

Biologically Active Compounds. IV.* The Synthesis of α -Arylamino- γ -aryl- $\Delta^{\alpha,\beta}$ - and α -Arylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides.

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(Received May 9, 1970)

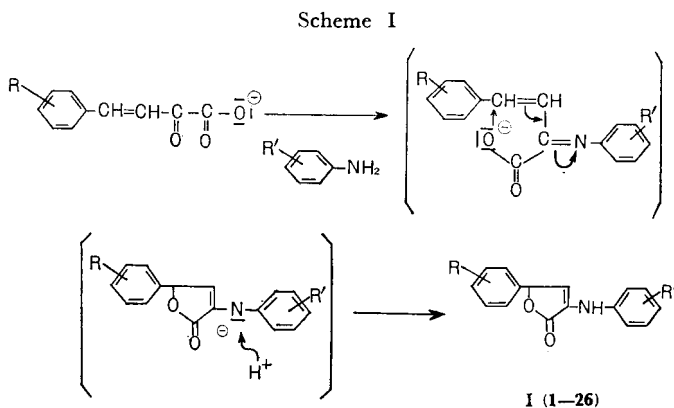
The importance of the presence of butenolide groupings in biologically active substances has been recognized increasingly.¹ In our search for new pesticides we have prepared 26 α -arylamino- γ -aryl- $\Delta^{\alpha,\beta}$ -butenolides (1–26) and 9 α -arylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides (27–35) which seemed to us of interest as test materials for the screening.

α -Arylamino- γ -aryl- $\Delta^{\alpha,\beta}$ -butenolides were prepared by the reaction of sodium or potassium arylidenepyruvate with arylamines in the medium of glacial acetic acid as is reported by Meyer and Vaughan² (Scheme I, see also Experimental Section). α -Arylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides were prepared by the condensation of aromatic aldehydes with β -aroylpropionic acids in the presence of anhydrous sodium acetate. The analogous procedure for this purpose has been reported by several authors³ (Scheme II). The physical properties, yields, and analytical data of these compounds have been summarized in Table I (1–26) and Table II (27–35).

The compounds listed in Table II had a color of yellow to dark red dependent on the degree of conjugation and were scarcely soluble in organic solvents such as acetone, cyclohexanone, and xylene (5%>).

An attempt to synthesize α -methoxy- β -arylamino- $\Delta^{\alpha,\beta}$ -butenolide as one of those structurally related to α -arylamino- γ -aryl- $\Delta^{\alpha,\beta}$ -butenolide was made by the reaction of arylamine with α -methoxy- β -bromo- $\Delta^{\alpha,\beta}$ -butenolide (37).

It was carried out in the manners analogous to the preparation of α -bromo- β -anilino- γ -methoxy- $\Delta^{\alpha,\beta}$ -butenolide⁴ from α , β -dibromo- γ -methoxy-butenolide but failed to afford the desired product. IR data of these unsaturated lactones (1–35) also support their structures. Examples are given in Fig. 1a-c.



Compounds 1–35 were tested for activities of fungicides, bacteriocides, insecticides, and nematocides but none of these compounds so far tested showed appreciable activities. Truitt⁵

* Preceding paper. *Memoirs School Eng., Okayama Univ.*, **3**, (1968) 113.

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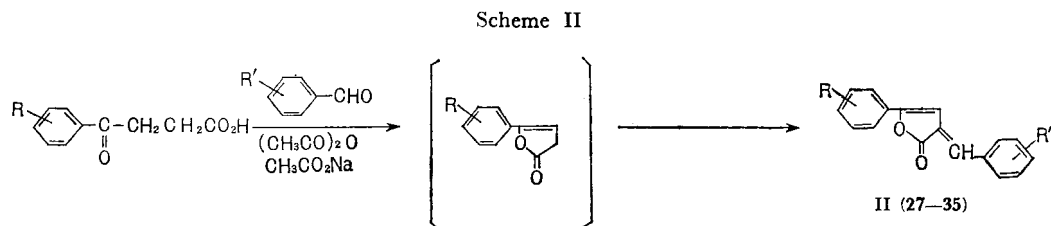
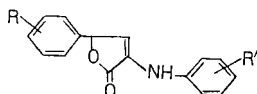


Table I
 α -Arylamino- γ -aryl- $\Delta^{\alpha,\beta}$ -butenolide

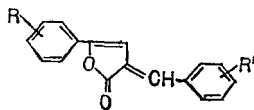


| Compd. | R | R' | yield, % ^a | Mp, °C | Formula | % calcd | | | % found | | |
|----------------|-------|---------------------|--------------------------|-------------------------------|---|---------|------|------|---------|------|------|
| | | | | | | C | H | N | C | H | N |
| 1 | H | 2-Cl | 31.0 | 87.5—88 | C ₁₆ H ₁₂ ClNO ₂ | 67.26 | 4.23 | 4.90 | 67.29 | 4.20 | 4.91 |
| 2 ^b | H | 3-Cl | 45.0 | 117—118 dec (lit. 123—124) | C ₁₆ H ₁₂ ClNO ₂ | 67.26 | 4.23 | 4.90 | 67.00 | 4.24 | 4.81 |
| 3 ^b | H | 4-Cl | 37.2 | 152—153 dec (lit. 158—160) | C ₁₆ H ₁₂ ClNO ₂ | 67.26 | 4.23 | 4.90 | 67.70 | 4.16 | 4.88 |
| 4 | H | 2,4-Cl ₂ | 46.0 | 138 | C ₁₆ H ₁₁ Cl ₂ NO ₂ | 60.02 | 3.46 | 4.38 | 59.90 | 3.57 | 4.68 |
| 5 | H | 3,4-Cl ₂ | 51.3 | 162—163 dec | C ₁₆ H ₁₁ Cl ₂ NO ₂ | 60.02 | 3.46 | 4.38 | 60.35 | 3.58 | 4.22 |
| 6 ^b | H | 3-Br | 54.5 | 127.5—128 (lit. 132—133.5) | C ₁₆ H ₁₂ BrNO ₂ | 58.20 | 3.66 | 4.24 | 58.02 | 3.76 | 3.83 |
| 7 ^b | H | 4-Br | 45.2 | 152—153 dec (lit. 157—158) | C ₁₆ H ₁₂ BrNO ₂ | 58.20 | 3.66 | 4.24 | 57.94 | 3.70 | 3.80 |
| 8 | H | 2-MeO | 31.4 | 124—125 | C ₁₇ H ₁₆ NO ₃ | 72.58 | 5.37 | 4.98 | 72.71 | 5.20 | 4.93 |
| 9 | H | 4-EtO | 25.7 | 100—101 | C ₁₈ H ₁₇ NO ₃ | 73.20 | 5.80 | 4.74 | 73.52 | 5.89 | 4.97 |
| 10 | 4-MeO | 2-Cl | 59.0 | 104—106 | C ₁₇ H ₁₄ ClNO ₃ | 64.66 | 4.47 | 4.44 | 65.01 | 4.63 | 4.37 |
| 11 | 4-MeO | 3-Cl | 55.3 | 118—119 | C ₁₇ H ₁₄ ClNO ₃ | 64.66 | 4.47 | 4.44 | 64.58 | 4.45 | 4.25 |
| 12 | 4-MeO | 4-Cl | 63.6 | 135—136 dec | C ₁₇ H ₁₄ ClNO ₃ | 64.66 | 4.47 | 4.44 | 64.68 | 4.52 | 4.32 |
| 13 | 4-MeO | 2,4-Cl ₂ | 58.7 | 132—133 | C ₁₇ H ₁₃ Cl ₂ NO ₃ | 58.31 | 3.74 | 4.03 | 58.61 | 3.88 | 4.26 |
| 14 | 4-MeO | 3,4-Cl ₂ | 68.6 | 146—146.5 dec | C ₁₇ H ₁₃ Cl ₂ NO ₃ | 58.31 | 3.71 | 4.03 | 58.25 | 3.82 | 3.75 |
| 15 | 4-MeO | 3-Br | 65.8 | 136—137 dec | C ₁₇ H ₁₄ BrNO ₃ | 56.68 | 3.92 | 3.92 | 56.70 | 3.80 | 3.64 |
| 16 | 4-MeO | 4-Br | 60.6 | 148—149 | C ₁₇ H ₁₄ BrNO ₃ | 56.68 | 3.92 | 3.92 | 56.75 | 4.25 | 3.61 |
| 17 | 4-MeO | 3-NO ₂ | 73.7 | 150 dec | C ₁₇ H ₁₄ N ₂ O ₅ | 62.58 | 4.32 | 8.58 | 61.98 | 4.33 | 8.01 |
| 18 | 4-Cl | H | 44.3 | 147.5—148 dec | C ₁₆ H ₁₂ ClNO ₂ | 67.26 | 4.23 | 4.90 | 67.39 | 4.41 | 4.69 |
| 19 | 4-Cl | 2-Cl | 37.8 | 140—141 | C ₁₆ H ₁₁ Cl ₂ NO ₂ | 60.02 | 3.46 | 4.38 | 60.13 | 3.64 | 4.15 |
| 20 | 4-Cl | 2,4-Cl ₂ | 29.8 | 167—168 dec | C ₁₆ H ₁₀ Cl ₃ NO ₂ | 54.19 | 2.84 | 3.95 | 54.33 | 2.98 | 3.54 |
| 21 | 4-Cl | 4-NO ₂ | 33.3 | 190—192 dec | C ₁₆ H ₁₁ ClN ₂ O ₄ | 58.11 | 3.35 | 8.45 | 57.96 | 3.36 | 8.46 |
| 22 | 4-Me | H | 54.7 | 161—162 dec | C ₁₇ H ₁₅ NO ₂ | 76.96 | 5.70 | 5.28 | 77.14 | 5.77 | 4.76 |
| 23 | 4-Me | 2-Cl | 55.0 | 99—100 | C ₁₇ H ₁₄ ClNO ₂ | 68.11 | 4.71 | 4.67 | 67.98 | 4.61 | 4.22 |
| 24 | 4-Me | 2,4-Cl ₂ | 52.2 | 151—152 | C ₁₇ H ₁₃ Cl ₂ NO ₂ | 61.09 | 3.92 | 4.19 | 61.19 | 3.90 | 4.01 |
| 25 | 4-Me | 3,4-Cl ₂ | 43.3 | 152—154 | C ₁₇ H ₁₃ Cl ₂ NO ₂ | 61.09 | 3.92 | 4.19 | 60.97 | 3.88 | 4.07 |
| 26 | 4-Me | 2,5-Cl ₂ | 30.0 | 125—126 | C ₁₇ H ₁₃ Cl ₂ NO ₂ | 61.09 | 3.92 | 4.19 | 60.88 | 4.07 | 4.02 |

(a) Yields calculated after one recrystallization.

(b) While this work was in progress Baumrucker *et al.* have published their work on the syntheses of these butenolides [J. Baumrucker, M. Calzadilla, T. Rodulfo, J. Archila, J. Albrizzio, and A. J. Peraza, *J. Org. Chem.*, **33**, 3991 (1968)].

Table II

 α -Arylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolide

| Compd | R | R' | Yield, % | Mp, °C | b | c | Formula | % calcd | | | % found | | |
|-----------------|-------|---------------------|-------------|-----------------------|----|---|---|---------|------|------|---------|------|------|
| | | | | | | | | C | H | N | C | H | N |
| 27 | 4-Br | 2-Cl | 41.0 | 242 | GY | A | C ₁₇ H ₁₀ BrClO ₂ | 56.46 | 2.79 | | 56.34 | 2.94 | |
| 28 | 4-Br | 4-Cl | 45.0 | 293.5 | GY | A | C ₁₇ H ₁₀ BrClO ₂ | 56.46 | 2.79 | | 56.46 | 2.89 | |
| 29 | 4-Br | 2,4-Cl ₂ | 62.0 | 264 | Y | A | C ₁₇ H ₉ BrCl ₂ O ₂ | 51.55 | 2.27 | | 51.56 | 2.35 | |
| 30 | 4-Br | 4-Me ₂ N | 20.0 | 218 | DR | A | C ₁₉ H ₁₆ BrNO ₂ | 61.09 | 4.36 | 3.79 | 61.18 | 4.37 | 3.40 |
| 31 ^d | 4-Cl | 2-Cl | 58.0 | 239 (lit. 244—246) | Y | A | C ₁₇ H ₁₀ Cl ₂ O ₂ | 64.38 | 3.18 | | 64.34 | 3.29 | |
| 32 | 4-Cl | 4-Cl | 52.0 | 295 | GY | A | C ₁₇ H ₁₀ Cl ₂ O ₂ | 64.38 | 3.18 | | 64.38 | 3.31 | |
| 33 ^d | 4-Cl | 4-MeO | 40.1 | 220 (lit. 228—229) | DY | A | C ₁₈ H ₁₃ ClO ₃ | 69.13 | 4.19 | | 68.84 | 4.27 | |
| 34 | 4-MeO | 2-Cl | 64.5 | 167 | GY | X | C ₁₈ H ₁₃ ClO ₃ | 69.13 | 4.19 | | 68.90 | 4.30 | |
| 35 | 4-MeO | 4-Cl | 70.5 | 240 | Y | A | C ₁₈ H ₁₃ ClO ₃ | 69.13 | 4.19 | | 69.13 | 4.29 | |

a Yields calculated after one recrystallization.

b Color of compounds: Y=yellow, DR=dark red, DY=dark yellow, GY=golden yellow.

c Solvents for recrystallization: A=acetic acid, X=xylene.

d While this work was in progress Truitt has published his work on the syntheses of these butenolides.

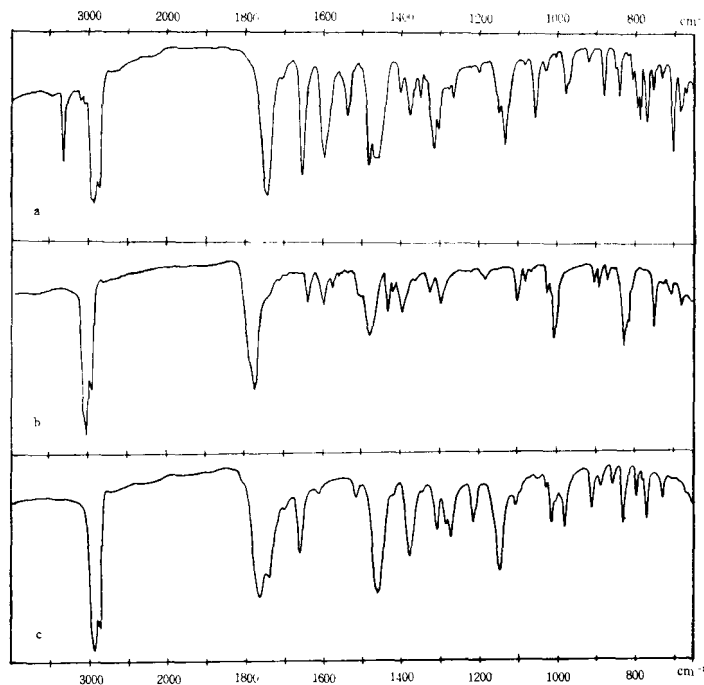
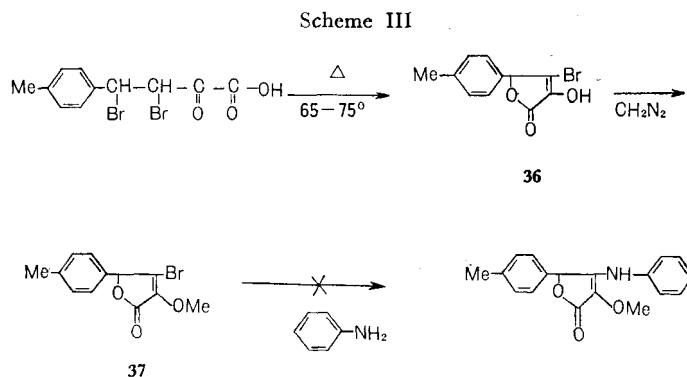


Figure 1. IR spectra of: (a) α -(3,4-Dichlorophenylamino)- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (5), nujol; (b) α -(*p*-Chlorobenzylidene)- γ -(*p*-bromophenyl)- $\Delta^{\beta,\gamma}$ -butenolide (28), nujol; (c) α -Methoxy- β -bromo- γ -(*p*-tolyl)- $\Delta^{\alpha,\beta}$ -butenolide (37), nujol.

also reports that several α -arylidene- γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides were inactive or showed only slight antileukemia activity.



Experimental Section

All melting points are uncorrected. The numbered compounds (1–37) except for 2, 3, 6, 7, 31, and 33 are new. Following materials were prepared in the manners described in the literature: sodium benzylidenepyruvate,⁶ yield 55.0%; potassium *p*-methylbenzylidenepyruvate,⁷ yield 84.0%; sodium *p*-methoxybenzylidenepyruvate,⁸ yield 85.1%; sodium *p*-chlorobenzylidenepyruvate,⁸ yield 89.6%; β -(*p*-bromobenzoyl) propionic acid, mp 137–139° (lit.⁹ mp 148–149°), yield 54.0%; β -(*p*-chlorobenzoyl) propionic acid, mp 126–128° (lit.¹⁰ mp 131°), yield 98.0%; β -(*p*-methoxybenzoyl) propionic acid, mp 144–146° (lit.¹¹ 146–147°), yield 68.2%. The following are the examples of the experiment in which the unsaturated lactones were prepared.

α -(3,4-Dichlorophenylamino)- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (5).... To a mixed solution of 16.2 g (0.18 mole) of pyruvic acid and 70 ml of 10% sodium hydroxide was added with stirring 19.1 g (0.18 mole) of benzaldehyde and then 35 ml of 10% sodium hydroxide at 0–10°. After 2 hr stirring at room temperature there was obtained a yellow paste, which after filtration, washing with cold methanol, and drying *in vacuo* gave 19.6 g (55.0%) of sodium benzylidenepyruvate.⁶ To a stirred solution of 5.0 g (0.025 mole) of sodium benzylidenepyruvate dissolved in a minimum amount of glacial acetic acid was added a solution of 4.0 g (0.025 mole) of 3,4-dichloroaniline in acetic acid at room temperature. Precipitation was complete in 2 hr. The solid, after one

recrystallization from ethanol-acetic acid, afforded 4.1 g (51.3%) of white crystals, mp 162–163° (dec). IR: 3325 (amine ν NH), 1745 (lactone ν C=O), 1655 (ν C=C), 1600 (benzene ring), 1535 cm^{-1} (amine δ NH).

α -(*p*-Chlorobenzylidene)- γ -(*p*-bromophenyl)- $\Delta^{\beta,\gamma}$ -butenolide (28).... A mixture of 20.7 g (0.08 mole) of β -(*p*-bromobenzoyl) propionic acid, 11.2 g (0.08 mole) of *p*-chlorobenzaldehyde, 6.7 g (0.08 mole) of anhydrous sodium acetate, and 25 ml of acetic anhydride was heated on a water bath with stirring. Heating

was continued for 90 min at 70–80° after a complete solution occurred. Water was added to separate the crude product. It was recrystallized from glacial acetic acid to give 13.0 g (45.0%) of 28, mp 293.5°. IR: 1760 (lactone ν C=O), 1630 cm^{-1} (ν C=C).

α -Hydroxy- β -bromo- γ -(*p*-tolyl)- $\Delta^{\alpha,\beta}$ -butenolide (36).... This new compound was prepared according to the procedure reported by Stecher and others¹² for the preparation of α -hydroxy- β -bromo- γ -(3-nitrophenyl)- $\Delta^{\alpha,\beta}$ -butenolide. A suspension of 6.3 g (0.018 mole) of 3,4-dibromo-4-(*p*-tolyl)-2-oxobutanoic acid⁷ in 180 ml of water was stirred vigorously at 65–75° for 10 min. The precipitated solid was filtered and recrystallized from benzene-petroleum ether to yield 3.6 g (75.0%) of the product, mp 165–168°. IR: 1740 (lactone ν C=O), 1700 cm^{-1} (keto-form ν C=O). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{BrO}_3$: C, 49.09; H, 3.33. Found: C, 49.44; H, 3.50.

α -Methoxy- β -bromo- γ -(*p*-tolyl)- $\Delta^{\alpha,\beta}$ -butenolide (37).... An ethereal solution of 1.1 g (0.004 mole) of α -hydroxy- β -bromo- γ -(*p*-tolyl)- $\Delta^{\alpha,\beta}$ -butenolide (36) was treated with an excess of diazomethane in ether for 30 min. The crystal separated after the solution was concentrated and chilled was recrystallized from acetone-petroleum ether to afford 0.7 g (63.6%) of the product, mp 65–67°. IR: 1765, 1740 (lactone ν C=O), 1660 cm^{-1} (ν C=C). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{BrO}_3$: C, 50.91; H, 3.91. Found: C, 50.76; H, 3.90.

The attempted reaction of 37 with aniline.... To a cold solution of 1.0 g (0.0037

mole) of α -methoxy- β -bromo- γ -(*p*-tolyl)- $\Delta^{\alpha,\beta}$ -butenolide in 2 ml of methanol was added 0.9 g (0.0097 mole) of aniline with stirring. The resulting solution was cooled overnight in a refrigerator. The crystalline material precipitated was identical in every respect with the starting material, which was recovered also from the filtrate.

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