# Synthesis and Fungicidal Activity of *N,S*-Substituted α-Thio-β-aminocrotonanilides

JAMES BENJAMIN PIERCE, ROBERT JAMES FANNING, AND ROBERT ALLAN DAVIS

*Uniroyal Ltd. Research Laboratories, Guelph, Ontario and Uniroyal Chemical, Division of Uniroyal Inc., Naugatuck, Connecticut*

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A number of *N,S*-substituted α-thio-β-aminocrotonanilides have been synthesized. Their fungicidal activity on a number of organisms has been studied and in general it has been found that it is inferior to that of the 1,4-oxathiins to which these compounds bear some structural similarities.

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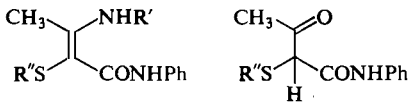
On a synthétisé un certain nombre d'α-thio β-aminocrotonanilides substitués sur l'azote et le soufre. On a étudié leur activité fungicide sur un certain nombre d'organismes et on a trouvé qu'en général ces composés sont moins actifs que les oxathiinnes-1,4 avec lesquels ils sont reliés par leur structure. [Traduit par le journal]

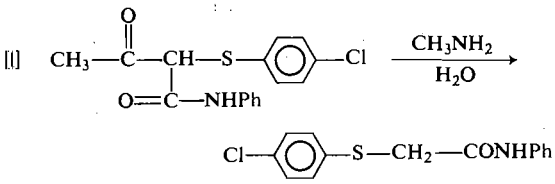
The discovery that certain 1,4-oxathiins and more particularly 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (Vitavax®) possess systemic fungicidal activity (1) has led us to study this and other closely related systems with the expectation that they too might exhibit biological activity (2). Among the compounds that we have synthesized and tested are the *N,S*-substituted α-thio-β-aminocrotonanilides (**I**). These compounds are derivatives of acetoacetanilide α-thioethers (**II**), a group which includes the intermediate compounds often used to produce the systemic 1,4-oxathiins (1).



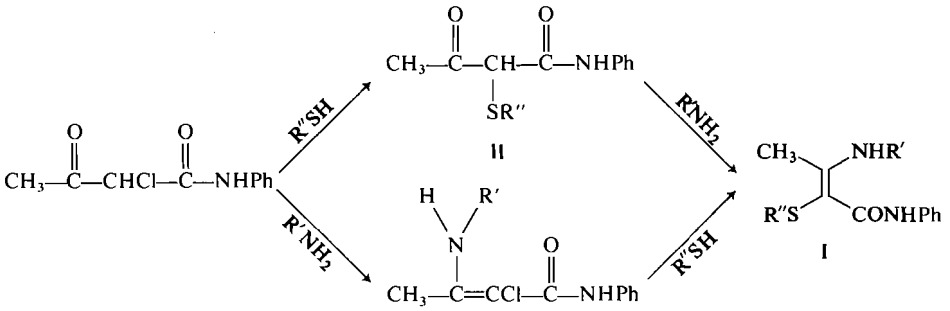

**I** **II**

After this work had begun a report by Mattsson and Bertilsson (3) appeared which described the synthesis and fungicidal properties of some compounds of type **I** and in particular 2-(2-hydroxyethylthio)-3-pentylamino crotonanilide which can be made by treating Vitavax with pentylamine. We wish to record here our syntheses of compounds of type **I** and our findings about their biological activities.

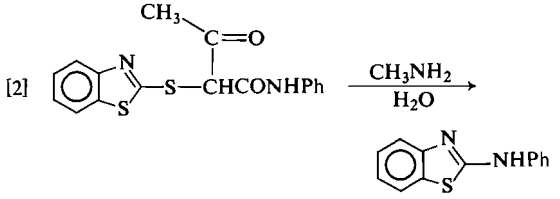
We have synthesized the compounds **I** by one of two routes as shown in Scheme 1. The choice of route depended largely upon the nature of the amine as it was found that in some cases the intermediate **II** underwent undesired side reactions. Thus treatment of α-(4-chlorophenylthio)acetoacetanilide (**II**, R'' = 4-chlorophenyl) with aqueous methylamine gave the deacetylated product α-(4-chlorophenylthio)acetanilide (eq. 1). The desired product **I** (R'' = *p*-chlorophenyl; R' = $CH_3$) could be prepared, however, using **III** (R' = $CH_3$) (4) and *p*-chlorothiophenol. Deacetylations such as that shown in equation (1) have previously been shown to occur when α-cyano (5), α,α-dichloro (6), and other α-sulfur substituted (2) acetoacetanilides are treated with base.




While deacetylation reactions such as the above are not too surprising, in one case of attempting to convert **II** to **I** we did discover a rather unique reaction. Thus treatment of **II** (R'' = 2-benzothiazolyl) with 40% aqueous methylamine led not to the expected **I** (R' = $CH_3$; R'' = 2-benzothiazoyl) but to 2-anilinobenzothiazole in high yield (eq. 2). The product was identified by comparison of its melting point and i.r. spectrum with those of authentic ma-

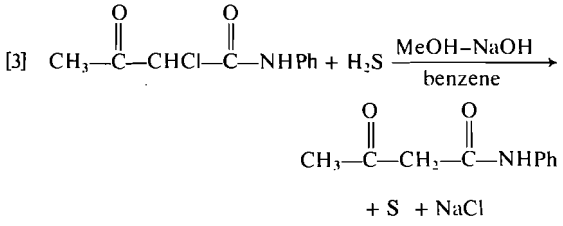


SCHEME 1



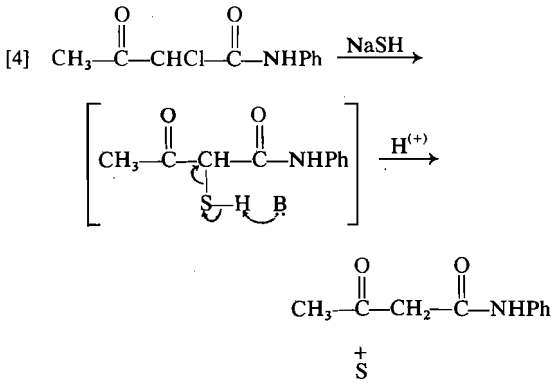
terial made by the method of Hofmann (7). At present we have no evidence concerning the mechanism of this reaction but it is hoped to study it further in the near future.

In this connection it should be mentioned that whereas the reaction of mercaptans with α-chloroacetoacetanilide in general gives excellent yields of the compounds **II**, reaction with hydrogen sulfide results predominantly in production of acetoacetanilide and sulfur (eq. 3).



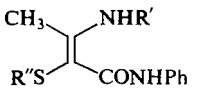
Thus repetition of the experiment of Mattsson and Bertilsson (3) in which 2-mercaptoacetoacetanilide (**II**, R″ = H) is claimed, in our hands, gave only a 78% yield of acetoacetanilide. The product, m.p. 78–84 °C, gave an i.r. spectrum identical in every way to that of authentic material. The above reaction may well proceed via the expected 2-mercaptoacetoacetanilide which then eliminates sulfur by further reaction with sodium hydrogen sulfide or sodium hydroxide (eq. 4).

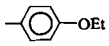
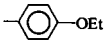
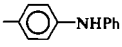
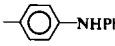
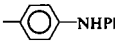
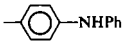
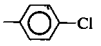
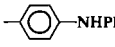
In Tables 1 and 2 we have listed the compounds **I** that have been prepared for this study. Table 1 gives those prepared via intermediates



**II** (Scheme 1) and Table 2 those prepared via intermediates **III** (Scheme 1). The melting points, analyses, and yields obtained in going from **II** or **III** to **I** are also recorded.

We have found the fungicidal activity of these compounds to be much inferior to that of oxathiins such as Vitavax. The activity of the compounds α-(2-hydroxyethylthio)-β-aminocrotonanilide (**I**, R′ = H; R″ = HO—$CH_2$—$CH_2$—), α-(2-hydroxyethylthio)-β-methylaminocrotonanilide (**I**, R′ = Me; R″ = HO—$CH_2$—$CH_2$—), and α-(2-hydroxyethylthio)-β-anilinocrotonanilide (**I**, R′ = Ph; R″ = HO—$CH_2$—$CH_2$—) were of particular interest to us because of their close relationship to Vitavax and the intermediate used to produce Vitavax (1). However, in *in vitro* tests these compounds did not control *Alternaria solani*, *Fusarium oxysporum*, *Pythium* Spp., or *Rhizoctonia solani* at 500 p.p.m. This is in contrast to Vitavax which gives excellent control of most basidiomycetes such as *Rhizoctonia solani* and is also active on the other fungal species (8). In addition *in vivo* greenhouse tests on tomato early blight and powdery mildew on beans at 500 p.p.m. also showed these com-

TABLE 1. Compounds  via intermediate **II** Scheme 1

| R′ | R″ | Melting point (°C) | Yield (%) | Analysis: Calculated C | Calculated H | Calculated N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| Ph | $HO—CH_2—CH_2—$ | 92–95 | 75 | 65.84 | 6.14 | 8.53 | 65.67 | 6.43 | 8.61 |
| Ph | Ph | 97–98.5 | 90 | 73.30 | 5.59 | 7.77 | 73.08 | 5.68 | 7.63 |
| Ph | $Ph—CH_2—$ | 68–70 | 64 | 73.78 | 5.92 | 7.48 | 73.41 | 6.03 | 7.56 |
| Ph |  | 131–133 | 70 | 67.00 | 4.82 | 7.10 | 66.73 | 4.82 | 7.17 |
| Ph |  | 152–155 | 61 | 66.18 | 4.59 | 10.07 | 66.37 | 4.66 | 9.86 |
| Ph | $Et_2N—\overset{\overset{S}{\|}}{C}—$ | 108–109.5 | 77 | 63.14 | 6.31 | 10.52 | 62.81 | 6.38 | 10.77 |
|  | $HO—CH_2—CH_2—$ | 113.5–115 | 90 | 64.50 | 6.50 | 7.52 | 64.83 | 6.72 | 7.35 |
|  | $Et_2N—\overset{\overset{S}{\|}}{C}—$ | 119–120 | 78 | 62.29 | 6.59 | 9.48 | 62.02 | 6.72 | 8.86 |
|  | $HO—CH_2—CH_2—$ | 118–120 | 57 | 68.72 | 6.01 | 10.02 | 67.69 | 6.93 | 9.87 |
|  | Ph | 119–121 | 99 | 74.48 | 5.58 | 9.31 | 74.63 | 5.67 | 9.29 |
|  | $Ph—CH_2—$ | 96–97.5 | 82 | 74.82 | 5.85 | 9.03 | 75.16 | 5.69 | 8.05 |
|  |  | 148.5–149.5 | 82 | 69.19 | 4.98 | 8.65 | 69.31 | 4.95 | 8.58 |
|  |  | 166–168.5 | 81 | 68.49 | 4.76 | 11.02 | 68.40 | 4.38 | 10.98 |
|  | $Et_2N—\overset{\overset{S}{\|}}{C}—$ | 142.5–144 | 82 | 66.10 | 6.16 | 11.42 | 66.41 | 6.21 | 11.57 |

pounds to have little activity compared to the activity of Vitavax under these conditions.

Some of the compounds listed in Tables 1 and 2 did show some *in vitro* fungicidal activity. These activities are recorded in Table 3. The activities recorded for these crotonanilides all fell rapidly as the dosage of the chemical was lowered. Thus on the basis of our tests we have concluded that the fungicidal activity of these compounds is much inferior to that of oxathiins.

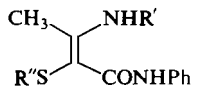
## Experimental

The experiments described below were chosen as typical of the preparation of *N,S*-substituted α-thio-β-aminocrotonanilides (**I**) via intermediates **II** and **III**. Spectral data are given for the compounds described in these typical preparations; spectral data for the other compounds shown in Tables 1 and 2 were in full accord with their proposed structures.

*Preparation via Intermediate II*

*α-(2-Hydroxyethylthio)-β-(4-ethoxyanilino)crotonanilide*

A mixture consisting of 2-(2-hydroxyethylthio)aceto-

TABLE 2. Compounds  via intermediate **III** Scheme 1

| R′ | R″ | Melting point (°C) | Yield (%) | Analysis: Calculated C | Calculated H | Calculated N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| H | $HO—CH_2—CH_2—$ | 98–100 | 86 | 57.13 | 6.39 | 11.11 | 57.00 | 6.02 | 10.73 |
| H | Ph | 141–143 | 76 | 67.59 | 5.67 | 9.85 | 67.57 | 5.62 | 10.03 |
| H | $EtO_2C—CH_2—CH_2—$ | 89–91 | 94 | 57.13 | 6.17 | 9.52 | 57.42 | 6.29 | 9.29 |
| H |  | 117–118.5 | 53 | 60.27 | 4.74 | 8.79 | 60.49 | 4.76 | 8.69 |
| H |  | 180–183 | 83 | 59.82 | 4.43 | 12.31 | 59.46 | 4.70 | 12.08 |
| H | $Et_2N—\overset{\overset{S}{\|\|}}{C}—$ | 124–126 | 87 | 55.72 | 6.55 | 13.00 | 56.85 | 6.52 | 13.35 |
| H | $Ph—\overset{\overset{Me}{\|}}{N}—\overset{\overset{S}{\|\|}}{C}—$ | 177–181 | 70 | 60.49 | 5.36 | 11.76 | 60.72 | 5.52 | 11.38 |
| Me | $HO—CH_2—CH_2—$ | 74–77 | 75 | 58.63 | 6.81 | 10.52 | 59.24 | 6.96 | 10.43 |
| Me | Ph | 146–147.5 | 77 | 68.44 | 6.08 | 9.39 | 68.26 | 6.12 | 9.18 |
| Me | $EtO_2C—CH_2—CH_2—$ | 72–75 | 65 | 58.43 | 6.54 | 9.09 | 58.51 | 6.58 | 9.10 |
| Me |  | 123.5–125.5 | 71 | 61.34 | 5.15 | 8.42 | 65.46 | 5.35 | 8.79 |
| Me |  | 150–153 | 78 | 60.84 | 4.82 | 11.83 | 60.91 | 4.85 | 11.61 |
| Me | $Et_2—N—\overset{\overset{S}{\|\|}}{C}—$ | 141–143 | 80 | 56.96 | 6.87 | 12.46 | 56.83 | 7.03 | 12.45 |
| Me | $Ph—\overset{\overset{Me}{\|}}{N}—\overset{\overset{S}{\|\|}}{C}—$ | 138–140 | 73 | 61.44 | 5.70 | 11.32 | 61.23 | 5.91 | 11.42 |

acetanilide (12.7 g, 0.05 mol) (2), 4-ethoxyaniline (6.9 g, 0.05 mol), 4-toluenesulfonic acid (0.1 g), and benzene (100 ml) was brought to reflux and the water formed was removed azeotropically. After 2.5 h the reaction mixture was filtered to remove a small amount of 4-ethoxyanilinium-4-toluenesulfonate salt and the benzene was then removed from the filtrate. The crude oil crystallized upon standing and was recrystallized from isopropanol to give 16.8 g or 90% of product, m.p. 113.5–115 °C; n.m.r. (DMSO-$d_6$): 1.30 (3H, t, $J$ = 6 Hz), 2.33 (3H, S), 2.65 (2H, t, $J$ = 5 Hz), 3.30–3.80 (2H, m), 3.95 (2H, q, $J$ = 6 Hz), 5.11 (1H, t, $J$ = 5 Hz exchange), 6.70–7.80 (5H, m), 9.78 (1H, S, exchange); i.r. (KBr): 3350, 3260, 1600, 1560, 1500, 1430, 1210 $cm^{-1}$.

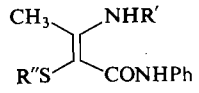
*α-(2-Benzothiazolyl)acetoacetanilide*

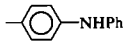
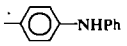
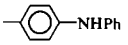
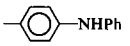
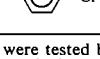
A mixture of 2-mercaptobenzothiazole (34.4 g, 0.21 mol), 2-chloroacetoacetanilide (43.2 g, 0.21 mol), benzene (150 ml), sodium bicarbonate (17.6 g, 0.21 mol), and water (100 ml) was brought to reflux for 4 h. The phases of the hot mixture were separated and the product crystallized from the benzene phase upon cooling. Thus were obtained 51.9 g or 74% of the title compound, m.p. 123–124.5 °C.

*α-(2-Benzothiazolyl)-β-(4-phenylaminoanilino)-crotonanilide*

A mixture of α-(2-benzothiazolyl)acetoacetanilide (prepared as above) (17.1 g, 0.05 mol), 4-(phenylamino)-aniline (9.2 g, 0.05 mol), 4-toluenesulfonic acid (0.1 g), and benzene (125 ml) was refluxed and the water was removed azeotropically. After 2.5 h the benzene was removed and the dark residue was crystallized from ethanol giving 20.5 g or 81% of product, m.p. 166–168.5 °C; n.m.r. ($CDCl_3$): 2.32 (3H, S), 5.88 (1H, S, exchange), 6.85–7.90 (18H, m), 8.70 (1H, S, exchange), 12.77 (1H,

TABLE 3. Fungicidal activities* of some of the crotonanilides **I**



| Compound **I** | | Fungicidal activity (% inhibition of growth) at 500 p.p.m. on | | | |
|---|---|---|---|---|---|
| R′ | R″ | *Alternaria* | *Fusarium* | *Pythium* | *Rhizoctonia* |
|  | $HO-CH_2-CH_2-$ | 0 | 0 | 40 | 0 |
| Ph | $(Et)_2N-\overset{\overset{S}{\|}}{C}-$ | 25 | 35 | 0 | 65 |
|  | Ph | 5 | 0 | 15 | 0 |
|  | $(Et)_2N-\overset{\overset{S}{\|}}{C}-$ | 10 | 5 | 10 | 25 |
|  | $Ph-CH_2-$ | 0 | 55 | 0 | 90 |
| H |  | 100 | 35 | 0 | 40 |
| Me | $EtO_2C-CH_2-CH_2-$ | 35 | 20 | 35 | 0 |
| H | $Et_2N-\overset{\overset{S}{\|}}{C}-$ | 25 | 55 | 0 | 45 |
| Me |  | 50 | 0 | 25 | 25 |

*The compounds were tested by incorporating an acetone solution of the chemical on filter paper antibiotic testing discs, placing a fungus plug in contact with the disc on a surface of an agar plate and measuring the inhibition of radial growth from the treated disc.

S, exchange); i.r. (KBr): 1555, 1600, 1435, 1425, 1300, 1210 $cm^{-1}$).

*Preparation via Intermediate III*

*α-(2-Hydroxyethylthio)-β-(methylamino)crotonanilide*

A solution of 2-mercaptoethanol (3.7 g, 0.045 mol), triethylamine (6.3 ml, 0.045 mol), and benzene (50 ml) was added to a solution of α-chloro-β-(methylamino)-crotonanilide (10 g, 0.045 mol) (4) in benzene (100 ml). After refluxing for 15 min a precipitate of triethylamine hydrochloride began to separate. The mixture was refluxed for 2.5 h, cooled, and extracted with water. The benzene was removed from the organic layer and the residue crystallized from isopropanol giving 9.0 g or 75% of the product, m.p. 74–77 °C; n.m.r. ($CDCl_3$): 2.30 (3H, S), 2.49 (2H, t, $J$ = 6 Hz), 2.83 (3H, d, $J$ = 6 Hz), 3.58 (2H, t, $J$ = 6 Hz), 3.40 (1H, bs), 6.9–7.6 (5H, m), 9.30 (1H, S, exchange), 10.55 (1H, q, $J$ = 6 Hz, exchange); i.r. ($CCl_4$): 3325, 1615, 1580, 1510, 1435, 1310, 1200 $cm^{-1}$.

*α-(N,N-Diethyldithiocarbamoyl)-β-aminocrotonanilide*

A mixture containing α-chloro-β-aminocrotonanilide (15 g, 0.071 mol), (4) the sodium salt of *N,N*-diethyldithiocarbamate trihydrate (16.1 g, 0.071 mol), and dimethylsulfoxide (50 ml) was warmed on a steam bath for 0.5 h and then poured into 500 ml of water. The precipitate was separated by filtration and recrystallized from ethanol to give 20.1 g or 87% of product, m.p. 124–126 °C; n.m.r. ($CDCl_3$): 1.28 (6H, m), 2.03 (3H, S), 3.85 (4H, m), 7.30 (5H, m), 8.08 (1H, S); i.r. ($CHCl_3$): 3490, 3375, 2975, 1625, 1580, 1500, 1430, 1310, 1270 $cm^{-1}$.

*Reaction of α-(2-Benzothiazolyl)acetoacetanilide with Methylamine*

A solution of α-(2-benzothiazolyl)acetoacetanilide (2.0 g, 0.0059 mol) in 30 ml of 40% aqueous methylamine was allowed to sit at room temperature for 4 days. Long white needles of 2-anilinobenzothiazole were gradually formed. These were filtered off, washed with a little fresh methylamine solution and air dried. Thus were obtained 1.2 g or 90.8% of 2-anilinobenzothiazole, m.p. 157–159 °C, identical in every way with an authentic sample made by the method of Hofmann (7).

*Reaction of α-(4-Chlorophenylthio)acetoacetanilide with Methylamine*

A sample of α-(4-chlorophenylthio)acetoacetanilide (10 g, 0.031 mol) was dissolved in 150 ml of 40% aqueous methylamine. The solution was allowed to stand at room temperature for 2.5 h and then filtered to remove the

product. A second crop was also obtained from the filtrate. The product was recrystallized from ethanol yielding 4.7 g or 51.5% of α-(4-chlorophenylthio)acetanilide, m.p. 108–110 °C. The identity of the product was proved by comparison with an authentic sample made by the reaction of α-chloroacetanilide with 4-chlorothiophenol.

*Attempted Preparation of α-Mercaptoacetoacetanilide*

The method of German Offen. 2,133,450 (3) was followed. Thus a solution of sodium hydroxide (8 g) in water (100 ml) was saturated with hydrogen sulfide and to this solution was added dropwise a solution of α-chloroacetoacetanilide (42.3 g) in methanol (150 ml) and benzene (150 ml). When the addition was complete (about 1 h) the mixture was stirred an additional 15 min and then filtered to remove 4.0 g or 62.5% of sulfur, m.p. 120 °C, burning with a blue flame smelling strongly of sulfur dioxide. The filtrate consisted of two phases. These were separated and the lower phase was extracted with 2 × 100 ml of ether and these ether phases combined with the upper phase. These organic phases were dried with anhydrous sodium sulfate and the solvents were then removed. The residue was recrystallized from toluene to give 28.5 g or 77.5% of acetoacetanilide, m.p. 78–84 °C. The identity of the product was confirmed as being acetoacetanilide rather than 2-mercaptoacetoacetanilide by comparison of its i.r. spectrum with that of authentic material.

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