The Potato Eelworm Hatching Factor

6. ATTEMPTS TO PREPARE ARTIFICIAL HATCHING AGENTS.

PART II. SOME ACTIVE ARYLIDENE- $\Delta^{\beta:\gamma}$ -BUTENOLIDES AND RELATED COMPOUNDS

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In a previous paper (Russell, Todd & Waring, 1949) the synthesis of a number of furan derivatives for examination as possible hatching agents for cysts of the potato eelworm (*Heterodera rostochiensis* Wollenweber) was reported. None of these materials showed any activity; indeed, out of a large number of substances, both synthetic and natural, belonging to a wide variety of chemical types, only anhydrotetrone acid (I) showed any appreciable activity (Calam, Todd & Waring, 1949). In the course of establishing the structure of anhydrotetrone acid (Marrian, Russell, Todd & Waring, 1947) it was shown that γ -substituted tetrone acids do not yield substituted anhydrotetrone acids, so that the more obvious homologues and analogues of (I) are not readily obtainable. In these circumstances the search for synthetic hatching agents was directed to the preparation of rather different types of compounds, the molecules of which, however, contained conjugated systems analogous to that present in anhydrotetrone acid, e.g. compounds based on α -arylidene- $\Delta^{\beta:\gamma}$ -butenolides. The present memoir describes some of this work which has led to the discovery of several biologically active compounds.

(I)

(II)

(III)

α -(*p*-Methoxybenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = \text{OMe}$, $R' = \text{H}$) was first prepared by Thiele, Tischbein & Lössow (1901) by condensation of anisaldehyde with $\Delta^{\beta:\gamma}$ -angelicalactone in the presence of a base. Condensations of this type were also carried out by von Oettingen (1930), who prepared a number of compounds including (II, $R = \text{OH}$, $R' = \text{OMe}$), (II, $R = R' = \text{OMe}$) and (II, R and R'

being replaced by a methylenedioxy-group). As previously reported, the same general method has been utilized for the preparation of unsaturated lactones containing furan nuclei (Russell *et al.* 1949).

Condensation of *p*-hydroxybenzaldehyde with $\Delta^{\beta:\gamma}$ -angelicalactone in the absence of solvent but in presence of a little piperidine, triethylamine or methylmorpholine, gave α -(*p*-hydroxybenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = \text{OH}$, $R' = \text{H}$). With *m*-hydroxybenzaldehyde the reaction had to be carried out in ethanol as solvent, when α -(*m*-hydroxybenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = \text{H}$, $R' = \text{OH}$) resulted; under other conditions only a resinous product was formed. Protocatechuic aldehyde gave α -(3:4-dihydroxybenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = R' = \text{OH}$). Condensation of *o*-hydroxyaldehydes did not give compounds of type II, but gave 3-acetonylecoumarins (Marrian & Russell, 1946). The preparation of *o*-hydroxyarylidenebutenolides corresponding to (II) was attempted without success by other methods, e.g. preparation of a butenolide in which the *o*-hydroxy group was blocked by an acid-labile group such as methoxymethyl, followed by acid hydrolysis, failed, although

the product obtained by condensation of *p*-methoxymethoxybenzaldehyde with $\Delta^{\beta:\gamma}$ -angelicalactone gave an excellent yield of (II, $R = \text{OH}$, $R' = \text{H}$) on acid hydrolysis.

p-Acetamidobenzaldehyde and $\Delta^{\beta:\gamma}$ -angelicalactone in the presence of base, with or without solvent, gave α -(*p*-acetamidobenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = \text{NHAc}$; $R' = \text{H}$). *p*-Aminobenzaldehyde

in ethanol gave under the same conditions α -(*p*-aminobenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = \text{NH}_2$, $R' = \text{H}$); the constitution of this compound was proved by acetylation with acetic anhydride, which gave (II, $R = \text{NHAc}$, $R' = \text{H}$), identical with the sample prepared as above. With succinic anhydride (II, $R = \text{NH}_2$, $R' = \text{H}$) gave α -(*p*-succinamidobenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = -\text{NHCO}(\text{CH}_2)_2\text{COOH}$, $R' = \text{H}$) and with benzene sulphonyl chloride α -(*p*-benzenesulphonamidobenzylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (II, $R = \text{PhSO}_2\text{NH}$, $R' = \text{H}$) was formed. Two cinnamylidene lactones were also prepared. Despite reports to the contrary (von Oettingen, 1930), cinnamaldehyde condensed with $\Delta^{\beta:\gamma}$ -angelicalactone to give α -cinnamylidene- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (III, $R = \text{H}$). *p*-Hydroxycinnamaldehyde (Pauly & Wäscher, 1923) did not appear to condense, but *p*-acetamidocinnamaldehyde, prepared by condensation of acetaldehyde with *p*-acetamidobenzaldehyde in presence of potassium hydroxide, gave α -(*p*-acetamidocinnamylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide (III, $R = -\text{NHAc}$).

Other compounds prepared for testing were (II, $R = \text{OH}$, $R' = \text{OMe}$) (von Oettingen, 1930), *p*-hydroxybenzylideneacetone (Zincke & Mulhausen, 1903), *o*-hydroxybenzylideneacetone (Harries, 1891), *m*-hydroxybenzylideneacetone, 3-*o*-hydroxybenzylidene-2:4-diketochroman (Sullivan, Huebner, Stahmann, & Link, 1943), β -(*p*-hydroxybenzoyl)-propionic acid (Swain, Todd & Waring, 1944), methyl-*p*-hydroxycinnamate (Fischer & Nouri, 1917), the amide of *p*-hydroxycinnamic acid, 7-hydroxy-4-methylcoumarin (von Pechmann & Cohen, 1884) and 7-hydroxy-3-acetyloumarin (Marrian & Russell, 1946). Attempts were also made to condense 1-acetoxy-4-formylbutadiene-1:4 (glutacondialdehyde-enolacetate), 4-hydroxy-1-naphthaldehyde and indole-3-aldehyde with $\Delta^{\beta:\gamma}$ -angelicalactone, but no identifiable product was obtained in any of these cases.

Most of the above compounds were tested as hatching agents for potato eelworm cysts, using the technique already described (Calam, Raistrick & Todd, 1949). The results are shown in Table 1.

In view of the weak activity shown by certain compounds of type (II) it seemed of interest to prepare and test a number of analogously constituted oxazolone derivatives of general formula (IV). For the preparation of such compounds the well-established oxazolone synthesis from aromatic aldehydes and *N*-acylglycines was employed. *p*-Acetamidobenzaldehyde and hippuric acid gave 2-phenyl-4-(*p*-acetamidobenzylidene)-oxazolone-5 (IV, $R = -\text{NHAc}$, $R' = \text{Ph}$); with *N*-caproylglycine, 2-n-amylyl-4-(*p*-acetamidobenzylidene)-oxazolone-5 (IV, $R = -\text{NHCOCH}_3$, $R' = n\text{-C}_5\text{H}_{11}$) together with α -(*N*-caproylamino)-*p*-acetamidocinnamic acid (V, $R = -\text{NHAc}$, $R' = -\text{COC}_6\text{H}_{11}$) resulted. Condensa-

tion of *p*-acetamidobenzaldehyde with *N*-acetylglycine gave an unidentified red acid $\text{C}_{13}\text{H}_{16}\text{O}_5\text{N}_2$, m.p. 246–7°.

Table 1. Activity of synthetic substances as hatching agents for the potato eelworm

(+, active at concentrations, about 1/5000 to 1/10000; +, active at concentrations, about 1/1000 to 1/5000; $\pm$, active at concentrations, > 1/5000 but variable hatches obtained; –, inactive.)

Substance	Activity
Anhydrotetroneic acid	+

$R = \text{OH}$, $R' = \text{H}$	++
$R = \text{NHAc}$, $R' = \text{H}$	+
$R = \text{NH}_2$, $R' = \text{H}$	–
$R = \text{OH}$, $R' = \text{OMe}$	++
$R = \text{H}$, $R' = \text{OH}$	–
$R = R' = \text{OH}$	$\pm$

$R = \text{OH}$, $R' = R'' = \text{H}$	$\pm$
$R = R' = \text{H}$, $R'' = \text{OH}$	–
$R = R'' = \text{H}$, $R' = \text{OH}$	–
$\pm$
7-Hydroxy-4-methylcoumarin	–
7-Hydroxy-3-acetyloumarin	–
Methyl <i>p</i> -hydroxycinnamate	–
Amide of <i>p</i> -hydroxycinnamic acid	–
* 3-(<i>o</i> -Hydroxybenzylidene)-2:4-diketochroman	–
* α -(<i>p</i> -Acetamidocinnamylidene)- γ -methyl- $\Delta^{\beta:\gamma}$ -butenolide	–
* Very low solubility.	

Condensation of the methoxymethyl ether of *p*-hydroxybenzaldehyde with hippuric acid gave 2-phenyl-4-(*p*-methoxymethoxybenzylidene)-oxazolone-5 (IV, $R = -\text{OCH}_2\text{OMe}$, $R' = \text{Ph}$), which was hydrolysed by a little sulphuric acid in 20% aqueous acetic acid to α -benzamide-*p*-hydroxycinnamic acid (V, $R = \text{OH}$, $R' = \text{COPh}$), apparently identical with Erlenmeyer & Halsey's (1899) preparation. Sublimation of this material *in vacuo* at 200° gave 2-phenyl-4-(*p*-hydroxybenzylidene)-oxazolone-5 (IV, $R = \text{OH}$, $R' = \text{Ph}$); a second route to this compound was the hydrolysis of (IV, $R = \text{OCH}_2\text{OMe}$, $R' = \text{Ph}$) with a small amount of H_2SO_4 in glacial acetic acid. The methoxymethyl ether of salicylaldehyde gave 2-phenyl-4-(*o*-methoxymethoxybenzylidene)-oxazolone-5 with hippuric acid. On hydrolysis with concentrated H_2SO_4 in 20% aqueous acetic acid, the compound gave 3-benzamidocoumarin (VI), identical with a specimen prepared by the method of Erlenmeyer & Stadlin (1904). Condensation of these methoxymethoxybenzaldehydes with *N*-acetylgly-

cine gave no identifiable product, although condensation of anisaldehyde and *N*-acetylglycine gave the expected product (IV, $R = \text{OMe}$, $R' = \text{CH}_3$; cf. Sugasawa & Tsuda, 1935). Compounds (IV, $R = \text{—NHAc}$, $R' = \text{Ph}$) and (IV, $R = \text{—NHAc}$, $R' = n\text{-C}_5\text{H}_{11}$) were tested, but were very insoluble and appeared to be inactive. (IV, $R = \text{OH}$, $R' = \text{Ph}$) was again very insoluble (1/10,000) in water and showed no activity at this great dilution.

The biological test results recorded in Table 1 show that the *p*-hydroxy compounds (II, $R = \text{OH}$, $R' = \text{H}$), (II, $R = \text{OH}$, $R' = \text{OMe}$) and (II, $R = R' = \text{OH}$) show definite if weak activity as hatching agents. It is noteworthy that the corresponding *m*-hydroxy compound (II, $R = \text{H}$, $R' = \text{OH}$) is quite inactive. *p*-Hydroxybenzylideneacetone and β -(*p*-hydroxybenzoyl)-propionic acid also show some activity, while *p*-hydroxyacetophenone, which was also tested, showed a doubtful activity. The *p*-amino compound (II, $R = \text{NH}_2$, $R' = \text{H}$) was inactive, but replacement of the amino group by the feebly acidic acetamido group as in (II, $R = \text{—NHAc}$, $R' = \text{H}$) gave an active substance. Extremely low solubility made the testing of (II, $R = \text{NHCO}(\text{CH}_2)_2\text{COOH}$, $R' = \text{H}$) and (II, $R = \text{NHSO}_2\text{Ph}$, $R' = \text{H}$) impossible. Examination of the structure of the active compounds shows that they contain in common with anhydrotetrone acid a weakly acidic group joined through a conjugated system to a >C=O group, i.e. $\text{HO}-(\text{C}=\text{C})_n-\text{CO}-$ or $\text{RCONH}-(\text{C}=\text{C})_n-\text{CO}-$. Such systems when ionized would exist as resonance hybrids, the negative charge making its appearance at both ends of the system—a state of affairs conducive to hydrogen bonding, which may well play a part in attachment of the hatching agent to some specific protein in the eelworm cysts. Whilst this may be a factor in determining whether a compound can display activity, it is evidently not by any means the only one, as can be seen from the comparatively enormous activity of the natural material and its high specificity. Moreover, the lack of activity in

the derivatives of *p*-hydroxycinnamic acid and in the oxazolones examined is evidence pointing in the same direction, since these compounds appear to satisfy the requirements as far as the conjugated system goes. The inactivity of *o*-hydroxybenzylideneacetone, which contains the system

although at first sight surprising, may be due to the

fact that this compound normally exists in the ψ -base form VII (Decker & von Fellenberg, 1909).

In passing, it may be observed that the degree of activity of the compounds may be expressed in a slightly different way from that given in Table 1; anhydrotetrone acid exhibits full hatching activity in water at a dilution of about 1/2000 and α -(*p*-hydroxybenzylidene)- γ -methyl- $\Delta^{\beta}:\gamma$ -butenolide (II, $R = \text{OH}$, $R' = \text{H}$) at a dilution about 1/7500. These activities are much too low for the compounds to have any practical value (purified concentrates of the natural hatching factor show equal activity at dilutions of 1/10⁷), but in view of the high specificity we consider that the results are significant and can form a basis for further synthetic work.

EXPERIMENTAL

α - (*p* - Hydroxybenzylidene) - γ - methyl - $\Delta^{\beta}:\gamma$ - butenolide. *p*-Hydroxybenzaldehyde (1.2 g., 1 mol.) and $\Delta^{\beta}:\gamma$ -angelicalactone (0.98 g., 1 mol.) were mixed together and warmed until liquid. Piperidine (2–3 drops) was added to the mixture and the whole warmed on a steam bath for 15 min. More piperidine (3 drops) was added and the mixture allowed to stand overnight, then dissolved in ether and the solution washed with dilute HCl, water, and dried over Na_2SO_4 . The ether was removed and the product recrystallized from benzene giving deep yellow needles, m.p. 133–134°. (Found: C, 71.1; H, 5.3. $\text{C}_{12}\text{H}_{10}\text{O}_3$ requires C, 71.4; H, 5.0%.) The substance gives a brick-red colour with NaOH, no colour with FeCl_3 and no Legal reaction.

α - (*m* - Hydroxybenzylidene) - γ - methyl - $\Delta^{\beta}:\gamma$ - butenolide. *m*-Hydroxybenzaldehyde (1.2 g., 1 mol.) and $\Delta^{\beta}:\gamma$ -angelicalactone (0.98 g., 1 mol.) were dissolved in absolute

ethanol (10 ml.) and triethylamine (5–10 drops) added. The mixture was refluxed for 5 hr., the solution cooled and water added until it became opalescent. On allowing to stand crystalline material separated, which on recrystallization from aqueous ethanol gave pale yellow needles, m.p. 134°. (Found: C, 70.9; H, 5.0. $C_{12}H_{10}O_3$ requires C, 71.3; H, 4.9%.)

α - (3,4 - Dihydroxybenzylidene) - γ - methyl - Δ^{β} : γ - butenolide. Protocatechuic aldehyde (2.8 g.) and Δ^{β} : γ - angelicalactone (1.96 g.) were mixed with triethylamine (5 drops), the mixture warmed for 30 min. on a steam bath and allowed to stand overnight. The mixture was dissolved in ether and the ethereal solution washed with water and dilute HCl, and finally washed free from acid with water and then dried. The ether was evaporated and the residual yellow solid recrystallized from benzene. The product had no definite crystalline form even under the microscope, but repeated recrystallization from benzene left the melting point unchanged at 135°; analysis indicated that it was probably a complex of the desired product with starting material. (Found: C, 62.9; H, 5.0. $C_{12}H_{10}O_4 \cdot 2C_7H_6O_3$ requires C, 63.1; H, 4.5%.) This material, after several recrystallizations from water, gave the expected lactone as bright yellow needles, m.p. 186°. (Found: C, 65.9; H, 4.8. $C_{12}H_{10}O_4$ requires C, 66.0; H, 4.6%.)

Attempts to prepare α - (o-hydroxybenzylidene) - γ - methyl - Δ^{β} : γ - butenolide. While condensation of the methoxymethyl ether of *p*-hydroxybenzaldehyde with Δ^{β} : γ - angelicalactone under the above conditions gave an oil, which on hydrolysis with dilute H_2SO_4 in 50% acetic acid gave formaldehyde and α - (p-hydroxybenzylidene) - γ - methyl - Δ^{β} : γ - butenolide, m.p. 134°, the condensation product from the methoxymethyl ether of salicylaldehyde and Δ^{β} : γ - angelicalactone gave, on acid hydrolysis under the same conditions, a resinous product from which no pure compound could be isolated.

α - (p - Acetamidobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide. *p*-Acetamidobenzaldehyde (1.65 g.; 1 mol.) was mixed with Δ^{β} : γ - angelicalactone (0.98 g., 1 mol.) and piperidine (5 drops) added. The mixture was warmed for 1 hr., allowed to stand for 3 hr., and then triturated with ether and the solid recrystallized from methanol. It gave bright yellow needles, m.p. 196–197° (sintered 185°). (Found: C, 69.5; H, 5.8; N, 6.0. $C_{14}H_{13}O_3N$ requires C, 69.3; H, 5.4; N, 5.8%.) The condensation could be carried out just as effectively in absolute ethanol (25 ml. for above quantities) using triethylamine as catalyst.

α - (p - Aminobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide. *p*-Aminobenzaldehyde (1.2 g., 1 mol.) and Δ^{β} : γ - angelicalactone (0.98 g., 1 mol.) were refluxed in ethanol (10 ml.) with triethylamine (6 drops) for 3 hr. The solution was diluted with water until it became opalescent, on cooling orange needles separated, m.p. 138–139°, after recrystallization from methanol. (Found: C, 71.4; H, 5.6; N, 7.1. $C_{12}H_{11}O_3N$ requires C, 71.6; H, 5.5; N, 7.0%.) Treatment with acetic anhydride gave α - (p-acetamidobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide, identical with a sample prepared as above.

α - (p - Succinamidobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide. α - (p - Aminobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide (1.0 g.) was well mixed with succinic anhydride (0.5 g.), the mixture warmed on a steam bath for 0.5 hr. and then allowed to stand overnight at room temperature. The solid was extracted with saturated $NaHCO_3$ solution, the insoluble portion filtered off and the $NaHCO_3$ solution acidified.

The precipitate was collected and washed with water; recrystallized from aqueous ethanol it gave brownish orange needles, m.p. 195–196°. (Found: C, 63.4; H, 4.8; N, 4.7. $C_{16}H_{15}O_5N$ requires C, 63.7; H, 5.0; N, 4.7%.) The $NaHCO_3$ -insoluble portion was found to be unchanged α - (p-aminobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide.

α - (p - Benzenesulphonamidobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide. α - (p - aminobenzylidene) - γ - methyl - Δ^{β} : γ - butenolide (1.0 g.), benzenesulphonyl chloride (0.8 ml.) and pyridine (5 ml.) were warmed on a steam bath for 30 min. The mixture was poured on ice (30 g.), the solid washed with $NaHCO_3$ solution and recrystallized from ethanol giving yellow needles, m.p. 200–201°. (Found: C, 63.1; H, 4.4; N, 4.2. $C_{18}H_{15}O_5NS$ requires C, 63.4; H, 4.4; N, 4.1%.)

α - Cinnamylidene - γ - methyl - Δ^{β} : γ - butenolide. Cinnamaldehyde (1.3 g.) and Δ^{β} : γ - angelicalactone (0.98 g.) were mixed together with triethylamine (3–4 drops) heated for 1 hr. and then allowed to stand overnight. The solid which separated was filtered off and washed with ether; recrystallized from ethanol it gave orange yellow needles, m.p. 139–140°. Found: C, 79.0; H, 5.8. $C_{14}H_{12}O_2$ requires C, 78.8; H, 5.7%.)

p-Acetamidocinnamaldehyde. A solution of acetaldehyde (0.4 ml.) in ethanol (15 ml.) was slowly added to an ice-cold stirred solution of *p*-acetamidobenzaldehyde (1.0 g.), and ethanolic KOH (30 ml., 2%). Stirring was continued at 0° for a further 3 hr., the mixture exactly neutralized, evaporated *in vacuo* and the residue extracted thoroughly with ether. The extract was evaporated and the residual red oil dissolved in water (120 ml., with charcoal), filtered and set aside overnight. The solid which separated was recrystallized several times from water giving deep yellow needles, m.p. 175–176° (decomp.). Found: C, 69.7; H, 5.8; N, 7.7. $C_{11}H_{11}O_3N$ requires C, 69.8; H, 5.8; N, 7.4%.) The substance gave a semicarbazone, m.p. 229° (decomp.). (Found: N, 22.3. $C_{12}H_{14}O_3N_2$ requires N, 22.8%.)

α - (p - Acetamidocinnamylidene) - γ - methyl - Δ^{β} : γ - butenolide. *p*-Acetamidocinnamaldehyde (0.65 g.) and Δ^{β} : γ - angelicalactone (0.31 g.) were mixed together and triethylamine (3–4 drops) added. The mixture was heated on a steam bath for 15 min. and allowed to stand overnight at room temperature. The semi-crystalline mass which separated was triturated with methanol giving orange prisms, m.p. 203–206°. On recrystallization from the same solvent it had m.p. 204–205° (softens 195°). (Found: C, 71.7; H, 5.4; N, 5.2. $C_{16}H_{15}O_3N$ requires C, 71.4; H, 5.6; N, 5.2%.)

m-Hydroxybenzylideneacetone. *m*-Hydroxybenzaldehyde (5 g.), acetone (20 ml.) and KOH (14 ml. of 10%) were left to stand at room temperature for 3 days. The solution was acidified with HCl and the oil extracted with ether. After washing with water and drying, the ether was evaporated and the residue recrystallized from benzene giving yellow prisms, m.p. 95–96°. (Found: C, 74.3; H, 6.3. $C_{10}H_{10}O_2$ requires C, 74.1; H, 6.2%.)

2 - Phenyl - 4 - (p - acetamidobenzylidene) - oxazolone - 5. *p*-Acetamidobenzaldehyde (3.26 g.), hippuric acid (3.58 g.), anhydrous sodium acetate (1.68 g.) and acetic anhydride (5.1 g.) were heated together on a steam bath for 45 min. The mixture was cooled and the orange solid triturated with ethanol, filtered and recrystallized from acetic acid; yellow prisms, m.p. 237–239°. (Found: C, 70.4; H, 4.7; N, 9.2. $C_{18}H_{14}O_5N_2$ requires C, 70.6; H, 4.6; N, 9.2%.)

2 - n - Amyl - 4 - (p - acetamidobenzylidene) - oxazolone - 5. *N*-Caproylglycine (3.0 g.) and *p*-acetamidobenzaldehyde

(3.0 g.) were condensed as described above and the resulting solid on recrystallization from methanol gave deep yellow prisms, m.p. 141–142°. (Found: C, 68.2; H, 6.3; N, 9.4. $C_{17}H_{20}O_5N$ requires C, 68.0; H, 6.6; N, 9.3%.) The mother liquors on dilution with water gave a substance which crystallized in pale yellow needles; after recrystallization from aqueous methanol it had m.p. 225–226° (decomp.). (Found: C, 64.5; H, 7.0; N, 9.1. $C_{17}H_{20}O_5N$ requires C, 64.3; H, 6.9; N, 9.2%.) This compound was α -*n*-caproylamino-*p*-acetamidocinnamic acid.

Condensation of acetyl glycine with p-acetamidobenzaldehyde. Acetyl glycine and *p*-acetamidobenzaldehyde were condensed together in the usual manner. The product formed orange-red prisms, m.p. 246–247° from water. After drying *in vacuo* it gave the following analysis. (Found: C, 55.6; H, 5.9; N, 10.0; Equiv., 302. $C_{15}H_{16}O_5N_2$ requires C, 55.7; H, 5.7; N, 10.0%; Equiv., 280.)

2-Phenyl-4-(*o*-methoxymethoxybenzylidene)-oxazolone-5. Salicylaldehyde methoxymethyl ether (3.32 g.; Hoering & Baum, 1909), and hippuric acid (3.58 g.) were condensed together in the usual manner. The product crystallized from acetic acid in yellow needles, m.p. 139–140°. (Found: C, 69.6; H, 5.0; N, 4.6. $C_{18}H_{16}O_4N$ requires C, 69.8; H, 4.9; N, 4.5%.)

This material (0.8 g.) was heated on a steam bath for 1.5 hr. with aqueous acetic acid (10 ml., 20%) and H_2SO_4 (4 drops); formaldehyde was evolved. On cooling, colourless needles separated, m.p. 175–176°, undepressed in admixture with 3-benzamidocoumarin prepared by the method of Erlenmeyer & Stradlin (1904).

2-Phenyl-4-(*p*-methoxymethoxybenzylidene)-oxazolone-5. This was prepared as above from *p*-methoxymethoxybenzaldehyde (Pauly & Wäscher, 1923) and hippuric acid; bright yellow needles from glacial acetic acid, m.p. 122–123°. (Found: C, 70.1; H, 5.1; N, 4.9. $C_{18}H_{16}O_4N$ requires C, 69.8; H, 4.9; N, 4.5%.)

α -Benzamido-*p*-hydroxycinnamic acid. The above azlactone (0.5 g.) was hydrolysed with aqueous acetic acid (20 ml., 20%) and H_2SO_4 (4 drops) on a steam bath for 1 hr., by which time no more formaldehyde was evolved. On cooling, colourless prisms separated which on recrystallization from acetic acid had m.p. 227–228° (decomp.), turning yellow at about 200° (Erlenmeyer & Halsey (1899) give m.p. 228–229°).

2-Phenyl-4-(*p*-hydroxybenzylidene)-oxazolone-5. The above acid was sublimed in a high vacuum at 200° yielding a yellow solid m.p. 220°, undepressed in admixture with a sample prepared by method (ii) below.

(ii) 2-Phenyl-4-(*p*-methoxymethoxybenzylidene)-oxazolone-5 (1.0 g.) was heated to boiling with acetic acid (2 ml.) containing a trace of conc. H_2SO_4 . On cooling, a yellow solid separated which, when purified on an alumina column followed by vacuum sublimation at 160°/10⁻⁶ mm., had m.p. 220–221°. (Found: C, 72.0; H, 4.2; N, 5.2. $C_{18}H_{16}O_4N$ requires C, 72.5; H, 4.2; N, 5.3%.)

SUMMARY

1. A series of compounds has been prepared based on the α -arylidene- $\Delta^{\beta\gamma}$ -butenolide skeleton, and containing conjugated systems analogous to that present in anhydrotetrone acid. Several of the synthetic products show definite, if rather low, activity as hatching agents for the potato eelworm. The structural similarity between the active substances is discussed.

2. No hatching activity was detected in a number of coumarin and oxazolone derivatives.

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REFERENCES

- Calam, C. T., Raistrick, H. & Todd, A. R. (1949). *Biochem. J.* **45**, 513.
 Calam, C. T., Todd, A. R. & Waring, W. S. (1949). *Biochem. J.* **45**, 520.
 Decker, H. & Fellenberg, Th. von (1909). *Liebigs Ann.* **364**, 17.
 Erlenmeyer, E. jun. & Halsey, J. T. (1899). *Liebigs Ann.* **307**, 140.
 Erlenmeyer, E. jun. & Stadlin, W. (1904). *Liebigs Ann.* **337**, 290.
 Fischer, E. & Nouri, O. (1917). *Ber. deutsch. chem. Ges.* **50**, 619.
 Harries, C. D. (1891). *Ber. deutsch. chem. Ges.* **24**, 3180.
 Hoering, P. & Baum, F. (1909). *Friedl.* **9**, 904.
 Marrian, D. H. & Russell, P. B. (1946). *J. chem. Soc.* p. 753.
 Marrian, D. H., Russell, P. B., Todd, A. R. & Waring, W. S. (1947). *J. chem. Soc.* p. 1365.
 Marrian, D. H., Russell, P. B., Todd, A. R. & Waring, W. S. (1949). *Biochem. J.* **45**, 524.
 Oettingen, W. F. von (1930). *J. Amer. chem. Soc.* **52**, 2024.
 Pauly, H. & Wäscher, K. (1923). *Ber. deutsch. chem. Ges.* **56**, 607.
 Pechmann, H. von & Cohen, J. B. (1884). *Ber. deutsch. chem. Ges.* **17**, 2188.
 Russell, P. B., Todd, A. R. & Waring, W. S. (1949). *Biochem. J.* **45**, 530.
 Sugawara, S. & Tsuda, T. (1935). *J. pharm. Soc. Japan*, **55**, 1981.
 Sullivan, W. R., Huebner, C. F., Stahmann, M. A. & Link, K. P. (1943). *J. Amer. chem. Soc.* **65**, 2288.
 Swain, G., Todd, A. R. & Waring, W. S. (1944). *J. chem. Soc.* 548.
 Thiele, J., Tischbein, R. & Lössow, E. (1901). *Liebigs Ann.* **319**, 185.
 Zincke, Th. & Mulhausen, G. (1903). *Ber. deutsch. chem. Ges.* **36**, 134.