# Technical Papers

## s-Triazine Derivatives—A New Class of Fungicides

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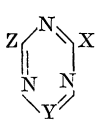
In the course of a study of the fungitoxicity of substituted *s*-triazines, it was found that compounds selected from the class of 2,4-dichloro-*s*-triazines, having arylamino or aryloxy groups in the 6-position, possess high fungitoxic activity. Several members of this class were prepared and tested. The results of preliminary evaluation are summarized in this paper.

The triazine derivatives were prepared by reaction of cyanuric chloride with arylamines or with phenols. By control of reaction conditions, it is possible to replace the halogens of cyanuric chloride in a stepwise manner (*1*). In general the products were obtained in high yield as stable solids suitable for formulation as micronized wettable powders.

The slide germination method (*2*) was used for determination of the $LD_{50}$ values. The compounds were formulated as aqueous solutions or suspensions, using 5-percent acetone and 0.01-percent Triton X-155. The test organisms were *Alternaria oleracea* Mil. and *Sclerotinia fructicola* (Wint.).

Table 1. Fungistatic values of aryloxy-*s*-triazines.

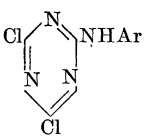


| x | y | z | $LD_{50}$ values (ppm) | |
|---|---|---|---|---|
| | | | *A. oleracea* Mil. | *S. fructicola* (Wint.) |
| Cl | Cl | Phenoxy | 7.0 | 8.5 |
| Cl | Cl | β-Naphthoxy | 0.3 | 0.7 |
| Cl | Cl | *o*-Chlorophenoxy | 3.0 | 1.0 |
| Cl | Cl | *p*-Chlorophenoxy | 0.05 | 0.5 |
| Cl | Cl | 2,4-Dichlorophenoxy | 5.0 | 2.0 |
| Cl | Z | 2,4-Dichlorophenoxy | 250.0 | 140.0 |
| Z | Z | 2,4-Dichlorophenoxy | > 1000 | > 1000 |
| Cl | Cl | 2,4,5-Trichlorophenoxy | 0.7 | 1.5 |
| Cl | Cl | 2,3,4,6-Tetrachlorophenoxy | 3.0 | 6.0 |
| Cl | Cl | Pentachlorophenoxy | > 1000 | > 1000 |

The data for a group of aryloxy-substituted *s*-triazines are presented in Table 1. In the case of the 2,4-dichlorophenoxy series, introduction of more than one aryloxy group caused marked reduction of fungistatic activity. In general, it appears that replacement of more than one chlorine of cyanuric chloride yields products of inferior fungitoxic activity. The pentachlorophenoxy compound was notable among the monoaryloxy derivatives for lack of activity and was unusually phytotoxic to tomato foliage. Most of the aryloxy derivatives showed some slight phytotoxicity in greenhouse tests on bean, corn, and tomato plants.

The 2,4-dichloro-6-arylamino-*s*-triazines were found to be of greater interest as potential foliage fungicides. The slide germination data for a series of arylamino derivatives are presented in Table 2. These tests

Table 2. Fungistatic values of 2,4-dichloro-6-arylamino-*s*-triazines.



| Aryl | $LD_{50}$ values (ppm) | |
|---|---|---|
| | *A. oleracea* Mil. | *S. fructicola* (Wint.) |
| Phenyl | 0.02 | 4.0 |
| *p*-Tolyl | .05 | 9.0 |
| *p*-Nitrophenyl | .04 | > 1000 |
| *p*-Azobenzene | > 1000 | > 1000 |
| α-Napththyl | 0.2 | 2.0 |
| β-Napththyl | .2 | 60 |
| *o*-Diphenyl | 1.0 | > 1000 |
| *p*-Diphenyl | 200 | > 1000 |
| *o*-Chlorophenyl | 0.04 | 1.5 |
| *m*-Chlorophenyl | .1 | 5.0 |
| *p*-Chlorophenyl | .02 | 8.0 |
| 2,5-Dichlorophenyl | .2 | 2.0 |
| *o*-Bromophenyl | .01 | 1.5 |
| *m*-Bromophenyl | .01 | 5.0 |
| *p*-Bromophenyl | .02 | 6.0 |

showed that the chloroanilino and bromoanilino derivatives were highly effective against both test organisms. In general, the arylamino-*s*-triazines showed little or no phytotoxicity to the foliage of bean, corn, and tomato plants when applied as a 1-percent spray.

In greenhouse tomato-foliage disease tests (*3*) employing the early blight fungus, *Alternaria solani* (Ell. and Mart.) Jones and Grout, and the late blight fungus, *Phytophthora infestans* (Mont.) deBary, the most effective compound was 2,4-dichloro-6-(*o*-chloroanilino)-*s*-triazine. This compound has been submitted to field evaluation under the code identification "B-622," and it has shown promise of effective con-

trol of apple scab, celery early blight, muskmelon leaf spot, onion-foliage diseases, leaf diseases of ornamentals, potato late blight, tomato anthracnose, dollar spot, and diseases of turf caused by Helminthosporium. The results of advanced evaluation studies will be reported elsewhere.

### References and Notes


1. H. E. Fierz-David and M. Mater, *J. Soc. Dyers Colourists* **53**, 424 (1937).
2. American Phytopathological Society, Committee on the Standardization of Fungicidal Tests, *Phytopathology* **37**, 354 (1947).
3. S. E. A. McCallan and R. H. Wellman, *Contribs. Boyce Thompson Inst.* **13**, 93 (1943).


20 August 1954.

## Antithyroid Activity of Some S-Substituted Thiouracils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Since S-alkyl derivatives of thiouracil do not possess antithyroid properties (*1*), it is generally assumed that the activity of thiouracil and its derivatives depends upon the presence of unsubstituted sulfur in the thiourylene group. Available evidence supports this assumption insofar as the ultimate antithyroid mechanism is concerned, but the possibility remains that other S-substituted derivatives might be active either *per se* or through the removal *in vivo* of the S-substituent. Thus, Lawson and Searle (*2*) have recently described the antithyroid activity of thioimidazole derivatives of the —S—CO—OR type (R=alkyl or aryl) and have suggested that these compounds are cleaved *in vivo* so as to produce the free thioimidazole. Chemically however, this type of thio derivative is readily hydrolyzed to produce a free sulfhydryl group; hence, in animal work, some cleavage might be demonstrated regardless of any possible enzymic attack. On the other hand, thiouracil derivatives of the thioether type are generally quite stable toward hydrolysis at physiological *p*H, and if they are converted to free thiouracil *in vivo*, enzymic cleavage may be assumed. Therefore, it was decided to test several thiouracil derivatives containing a thioether linkage and, if antithyroid activity were found, to determine whether these derivatives were active with or without removal of the S-substituent (*3*).

Table 1. Data on new S-substituted thiouracils.

| Thiouracil derivative | Capillary mp (°C) | Kjeldahl nitrogen (%) | |
|---|---|---|---|
| | | Calc. | Found |
| 2-Allyl | 145–149 | 16.68 | 17.00 |
| 2-Malonyl | 158–159* | 12.17 | 12.05 |
| 2-Glyceryl | 230*† | 13.39 | 13.49 |
| 6-Methyl-2-carboxyethyl | 200*† | 14.00 | 13.77 |

* With decomposition. † Preheated bath.

Of the seven derivatives prepared and tested, four have not been previously reported and are shown in Table 1. The allyl and malonyl derivatives were prepared by reacting sodium-2-thiouracil in a 1:1 alcohol-water solution and were subsequently acidified with acetic acid. The glyceryl derivative was prepared by the same method using epichlorohydrin. This derivative is readily soluble in cold water even after acidification but is precipitated by addition of acetone. It has a markedly bitter taste. 6-Methyl-2-carboxyethyl-thiouracil was prepared by condensing b-isothioureidopropionic acid with acetoacetic ester (*4*). All the compounds used here proved stable toward hydrolysis at physiological *p*H except the allyl derivative, which produced small amounts of allyl sulfide when heated in water.

For the animal testing, the compounds were ground with Purina Lab Chow, and the mixture was given *ad libitum* to Sprague Dawley male rats 2 to 3 mo

Table 2. Effect of S-substituted thiouracils on rat thyroid.

| S-substituent | No. of animals | Dosage (μM/day) | Days treated | Thyroid changes in percentage | |
|---|---|---|---|---|---|
| | | | | (wt., mg %) | ($I_2$, μg %) |
| —H (thiouracil) | 20 | 50 | 25 | +45† | −71† |
| —$CH_3$ | 10 | 45 | 25 | 0 | − 7 |
| —$CH_2CH_3$ | 15 | 50 | 25 | − 6 | − 9 |
| —$CH_2CH{=}CH_2$ | 15 | 40 | 20 | + 8 | −30† |
| | 10 | 100 | 10 | +12 | −50† |
| —$CH_2COOH$ | 15 | 51 | 25 | +28* | −68† |
| —$CH_2CH_2COOH$ | 15 | 52 | 25 | +26* | −70† |
| —$CH(COOH)2$ | 15 | 47 | 25 | − 9 | −18 |
| | 15 | 96 | 25 | +10 | −24* |
| —$CH_2CHOHCH_2OH$ | 15 | 50 | 25 | +12 | +10 |
| | 10 | 102 | 10 | − 4 | + 7 |

* $P < 0.05$; † $P < 0.01$. Control thyroid values, 20 animals: wt. = 7.6 mg %, $I_2$ = 64 μg %.