g.) being a straw coloured liquid, b. p. 92—94°/9 mm., n_D^{20} 1.4515. An approximately equal amount of tarry non-volatile residue remained. The 2 : 4-dinitrophenylhydrazone, yellow sheaves (from ethanol), had m. p. 135° alone or mixed with the 2 : 4-dinitrophenylhydrazone of the ester otherwise obtained as described below. On hydrolysis with 2*N*-hydrochloric acid the liquid yielded propionylacrylic acid (30—40%), identified by m. p. and mixed m. p. with the crystalline acid obtained as described below.

α -Bromo- β -carbethoxypropionyl Chloride.—(Cf. Volhard, *Annalen*, 1887, 242, 156.) Bromosuccinic acid (40 g.) and thionyl chloride (75 g.) were refluxed for 3 hours on the steam-bath. Excess of thionyl chloride was removed under reduced pressure, and ethyl alcohol (10 g.) was added to the residue in small portions at a time, with shaking. Finally the mixture was warmed on the steam-bath for 10 minutes, cooled, and treated with an equal volume of water. The resulting oil was washed 3 or 4 times with water to remove di-acid, dissolved in ice-cold sodium carbonate solution, and washed with ether to remove di-ester. The aqueous layer, after acidification with 2*N*-hydrochloric acid, was extracted with ether, and the ethereal solution was washed with water, treated with charcoal, filtered, and dried (CaCl₂). After removing the ether under reduced pressure, ethyl hydrogen bromosuccinate was obtained as a heavy brown oil (yield 32 g.) (Equiv. by titration, 230. Calc. for C₆H₉O₄Br: equiv., 225). It decomposed on attempted distillation under reduced pressure. It was converted to the acid chloride by refluxing for 2 hours with thionyl chloride (16 c.c.) followed by removal of excess of thionyl chloride under reduced pressure.

Condensation with ethylzinc iodide. The above acid chloride was dissolved in dry toluene (35 c.c.) and cooled to -20° (internal temperature). A solution of ethylzinc iodide (32 g., calculated on a 75% yield from ethyl iodide) in toluene was run in slowly with frequent shaking and at such a rate that the temperature of -20° was maintained. If the temperature fell below this, little or no reaction took place, while at higher temperatures tarring occurred. When the addition was complete the mixture was kept at -20° for about 5 hours with frequent shaking, by which time the

characteristic odour of acid chloride had disappeared. The temperature was raised to 0°, and ice water (100 c.c.) run in. The toluene solution was washed with 20% sulphuric acid, concentrated ammonium sulphate solution, water, saturated potassium bicarbonate, very dilute sodium thiosulphate solution, and finally with water. It was then dried (Na₂SO₄), and the toluene was removed under reduced pressure. There was thus obtained a heavy brown oil (ca. 18 g.). On attempted distillation at <1 mm., a few drops of distillate came over at about 80°; the temperature then rose steadily to above 100° and hydrogen bromide was given off. The small amount of distillate rapidly became dark brown and, on treatment with 2 : 4-dinitrophenylhydrazine, yielded the same crystalline derivative, m. p. 135°, as was obtained above from ethyl β-propionylacrylate.

Removal of hydrogen bromide. The crude reaction product (12.5 g.) was dissolved in a mixture of quinoline (12.5 g.) and alcohol (16 c.c.) and heated gently on the steam-bath for 90 minutes. After cooling, water (20 c.c.) was added and the oily layer separated by means of ether, washed with a small quantity of dilute hydrochloric acid and water, and dried (CaCl₂). After removing the solvent, the residue was distilled under reduced pressure and a fraction (4—5 c.c.), b. p. 97—100°/10 mm., was collected. The latter was redistilled, b. p. 109—110°/17 mm., n_D^{20} 1.4520 (Found : C, 60.5; H, 7.1. C₈H₁₂O₃ requires C, 61.5; H, 7.7%). It yielded a crystalline 2 : 4-dinitrophenylhydrazone, m. p. 135°, identical with that obtained from ethyl β-propionylacrylate made by the other methods.

While the same 2 : 4-dinitrophenylhydrazone was always obtained in these experiments, and the distillate usually had b. p. and refractive index similar to those given above, the figures for C and H were always considerably lower than those required for pure ethyl propionylacrylate. Hydrolysis of a sample with particularly low figures (Found : C, 56.3; H, 7.1%), with 2N-hydrochloric acid yielded mainly fumaric acid, and only a small amount of propionylacrylic acid which was identified as its 2 : 4-dinitrophenylhydrazone, m. p. 210—216° (see below).

Ethyl Propionylfumarate (-maleate).—A mixture of ethyl hydroxyethoxyacetate (34.5 g.) (Traube, *Ber.*, 1907, **40**, 4944), ethyl propionylacetate (35 g.) (Willstätter and Clarke, *Ber.*, 1914, **47**, 298), and acetic anhydride (48 g.) was heated under reflux on the steam-bath for 9 hours. After cooling, the mixture was diluted with ether (100 c.c.) and shaken with water (80 c.c.) to which ammonia (*d* 0.88) was added in small portions until the aqueous layer was faintly alkaline. The ethereal layer was finally washed with water and dried (Na₂SO₄). After removal of the ether the residue was fractionated in a vacuum. The product (31 g.) had b. p. 122—124°/1 mm., n_D^{20} 1.4568 (Found : C, 57.2; H, 6.95. C₁₁H₁₆O₅ requires C, 57.9; H, 7.0%). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol in yellow needles, m. p. 162—163° (Found : N, 13.7. C₁₇H₂₀O₈N₄ requires N, 13.7%).

β-Propionylacrylic Acid.—Ethyl propionylfumarate (41 g.) and 2N-hydrochloric acid (410 c.c.) were boiled under reflux for 3½ hours. The yellow solution was cooled, saturated with ammonium sulphate, and extracted several times with ether. After being washed with saturated ammonium sulphate solution, the ethereal solution was evaporated and the residue dried in a vacuum. It was dissolved in warm benzene (20 c.c.) and on cooling propionylacrylic acid (3.7 g.) crystallised in long narrow sheaves. On recrystallisation from benzene the acid had m. p. 107—108° (Found : C, 56.0; H, 6.4. C₆H₈O₃ requires C, 56.25; H, 6.25%). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol had m. p. 210—216° (Found : N, 18.15. C₁₂H₁₂O₆N₄ requires N, 18.2%).

Hydrolysis of ethyl propionylfumarate with boiling 20% hydrochloric acid yielded propionylacrylic acid and a small amount of a crystalline acid, minute rhombs (from water), m. p. 258—260° (decomp.) (Found : C, 60.7; H, 5.9. C₁₂H₁₄O₅ requires C, 60.6; H, 5.9%). The substance was obtained in too small amount for further examination.

Conversion into the ester. Finely divided calcium carbonate (2.5 g.) was added gradually to a warm solution of propionylacrylic acid (5.7 g.) in water (24 c.c.). The mixture was warmed on the steam-bath for a further 30 minutes and filtered hot, and the residue washed with warm water (10 c.c.). The cold filtrate was treated with a solution of silver nitrate (8.0 g.) in water (10 c.c.), and cooled in ice; the silver salt was then filtered off, washed with small quantities of ice water, and dried in a vacuum with protection from light (yield 9.3 g.). The finely powdered salt was heated under reflux on the steam-bath with a solution of ethyl iodide (7.73 g.) in dry chloroform (40 c.c.) for 2 hours. After cooling, the silver iodide was filtered off and washed several times with chloroform. The combined chloroform solutions were washed with sodium bicarbonate solution, then with water, and dried (Na₂SO₄). The solvent was removed under reduced pressure, and the ester then distilled as a pale straw coloured liquid (yield 4.0 g.), b. p. 103—104°/12 mm., 94—96°/8 mm., n_D^{20} 1.4532 (Found : C, 61.7; H, 7.7. C₈H₁₂O₃ requires C, 61.6; H, 7.7%). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol in long yellow sheaves, m. p. 135° (Found : N, 16.8. C₁₄H₁₆O₆N₄ requires N, 16.7%). The ester on hydrolysis with 2N-hydrochloric acid gave the acid in 40% yield.

Formylation of Ethyl β-Propionylacrylate.—To a stirred suspension of finely powdered sodium methoxide (1.37 g.) in dry ether (20 c.c.), cooled below 0°, a mixture of ethyl propionylacrylate (3.96 g.) and ethyl formate (1.98 g.) was added gradually during 30 minutes. The mixture which had become progressively yellow to dark brown was stirred below 0° for a further hour, then kept at 0° for 20 hours. The brick-red sodium salt was filtered, washed with dry ether, and dried in a vacuum (yield 4.6 g.). It was added in portions to a stirred mixture of 0.9N-acetic acid (25 c.c.) and ether (70 c.c.) cooled below 0°. The ethereal layer was washed several times with water, evaporated, and the residue dried in a vacuum. The product (1.8 g.) was a yellow brittle gum, m. p. 54—61° (Found : C, 59.9; H, 6.3. Calc. for C₉H₁₂O₄ (II) : C, 58.7; H, 6.5. Calc. for the β-diketone, C₁₄H₁₈O₅, which might arise from the condensation of two molecules of ethyl β-propionylacrylate : C, 63.2; H, 6.8%). The substance could not be rendered crystalline by treatment with solvents or by absorption on a column of alumina from benzene solution. It decomposed on attempted distillation (0.1 mm.). In alcoholic solution it gave a marked red colouration with ferric chloride solution. With saturated cupric acetate solution, an ethereal solution gave an olive-green copper salt which, after partial purification by fractional precipitation, crystallised (unsatisfactorily) from 70% ethanol, and had m. p. 210—215° (decomp.) (Found : C, 48.0; H, 5.3; Cu, 14.8. Calc. for C₁₈H₂₂O₈Cu : C, 50.3; H, 5.1; Cu, 14.7. Calc. for Cu salt of the possible β-diketone, C₂₈H₃₄O₁₀Cu : C, 56.7; H, 5.7; Cu, 10.6%). There was no improvement in C and H figures for the substance regenerated from this copper salt.

Formylation of Ethyl Propionylfumarate.—Attempted formylation with sodium methoxide as condensing agent resulted in a recovery of ca. 80% of starting material after 48 hours' action at 0°.

To a stirred suspension of powdered sodium (1.04 g.) in dry toluene (20 c.c.) cooled at 0° was added gradually a mixture of ethyl propionylfumarate (10.2 g.) and ethyl formate (3.5 g.); stirring at 0° was continued for 5 hours, and the mixture allowed to stand at 0° for a further 40 hours. The sodium salt was precipitated by stirring with light petroleum (b. p. 60—80°) (50 c.c.), filtered, washed with light petroleum, and dried in a vacuum (yield 9.7 g.). It was added in portions to a stirred mixture of 0.9N-acetic acid (40 c.c.) and ether (60 c.c.) at 0°. The ethereal layer was washed three times with water and dried (Na₂SO₄). After removal of solvent the residual oil was dried at 60°/20 mm. (5.9 g.). From this by solution in ether, addition of light petroleum, and scratching, a substance (0.5 g.) having the composition of (VI) or (VII) was obtained, m. p. 169—170° after recrystallisation from benzene (Found : C, 58.5; H, 6.35; OEt, 33.2. Calc. for C₂₀H₂₆O₉ : C, 58.5; H, 6.3; OEt, 32.9%). The substance was readily soluble in sodium bicarbonate solution, and in alcoholic solution gave a deep red colouration with ferric chloride. The residual oil was dissolved in ether, extracted with sodium bicarbonate solution, and, after evaporation of solvent, fractionated in high vacuum. The following fractions were collected : (a) b. p. 86—90° (bath temperature)/0.05 mm. (1 g.), (b) b. p. 164—170° (bath temperature)/0.05

mm. (2.8 g.). Fraction (b) was redistilled. It gave a deep red colouration with ferric chloride in alcoholic solution, and was presumed to be *ethyl 6-hydroxy-4-keto-3-carbethoxy-5-methyl- $\Delta^{2:5}$ -hexadienoate* (Found: C, 56.6; H, 6.8. $C_{12}H_{16}O_6$ requires C, 56.3; H, 6.3%). There were indications of crystallisation on standing in absence of air. Fraction (a) on redistillation had b. p. 105°/0.3 mm. (Found: C, 55.6; H, 7.5; OEt, 47.6. Calc. for $C_8H_7O_4(OEt)_3$: C, 55.6; H, 7.3; OEt, 44.7%). The substance, which has not been identified, gave no colouration with ferric chloride. With 2:4-dinitrophenylhydrazine it gave a derivative, crystallising from ethanol in yellow needles, m. p. 155° (Found: N, 14.3%).

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