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25. Compounds Related to Penicillic Acid. Part IV. Synthesis of a Phenyl Analogue.

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The preparation of an analogue of penicillic acid, in which the *iso* propenyl group is replaced by a phenyl group, is described. The properties of some of the intermediates have been studied; in particular it has been found that under certain conditions the acetylenic ester Ph·CH(OH)·C \equiv C·CO₂Me undergoes a novel prototropic rearrangement to give Ph·CO·CH \equiv CH·CO₂Me.

THE successful synthesis of penicillic acid (I) (Raphael, J., 1948, 1508) rendered it desirable to employ the methods used therein to prepare a series of compounds of the penicillic acid type in order to determine the features of the structure essential for biological activity. The analogue (V), in which the phenyl group takes the place of the *iso* propenyl group in penicillic acid, was found to be readily available by the following method. Phenylethynylcarbinol (Jones and McCombie, J., 1942, 733) was carbonated via the disodium salt (cf. Raphael, J., 1947, 805) to produce 3-hydroxy-3-phenylprop-1-yne-1-carboxylic acid (S-benzylisothiouronium salt) which was esterifiedwithout further purification to give a 58% overall yield of the*methyl*ester (II). Catalyticsemihydrogenation of the acid yielded the lactone of <math>3-hydroxy-3-phenylprop-2-ene-1-carboxylic acid (XII) obviously by way of the unstable lactone (XI) (cf. Thiele and Sulzberger, Annalen, 1901, **319**, 203).

After a preliminary treatment with charcoal, the ester (II) reacted smoothly with methanol in the presence of the boron trifluoride-mercuric oxide-trichloroacetic acid catalyst (cf. *inter al.*, Killian, Hennion, and Nieuwland, J. Amer. Chem. Soc., 1936, 58, 80), whereby the crystalline *methoxy-lactone* (III) was obtained. If the charcoaling was omitted the product isolated was a viscous oil containing about 30% of the methoxy-lactone. The lactone was readily brominated in carbon tetrachloride solution with evolution of hydrogen bromide to yield the highly reactive *bromo-lactone* (IV). Hydrolysis of (IV) with potassium carbonate in aqueous dioxan gave the penicillic acid analogue (V) directly. It was found to be considerably more stable than penicillic acid itself and, unlike the latter, gave no coloration with ammonia. The constitution of (V) was confirmed by sulphuric acid hydrolysis whereby 1-phenylpropane-1: 2-dione (characterised as its α -2: 4-dinitrophenylhydrazone) was formed.

It has been shown by Jones and Whiting (J., in the press) that acetylenic hydroxy-esters such as (II) react readily with diethylamine to give highly crystalline diethylamino-lactones of the type exemplified by (VI). Accordingly it was decided to prepare this diethylamino-lactone and subject it to the foregoing procedure of bromination and hydrolysis by the method of Jones and Whiting (loc. cit.) in order to obtain a further modification of the penicillic acid struc-The ester (II) reacted exothermically with excess of diethylamine, but the product was an ture. oil. Distillation gave the known methyl trans- β -benzoylacrylate (VIII) (2:4-dinitrophenylhydrazone). Suitable treatment of the undistillable residue yielded a small quantity of a crystalline solid which proved to be the desired diethylamino-lactone (VI). The constitution was confirmed by hydrolysis to the lactone of 2: 3-dihydroxy-3-phenylprop-1-ene-1-carboxylic acid (VII), which, on treatment with diazomethane gave (III). A good yield of (VI) was obtained by employing one mole of diethylamine in ethereal solution in the cold; under these conditions very little rearrangement took place. Attempted bromination of (VI) resulted in extensive decomposition.

As the above rearrangement seemed worthy of further study it was carried out in the presence of a tertiary amine, triethylamine, in order to obviate complications caused by addition to the triple bond. Under these conditions a 94% yield of (VIII) was obtained. The mechanism of the reaction is conjectured to be as follows:

$$\begin{array}{ccc} \mathrm{Ph}\text{\cdot}\mathrm{CH}(\mathrm{OH})\text{\cdot}\mathrm{C}{\equiv}\mathrm{C}\text{\cdot}\mathrm{CO}_{\mathtt{2}}\mathrm{Me} \longrightarrow [\mathrm{Ph}\text{\cdot}\mathrm{C}(\mathrm{OH}){=}\mathrm{C}{=}\mathrm{CH}\text{\cdot}\mathrm{CO}_{\mathtt{2}}\mathrm{Me}] \longrightarrow \mathrm{Ph}\text{\cdot}\mathrm{CO}\text{\cdot}\mathrm{CH}{=}\mathrm{CH}\text{\cdot}\mathrm{CO}_{\mathtt{2}}\mathrm{Me} \\ & (\mathrm{XIII.}) \end{array}$$

Under the influence of the base, prototropy occurs to form the allene enol (XIII) which then ketonises to the more stable configuration (VIII).

The very similar prototropic rearrangement of α -hydroxyethylenes to saturated ketones is very well known (cf. *inter al.*, Rambaud and Dondon, *Compt. rend.*, 1946, 223, 381; Tiffeneau, *Bull. Soc. chim.*, 1907, 1, 1209; Nomura, *ibid.*, 1925, 37, 1245), but, as far as the authors are aware, this is the first time such a transformation has been encountered in the acetylenic field. The scope and limitations of this novel reaction are being fully investigated.

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Oxidation of the ester (II) with chromium trioxide gave the crystalline *methyl benzoyl-propiolate* (IX) (2: 4-dinitrophenylhydrazone); catalytic semihydrogenation of this compound produced methyl cis- β -benzoylacrylate (X).

Preliminary biological tests have shown the analogue (V) to possess about a quarter of the antibacterial activity of penicillic acid itself; the methoxy-lactone (III), however, was found to be more than thirty times as active as the natural antibiotic.

Ultra-violet light absorptions in alcoholic solution.

	λ max. , Α.	ϵ_{\max} .		$\lambda_{max.}$, A.	€max.
Ph·CH(OH)·C=C·CO,H	2160	11,000	Methoxy-lactone (III)	2200	16,500
Ph·CO·C=C·CO ₂ Me	2210	9,500	Bromo-lactone (IV)	2420	10,500
	2690	15,500	Acid (V)	2250	13,500
cis-Ph•CO•CH=CH•CO ₂ Me	2510	12,000	Diethylamino-lactone (VI)	2670	24,000
trans-Ph·CO·CH=CH·CO ₂ Me	2350	12,000	Lactone of 2-diethylamino-3-		
-	2680	9,000	hydroxyhex-1-ene-1-carb-		
trans-Ph·CO·CH=CH·CO ₂ H	2420	12,500	oxylic acid ¹	2650	26,500
	2650	10,000	Lactone (XII)	2180	14,000
				2600	14,500

¹ Jones and Whiting, private communication.

The absorption data confirm the cyclic structure (V) for the analogue, similar to that obtaining in the case of penicillic acid itself (Raphael, J., 1947, 805). On the other hand the maximal



absorptions exhibited by *trans*- β -benzoylacrylic acid and the *cis*- and *trans*-methyl esters show these compounds to possess the straight-chain configuration as designated; Lutz and Scott (*J. Org. Chem.*, 1948, 13, 285) have recently come to similar conclusions from consideration of the chemical properties of the substances. This is in contrast to their aliphatic counterpart, β -acetylacrylic acid, where ultra-violet measurements indicate a cyclic structure (Shaw, *J. Amer. Chem. Soc.*, 1946, 68, 2510).

EXPERIMENTAL.

2-Hydroxy-2-phenylprop-1-yne-1-carboxylic Acid.—To a well-stirred solution of sodamide (prepared from 50 g. of sodium) in liquid ammonia (2.1.) was added a solution of phenylethynylcarbinol (132 g.) (Jones and McCombie, *loc. cit.*) in an equal volume of dry ether. After 30 minutes, dry toluene (1.1.) was solved with the ammonia had evaporated; the residual ammonia was removed by a current of nitrogen. To the resulting suspension of disodium salt in toluene, a large excess of solid carbon dioxide was added. The mixture was left until it had warmed to room temperature and was then treated with excess of dilute (4x) suphuric acid. The toluene layer was extracted with dilute sodium carbonate solution; the alkaline extract was acidified, the precipitated acid extracted with ether, and the ethereal extract washed well with water and dried (MgSO₄). Evaporation furnished the crude 2-hydroxy-2-phenylprop-1-yne-1-carboxylic acid (142 g.). For analysis a small sample was crystallised repeatedly from benzene; the pure acid separated in nacreous plates, m. p. 94—95° (Found : C, 67·15; H, 4·55. C₁₀H₈O₃ requires C, 68·15; H, 4·55%). The S-benzyliso-thiouronium salt crystallised from alcohol in needles, m. p. 161° (decomp.) (Found : N, 8·45. C₁₈H₁₈O₃N₂S

The crude acid was dissolved in dry methanol (750 c.c.) containing sulphuric acid (d 1.84; 30 g.), and the solution refluxed for 24 hours. The cooled solution was poured into water, and the precipitated oil isolated by means of ether. Distillation furnished the *methyl* ester (II) as a pale yellow oil, b. p.

140—143°/0.5 mm., $n_D^{16^*}$ 1.5455 (110 g.; 58%) (Found : C, 68.9; H, 5.4; OMe, 16.6. $C_{11}H_{10}O_3$ requires C, 69.45; H, 5.3; OMe, 16.3%). Semihydrogenation. A solution of the above acid (7 g.) in methanol (50 c.c.) was shaken with palladium-calcium carbonate catalyst (500 mg.; 5%) in an atmosphere of hydrogen until one mol. of hydrogen had been absorbed. After removal of catalyst and solvent, the residual oil was rapidly distilled over a free flame under 12 mm. pressure. The solidified distillate was crystallised once from a small volume of alcohol and then repeatedly from light petroleum (b. p. 80—100°). The product (2.3 g.) formed nacreous plates, m. p. 93—94°, undepressed on admixture with a specimen of the lactone (XII) prepared by the method of Fittig and Ginzberg (Annalen, 1898, 299, 17). Methoxy-lactone (III).—(a) A solution of (II) (22 g.) in dry methanol (80 c.c.) was refluxed with activated charcoal for 5 hours. The cooled, filtered solution was poured on a catalyst prepared by momentarily heating together red mercuric oxide (3 g.), boron trifluoride-ether complex (5 c.c.), trichloroacetic acid (100 mg.), and methanol (5 c.c.). After the initial exothermic reaction had subsided, the mixture was left at room temperature overnight, and then poured into sodium hydrogen carbonate solution. Isolation

left at room temperature overnight, and then poured into sodium hydrogen carbonate solution. Isolation by means of ether furnished an oil which rapidly solidified; crystallisation from light petroleum (b. p. $80-100^{\circ}$) yielded the *methoxy-lactone* (III) (10.3 g.; 47%) as prismatic plates, m. p. 97-98° (Found : C, 69.4; H, 5.5. $C_{11}H_{10}O_3$ requires C, 69.45; H, 5.3%).

(b) If the charcoaling were omitted a viscous oil was obtained which would not solidify. When this oil was heated at $120-130^{\circ}$ (bath temp.)/ 10^{-6} mm., about 30% of the product distilled as a colourless oil which rapidly solidified. Crystallisation as in (a) yielded the same methoxy-lactone, m. p. and mixed m. p. 97-98°. Bromo-lactone (IV).—A solution of (III) (5 g.) in carbon tetrachloride (25 c.c.) was treated with a

solution of bromine (1.34 c.c.; 1.1 mol.) in carbon tetrachloride (10 c.c.), and refluxed on the steam-bath solution of bromme (1.54 c.c.), 1.1 micri bin terration of de (10 c.c.), and Feinback on the steam-bath for 3 hours, by which time the evolution of hydrogen bromide had practically ceased. After evaporation of the solvent under reduced pressure the residual oil rapidly solidified. Crystallisation from ethanol followed by light petroleum (b. p. 80-100°) gave needles of the bromo-lactone (IV), m. p. 114-115° (3.5 g.; 50%) (Found : C, 49.2; H, 3.4; Br, 29.7; OMe, 11.7. C₁₁H₉O₃Br requires C, 49.1; H, 3.4; Br, 29.7; OMe, 11.6%). Lactone of 3-Bromo-3-hydroxy-2-methoxy-3-phenylprop-1-ene-1-carboxylic Acid (IV).—A mixture of (IV) (5.5 g.) protection or between between between between between between the steam betwee

(IV) (5.5 g.), potassium carbonate (5.5 g.), water (6 c.c.), and dioxan (30 c.c.) was heated on the steam-bath for 5 hours. The solution was evaporated to dryness under reduced pressure, the resulting solid dissolved for 5 hours. in water, and the solution extracted with ether to remove non-acid material. Acidification of the aqueous

In water, and the solution extracted with ether to remove non-acid material. Acidification of the aqueous layer and isolation by means of ether yielded a viscous oil which rapidly solidified. Crystallisation from benzene gave the acid (V) (2.3 g.; 55%) as needles, m. p. 140—141° (Found : C, 64·2; H, 4·8; OMe, 14·9; C₁₁H₁₀O₄ requires C, 64·1; H, 4·9; OMe, 15·0%). *Hydrolysis.* The acid (V) (200 mg.) was boiled with dilute sulphuric acid (2n; 8 c.c.) until, on cooling, no solid crystallised out (ca. 6 hours). The oil formed was isolated by means of ether and treated with alcoholic 2 : 4-dinitrophenylhydrazine sulphate. The precipitated derivative was thoroughly dried, dissolved in benzene, and chromatographed on alumina; an upper orange and a lower yellow band were formed. The lower band, containing the bulk of material, was washed through; evaporation and crystallisation from *is*oamyl alcohol gave orange-yellow needles, m. p. 187—188° undepressed on admixture with the a-2 : 4-dinitrophenylhydrazone of 1-phenylpropane-1 : 2-dione prepared according to the directions of von Auwers and Ludewig (Annalen, 1936, **526**, 130).

to the directions of von Auwers and Ludewig (Annalen, 1936, 526, 130). Action of Amines on the Ester (II).—(a) The ester (13 g.) was added slowly to cooled diethylamine (15 c.c.); after the initial exothermic reaction was over the mixture was left at room temperature overnight. The excess of diethylamine was evaporated and the residual liquid distilled in a vacuum. The main fraction (5.5 g.), b. p. 98-100°/0.5 mm., rapidly solidified to a mass of yellow needles, m. p. An inaction (5.5 g), b. p. 36–100 (75 min.) rapidly solution to a mass of yenow neededs, in p. 31°. Analysis indicated that the product was isomeric with the starting material; it was ultimately shown to be methyl *trans-β*-benzoylacrylate (VIII) (Kohler and Engelbrecht, J. Amer. Chem. Soc., 1919, 41, 768, give m. p. 32°) (Found : C, 69·75; H, 5·4. Calc. for $C_{11}H_{19}O_3$: C, 69·45; H, 5·3%). The 2 : 4-dinitrophenylhydrazone crystallised from isoamyl alcohol or ethanol-ethyl acetate in orange platelets, m. p. 203–205° (Found : C, 55·65; H, 3·9. $C_{17}H_{14}O_6N_4$ requires C, 55·15; H, 3·8%). Trituration of the undistillable period us ultitle addet before furnished a crystalling colid (1.2 g).

Trituration of the undistillable residue with a little cold ether furnished a crystalline solid (1·2 g.). Crystallisation from benzene-light petroleum (b. p. 60-80°) gave the *diethylamino-lactone* (VI) as rhombs, m. p. 76-77° (Found : C, 72·55; H, 7·4; N, 6·55. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·55. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·55.

(b) To a solution of the ester (5 g.) in dry ether (25 c.c.) was added a solution of diethylamine ($2 \cdot 7$ g.; 1 mol.) in ether (10 c.c.), the mixture being kept at 0° After being left overnight at 0° the solution was washed with acid followed by sodium hydrogen carbonate solution, and dried (MgSO₄). Evaporation furnished a brownish oil which solidified on trituration with a little cold ether. Filtration and crystallisation as in (a) gave the diethylamino-lactone ($4\cdot 2$ g.; 70%), m. p. 76—77°. Evaporation of the mother liquors and distillation yielded methyl *trans-β*-benzoylacrylate (650 mg.), m. p. 31°.

 (c) The ester (5 g.) was treated with triethylamine (15 c.c.) in a manner exactly similar to that described in (a). On distillation, methyl trans-β-benzoylacrylate (4.7 g.; 94%), m. p. 31°, was obtained. Lactone of 2: 3-Dihydroxy-3-phenylprop-1-ene-1-carboxylic Acid (VII).—A solution of (VI) (250 mg.) in concentrated hydrochloric acid (3 c.c.) was heated on the steam-bath for 2 hours. The turbid liquid was cooled, water added, and the solution extracted with ether. Removal of the acidic component with sodium hydrogen carbonate solution, followed by re-acidification, gave an oil which rapidly solidified. Crystallisation from water produced needles (130 mg.), m. p. 126—127°; the compound gave a red coloration with ferric chloride (Anschütz and Böcker, Annalen, 1909, **368**, 65, give m. p. 127·5—128·5°). Reaction of the acid with excess of ethereal diazomethane gave the methoxy-lactone (III), m. p. and mixed m. p. 98°.

Methyl Benzoylpropiolate (IX).—The ester (II) (10 g.) was dissolved in acetone (50 c.c.), and a dilute sulphuric acid solution of chromium trioxide (6N; 18 c.c.) added slowly with cooling. After 1 hour, water was added; isolation with ether gave a yellow oil which rapidly solidified. Crystallisation from

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light petroleum (b. p. 40—60°) or methanol gave plates (8·2 g.; 82%), m. p. 65—66° (Found : C, 70·4; H, 4·4; OMe, 16·7. $C_{11}H_8O_3$ requires C, 70·2; H, 4·25; OMe, 16·5%). Alcoholic 2 : 4-dinitrophenyl-hydrazine sulphate gave the 2 : 4-dinitrophenylhydrazone, crystallising in orange needles, m. p. 190° (decomp.), from glacial acetic acid (Found : N, 15·2. $C_{17}H_{12}O_6N_4$ requires N, 15·2%). Methyl cis- β -Benzoylacrylate (X).—A solution of methyl benzoylpropiolate (3·13 g.) in methanol (25 c.c.) was shaken with palladium-calcium carbonate catalyst (5%; 250 mg.) in an atmosphere of hydrogen until 1 mol. had been absorbed. After removal of catalyst and solvent, the residual oil was fractionated; the main fraction (2·2 g.) had b. p. 102—104°/0·5 mm., n_{20}^{20} 1·5450. After some time it solidified to a hard mass which, on crystallisation from light petroleum (b. p. 60—80°), gave white needles, m. p. 67° (Rice, J. Amer. Chem. Soc., 1914, **45**, 1226, gives m. p. 67° for methyl cis- β -benzoylacrylate) (Found : C, 68·95; H, 5·25. Calc. for $C_{11}H_{10}O_3$: C, 69·45; H, 5·3%).

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