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Okabe, Takayuki
Department of Water and Forests, Faculty of Agriculture, Kyushu University

Taniguchi, Eiji
Department of Water and Forests, Faculty of Agriculture, Kyushu University

Maekawa, Kazuyuki
Department of Water and Forests, Faculty of Agriculture, Kyushu University

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Syntheses of Triazolopyrimidine Derivatives from Amitrole and their Biological Activity

Takayuki Okabe, Eiji Taniguchi and
Kazuyuki Maekawa

3-Amino-1, 2, 4-triazole (Amitrole, Amizol or ATA) is known to be very effective as a herbicide to a great variety of weeds.[13] Amitrole penetrates easily by means of the aqueous phase in the phlloem and xylem cells and, after being released in the plant by the sap streams, rapidly causes chlorosis and decay due to inhibition or blocking of the main enzymes and disturbing the chlorophyll formation by interference with the development of the chloroplasts.[10][11][13]

As possible modes of action of amitrole, it has been presented that amitrole may inhibit incorporation of glycine into porphyrine, or deprive Mg of chlorophyll by chelating, or block the metabolism of histidine. Some purine and pyrimidine derivatives, as well as riboflavin and flavin nucleotide displayed in higher plants antagonism against amitrole.[1][6][18] We are interested in activities of pseudopurines derived from amitrole by condensing it with ketone.[14]

As to 5-amino-1, 2, 4-triazole the condensing ring-closure was often brought out. Namely, Bülow *et al.*[5] condensed acetylacetone and 5-amino-1, 2, 4-triazole in the presence of piperidine. They also prepared triazolo-pyrimidine by condensing acetoacetate with 5-amino-triazole. Birr *et al.*[4] reported that triazolo [4, 3-*a*] pyrimidine was obtained from β-chloro-crotonate and 5-amino-1, 2, 4-triazole. Later on Makisumi *et al.*[12] and Chambers *et al.*[7] synthesized triazolo [1, 5-*a*] pyrimidine from 5-amino-triazole by the similar procedure as Bülow.[5]

However, as it should be appreciated that with C-mono-substituted triazoles no substitution isomers exist, owing to the mobility of the hydrogen atom attached to the nitrogen atom,[15] it is likely imaginable that the compound obtained in this experiment might be identical with that described by Bülow[5] and Makisumi.[12]

In the fact, our compound had been identical with triazolo [1, 5-*a*] pyrimidine prepared by Makisumi *et al.* in every aspect such as IR spectrum and mixed melting point.

Recently Reimliger *et al.*[16] reported the condensation of amitrole with esters of propiolic acid or phenylpropiolic acid. The present paper deals with the synthesis of some 5-methyl-7-substituted-*s*-triazolo [1, 5-*a*] pyrimidine of which only a few compounds are newly described and with their biological activities. The synthetic route and the properties of products are illustrated in Fig. 1 and Table 1.

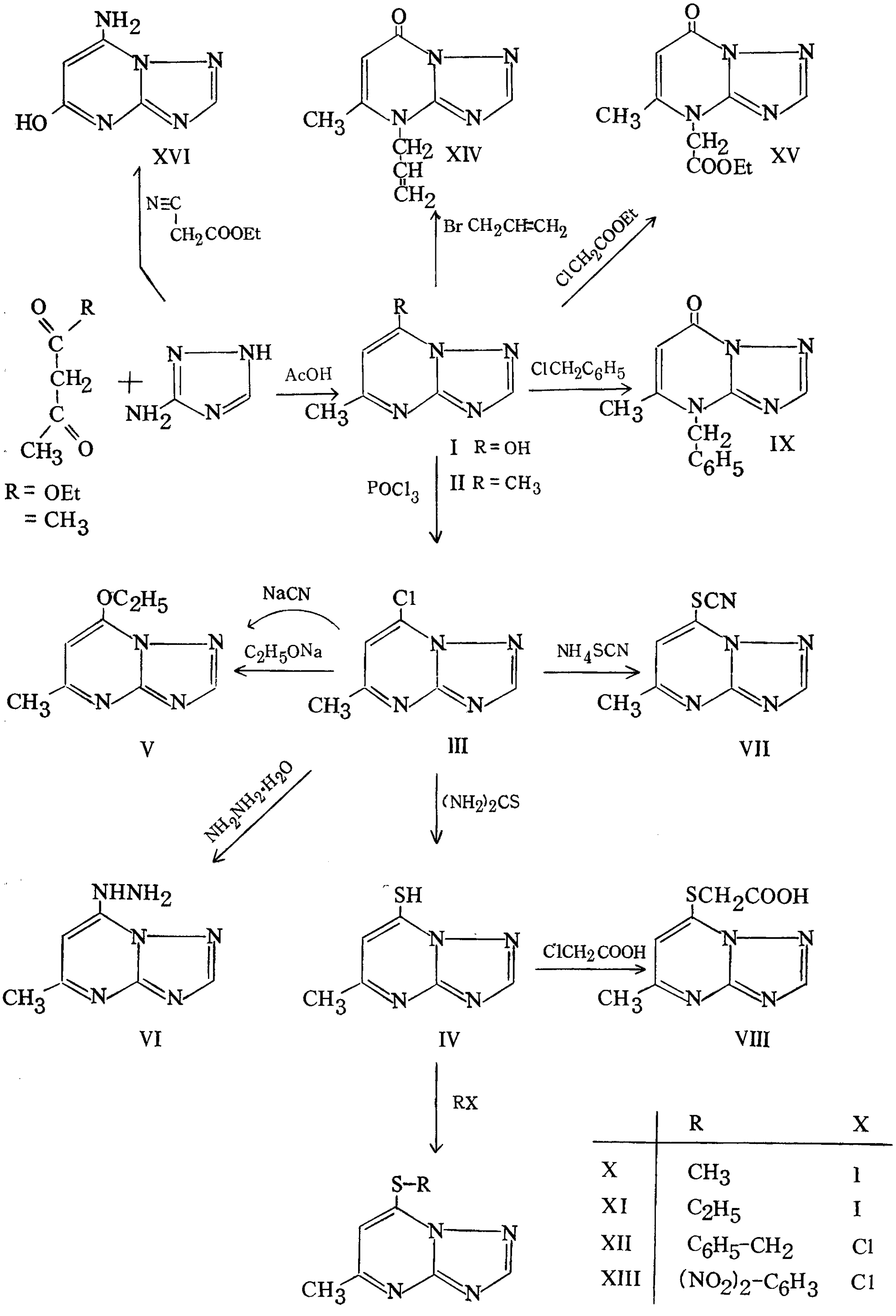
Some of them showed herbicidal or fungicidal activity, on which will be reported briefly.

Experimentals

(I) Chemistry

7-Hydroxy-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (I)

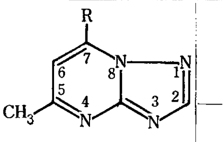
A mixture of 1.75 g of 3-amino-1, 2, 4-triazole[3] and 2.65 g of ethyl acetoacetate in 5 ml of acetic acid was refluxed on an oil bath for about 7 hours, during the reaction colorless crystals appeared. After being cooled, the resulting crystals were collected



	R	X
X	CH_3	I
XI	C_2H_5	I
XII	$C_6H_5-CH_2$	Cl
XIII	$(NO_2)_2-C_6H_3$	Cl

Fig. 1. Syntheses of Triazolo [1, 5-*a*] pyrimidine derivatives.

Table 1. Syntheses of triazolo [1, 5-*a*] pyrimidines.

 R=	Reaction		Solvent	Yield (%)	M.P. (°C)	λ_{max} (EtOH) mμ	Molecular formula	Ref.
	Temp. (°C)	Time (hrs.)						
-OH	130-140	6	AcOH	93	270.5	271	$C_6H_6ON_4$	5, 7, 12
-Cl	〃	2	$POCl_3$	43	150.5	—	$C_6H_5N_4Cl$	7, 12
-SH	80-90	1/2	EtOH	84	264	240.5	$C_6H_6N_4S$	2, 12
$-NHNH_2$	90-95	3/2	—	74	229	283.5	$C_6H_8N_6$	12
$-OC_2H_5$	〃	2	EtOH	50	149	284	$C_8H_{10}ON_4$	7, 12
-SCN	room temp.	12	aq.EtOH(30%)	40	140.5	280.5	$C_7H_5N_5S$	12
$-SCH_2COOH$	100	2/3	10% NaOH	51	233	296	$C_8H_8O_2N_4S$	2, 12
*$-OCH_2C_6H_5$	〃	5	8% NaOH	6	202	272	$C_8H_{10}ON_4$	17
$-SCH_3$	room temp.	36	1N-NaOH	70	181		$C_7H_8N_4S$	12
$-SCH_2CH_3$	〃	24	〃	78	131-2		$C_8H_{10}N_4S$	
$-SCH_2 \cdot C_6H_5$	70-75	1.5	〃	67	150-1		$C_{13}H_{13}N_4S$	
$-SC_6H_3(NO_2)_2$	80-90	0.7	〃	60	216.5-7		$C_{12}H_8O_4N_6S$	

* Combining site is N-3, therefore R is O.

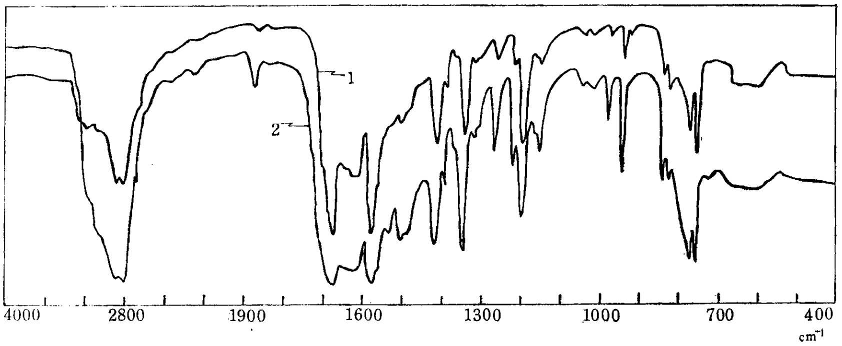


Fig. 2. IR-spectra of 7-hydroxy-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine.
1), Author's preparation (from 3-amino-1, 2, 4, -triazole).
2), Makisumi's preparation (from 5-amino-1, 2, 4, -triazole).

and recrystallized from ethanol to obtain 2.04 g of colorless needles.[5][7][12] IR spectra were shown in Fig. 2.

$C_6H_6ON_4$:	Calcd.	C, 48.00	H, 4.00	N, 37.33
	Found	C, 47.92	H, 4.07	N, 37.42

5,7-Dimethyl-*s*-triazolo [1, 5-*a*] pyrimidine, (II)

A mixture of 4.2 g of 3-amino-1, 2, 4-triazole and 6 g of acetyl acetone in 30 ml of acetic acid was refluxed on an oil bath for about 10 hours. Most of the excess acetic acid was removed *in vacuo* on a water bath. After being cooled, resulting crystals were collected, washed with ether and recrystallized from ethanol to give 5.2 g of colorless needles.[5][12] Melting point 134°C.

$C_7H_8N_4$:	Calcd.	C, 56.74	H, 5.44	N, 37.82
	Found	C, 56.96	H, 5.58	N, 37.67

7-Chloro-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (III)

Two and a half g of (I) was refluxed with 20 ml of $POCl_3$ on an oil bath for 2 hours. The excess $POCl_3$ was removed under a reduced pressure on a steam bath, and the resulting syrup was poured into an ice water. The solution was then neutralized with concd. NH_4OH and extracted repeatedly with $CHCl_3$. The extract was dried over

Na_2SO_4. The chloroform was removed under a reduced pressure on a steam bath and resulting yellow residue was recrystallized from ethanol to give 1 g of colorless prism.[7]

$C_6H_5N_4Cl$:	Calcd.	C, 42.76	H, 2.92	N, 33.25
	Found	C, 42.67	H, 2.98	N, 33.26

7-Mercapto-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (IV)

To a solution containing 0.3 g of (III) in 15 ml of ethanol was added 0.35 g of thiourea and the mixture was refluxed on a steam bath for about half an hour. After being cooled, the separated crystals were recrystallized from ethanol. Pale yellow needles of 0.2 g was obtained. IR spectrum was shown in Fig. 3.

$C_6H_6N_4S$:	Calcd.	C, 43.37	H, 3.61	N, 33.74
	Found	C, 43.19	H, 3.65	N, 33.84

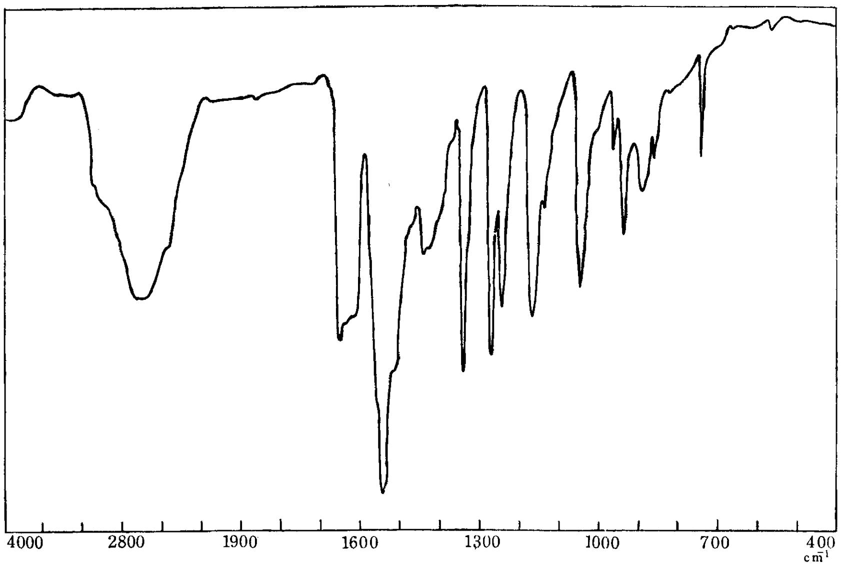


Fig. 3. IR-spectrum of 7-mercapto-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine.

7-Methylthio-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (X)

A solution of 0.17 g of (IV) dissolved in 3 ml of 1 N NaOH was shaken at room temperature with 0.2 g of CH_3I for 2 hours. The resulting precipitate was collected and recrystallized from ethanol. 0.15 g of colorless crystals were obtained.

$C_7H_8N_4S$:	Calcd.	C, 46.67	H, 4.49	N, 31.11
	Found	C, 46.92	H, 4.53	N, 30.91

7-Ethylthio-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (XI)

To a solution of 0.3 g of (IV) in 10 ml of 1 N NaOH was added 0.6 g of ethyl iodide. The mixture was treated as described above to obtain 0.25 g of colorless needles.

$C_8H_{10}N_4S$:	Calcd.	C, 49.48	H, 5.19	N, 28.85
	Found	C, 49.58	H, 5.58	N, 28.70

7-Benzylthio-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (XII)

A solution of 0.2 g of (IV) dissolved in 1.5 ml of 1 N NaOH was stirred at room temperature with 10 ml of ethanol solution containing 0.2 g of benzylchloride. To complete the reaction, the solution was heated at 70-75°C for 1.5 hours. Then, the solution was evaporated under a reduced pressure to obtain yellow crystals, which were recrystallized afterward from ethanol. Finally, 1.7 g of pale yellow prism were obtained.

$C_{13}H_{13}N_4S$:	Calcd.	C, 60.92	H, 4.72	N, 21.87
	Found	C, 60.79	H, 4.91	N, 21.35

7-(2, 4-Dinitrophenylthio)-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (XIII)

A solution of 0.2 g of (IV) dissolved in 0.5 ml of 1 N NaOH was stirred at room temperature with 60 ml of ethanol containing 0.2 g of 2, 4-dinitrochlorobenzene for a short time. Then, the solution was refluxed for half an hour to complete the reaction. The solution was evaporated under a reduced pressure to obtain yellow crystals, which were recrystallized from ethanol. The yield of pale yellow needles was 0.13 g.

$C_{12}H_8O_4N_6S$:	Calcd.	C, 43.38	H, 2.42	N, 25.30
	Found	C, 43.35	H, 2.40	N, 25.17

7-Carboxymethylthio-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (VIII)

To a solution of 0.6 g of (IV) dissolved in 3 ml of 0.25 N HaOH was added 0.34 g of monochloroacetic acid. The solution was heated on a steam bath for half an hour. After being cooled to room temperature, the solution was diluted with 15 ml of water, and acidified with concd. HCl. The resulting crystals were collected and recrystallized from ethanol to obtain 0.5 g of colorless needles.

$C_8H_8O_2N_4S$:	Calcd.	C, 42.86	H, 3.57	N, 25.00
	Found	C, 42.86	H, 3.64	N, 24.84

7-Ethoxy-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (V)

Three-tenth g of (III) was added to a solution prepared from 4 ml of abs. EtOH and 0.05 g of Na. The solution was refluxed on a steam bath for 2 hours. After being cooled, precipitated NaCl was filtered off and the filtrate was concentrated on a water bath under a reduced pressure. The resulting yellow residue was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting product was recrystallized from benzene to obtain 0.16 g of colorless prism.7)12)

$C_8H_{10}ON_4$:	Calcd.	C, 53.92	H, 5.66	N, 31.46
	Found	C, 53.79	H, 5.69	N, 31.47

7-Hydrazino-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (VI)

To a solution of 0.2 g of (III) dissolved in 2 ml of ethanol was added 3 ml of NH_2NH_2-H_2O. The mixed solution was refluxed on a steam bath for 3.5 hours. After being cooled, the resulting dark gray residue was collected and recrystallized from ethanol to give 0.15 g of colorless needles.

$C_6H_8N_6$:	Calcd.	C, 43.89	H, 4.91	N, 51.20
	Found	C, 44.03	H, 5.02	N, 50.98

5-Methyl-7-thiocyano-*s*-triazolo [1, 5-*a*] pyrimidine, (VII)

To a solution of 0.3 g of (III) dissolved in 10 ml of EtOH-H_2O (3 : 1) was added 0.2 g of NH_4SCN. The solution was stirred vigorously at room temperature for 4 hours, during the reaction the colorless crystals appeared. After being cooled, the resulting crystals were collected and recrystallized to give 0.12 g of colorless needles.

$C_7H_5N_5S$:	Calcd.	C, 43.98	H, 2.02	N, 36.65
	Found	C, 44.11	H, 2.60	N, 36.74

4-Ethylcarboxymethyl-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidin-7(1*H*)one, (XV)

To a mixture of 1 g of (I) and 0.85 g of K_2CO_3 in DMF was added 0.75 g of ethyl monochloroacetate. The mixture was stirred at room temperature for 2 days, then filtered.

The filtrate was evaporated on a steam bath under a reduced pressure. The resulting brown syrup was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated until to give brown syrup. The syrup was stood at room temperature over night in order to crystallize. The resulting crystals were washed with ether and recrystallized from methanol and $CHCl_3$ to obtain colorless prism.

$C_{10}H_{12}O_3N_4$: Calcd. C, 50.58 H, 5.12 N, 23.72
Found C, 50.87 H, 5.15 N, 23.66

4-Allyl-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidin-7(1*H*)one. (XIV)

To a mixture of 1.5 of (I) and 1.4 g of K_2CO_3 in 50 ml of DMF was added 1.5 g of allylbromide. The mixture was stirred at a room temperature for 24 hours, then filtered. The filtrate was evaporated under a reduced pressure on a steam bath. The resulting brown syrup was stood at room temperature over night to crystallize. Half a gram of colorless prism was obtained by recrystallization from ethyl acetate.

$C_9H_{10}ON_4$: Calcd. C, 56.83 H, 5.30 N, 29.46
Found C, 57.03 H, 5.42 N, 29.16

7-Amino-5-hydroxy-*s*-triazolo [1, 5-*a*] pyrimidine, (XVI)

Four and two-tenth g of amitrole and 8.4 g of ethyl cyanoacetate was added to 100 ml ethanol solution of ethanolate prepared by dissolving 1.2 g of Na. The mixture was refluxed on a steam bath for 8 hours, during the reaction the solution turned into red. After being cooled, the resulting precipitate was collected and dissolved in water. The aqueous solution was treated with charcoal and the filtrate was acidified with concd. HCl. After cooling, the precipitate was collected, washed with water and recrystallized from EtOH-H_2O to give 3.3 g of colorless needles.

$C_5H_5N_5O$: Calcd. C, 39.73 H, 3.33 N, 46.34
Found C, 38.38 H, 3.58 N, 44.26

7-Ethoxy-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (V from III and NaCN)

To a solution of 0.28 g of NaCN in 4 ml of water was added 100 ml of EtOH containing 0.9 g of (III). The solution was stood at room temperature for one day, during the reaction the solution turned into red. The solution was then filtered and concentrated in order to obtain dark red residue. The residue was again dissolved in water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness. By recrystallizing fom EtOH, 0.5 g of colorless crystals was finally obtained. M.p. 149°C. This compound was identical with which obtained from (III) and EtONa.

(II) Biological Activities

Some derivatives of (I), (III) and the related compounds(*) were examined in regard to plant regulatory activity, herbicidal, and inhibitory effect on spore germination of

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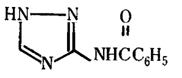
(*) Following compounds will be reported in a forthcoming report.



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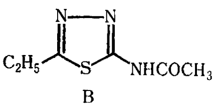

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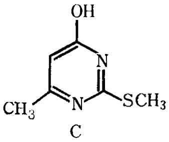

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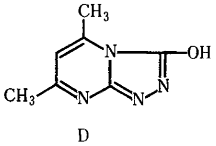

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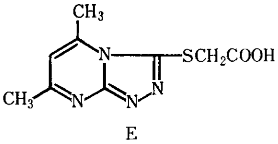

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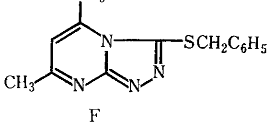

F

Ophiobolus miyabeanus, and antibiotic activities to *Phytophthora infestans* and *Pellicularia filamentosa*. As a result a quite few of these compounds had shown certain biological activities.

(1) Inhibitory effect on spore germination

Every 0.5 ml of test solutions was pipeted to petri dish ($\phi=4.2$ mm). After the solvent had been completely evaporated, 5 ml of 0.1 % sucrose solution, and 1 ml of a suspension of spores of *Ophiobolus miyabeanus* Ito et Kurib. (150 x 15-20 spores per a sight) were mixed to it and allowed to stand at 28°C. After 24 hours, the number of germinated spores was counted on 100 spores in two dishes. The results were indicated in Table 2.

Table 2. Inhibitory effect on spore germination of *Ophiobolus miyabeanus*.

Sample	III	VII	IX	X	XIV	A	B	C	D	E	F	Sankyo's Bordeaux*
Inhibitory rate on spore germination, (%)	51	95	6	3	6	4	4	8	16	97	48	99

* Commercial name
Conc. of the test solution was 1000 ppm.

(2) Antibiotic effect on *Bacillus subtillis*

About 15 ml agar medium was dissolved in a test tube and cooled till about 60°C, then mixed with 5 ml of a suspension of *B. subtillis*. The mixture was poured in petri dish to solidify. A paper disk ($\phi=6$ mm) which was dipped into a test solution (containing 1000 ppm of a sample) for 1-2 minutes and then freed from excess solution, was placed on the seeding layer. After had been incubated at 37°C for 20 hours, the diameter of the inhibiting zone was measured. Sankyo phytomycin was used as control. The results obtained are shown in Table 3.

Table 3. Effect on *Bacillus subtillis*.

Sample	Diameter of inhibiting zone
VII	11.5 mm
Sankyo's phytomycin	13.5 mm

(3) Antibiotic effect on soil microbes.

(i) Germicidal effect on *Phytophthora infestans* and *Pellicularia filamentosa*.

Soil sterilized in an autoclave was placed till about 4.5 cm height in a test tube ($\phi=15$ mm). To this tube colonies of *Phytophthora infestans* or *Pellicularia filamentosa* were added, then the sterilized soil was placed till about 4.5 cm in height. 5 ml of a test solution was added to it and kept at 28°C for 24 hours. After the soil and fungi were separated by adding water, the separated fungi were inoculated on PDA containing citric acid and incubated for 2 days. The growth rate of the fungi was measured and given in Table 4.

Table 4. Germicidal effect on soil microbes.

Sample	III	VII	IX	X	XIV	A	B	C	D	E	F	orthocide
Growth rate* of *Pellicularia filamentosa*	33	21	38	—	35	35	36	35	35	—	—	37
〃 *Phytophthora infestans*	—	—	—	—	37	38	37	38	38	—	—	38

* The growth rate was indicated as mm.
—: no trial. Conc. of the test solution was 1000 ppm.

(ii) Inhibitory effect on fungus-growing of *Phytophthora infestans* and *Pellicularia filamentosa.*

The fungi were inoculated in potato agar medium containing respectively 0, 1, 10 and 100 ppm of the test solution in petri dish and incubated for 2 days, thereafter the growth rate was measured. The results are illustrated in Fig. 4.

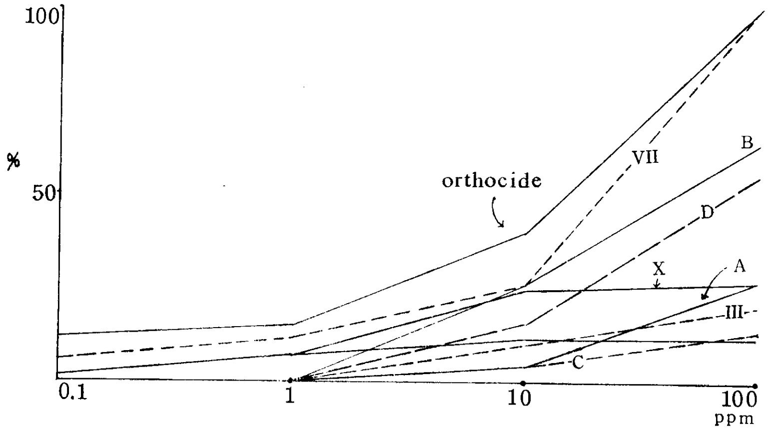

Fig. 4. Inhibitory rate on fungus-growing of *Phytophthora infestans* and *Pellicularia filamentosa.*

(4) Herbicidal and plant regulatory effects

In every dish containing 20 ml of the test solution of which concentration was respectively 0.1, 1. 10 and 500 ppm a filter paper was placed. Seeds of rice or of *Atriplex Gmelinii* C. A. Mey were sowed on it and cultured at 25°C in the dark. After 5–10 days, the length of roots grown, stalks and leaves were measured to appreciate the effect of the testing solution. Namely 10 seedlings were extracted from every section and measured the divided part of plants to obtain the mean value. The growth value in the test section compared with that of control was expressed as per cents to evaluate the growth rate of every section. The results are brought forth in Table 5.

In this test, VII and E inhibited above 95 % of the germination of the spores. Especially VII has shown a strong antibiotic activity to *B. subtillis* as well as to *Pellicularia filamentosa* and *Phytophthora infestans*, but other compounds did not have any antibiotic activity.

VII and E were also herbicidally active. It is interested that E, F, and C inhibit the growth of weeds and stimulate the growth of rice. These results are summarized in Table 6.

Although free amino group of amitrole seems to be important for the herbicidal activity,9) some of the amino blocked compounds were still active. Therefore, the herbicidal mechanism might be different from that of amitrole.

Considering the effectiveness of VII which was synthesized from amitrole,8)19) acetoacetate and NH_4NCS, the formation of certain compound like VII *in vivo* might be taking a part in a reinforcement of the herbicidal activity of amitrole brought about by adding NH_4NCS.

Summary

3-Amino-1, 2, 4-triazole was condensed with active methylene ketones such as ethyl cyanoacetate, acetylacetone, ethylacetoacetate to get corresponding 7-amino-5-hydroxy-

Table 5. Herbicidal and plant regulatory effects of triazolo [1, 5-*a*] pyrimidine derivatives.

Compounds	Concentration (ppm)	% Inhibition or stimulation			
		Rice (Hōnenwase)		*Atriplex Gmelinii*	
		Roots	Stalks & Leaves	Roots	Stalks & Leaves
III	500	+10-25*	15-45	0	0
	10	+10-25*	15-45	0	0
	1	30	15-45	0	0
VII	500	90	25-30		
	100			80	60
	10			+20*	
IX	500	65	25-45	0	0
	10	20-25	25-45	0	0
	1	20-25	25-45	0	0
X	500	60	40-50		
	100	30		+20*	0
	1	20			
XIV	500	40-50	30	0	0
	100	25		0	0
A	500		35-50		
	100	45-50	25-35	20	10
	1	45-50			
B	500	60-70	30	60-70	30
	100	20-30			
C	500	45-50			
	100	20	35-40	30	30
	10	+15-25*			
	1	+15-25*	+30*		
D	500	+40*	25-35		
	100		25-35	45	45
	10		25-35		
E	1	++*	+25-30*	30	15-25
F	100			20	20-25
	60		20-35		
	10		20-35	35	20-25
	1	+30-40*	+15-25*		

++* : highly stimulated at given conc.
+20* : stimulating effect was evaluated as 20% at given conc.

s-triazolo [1, 5-*a*] pyrimidine, 5, 7-dimethyl-*s*-triazolo [1, 5-*a*] pyrimidine and 7-hydroxy-5-methyl-*s*-triazolo [1, 5-*a*] pyrimidine, (I). Then, starting from (I), some 5-methyl-7-substituted-*s*-triazolopyrimidines were synthesized. As to some of derivatives, pesticidal, herbicidal and other biological activities were examined.

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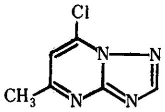
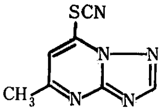
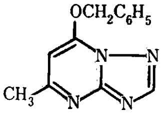
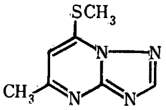
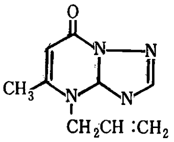
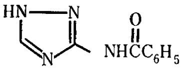
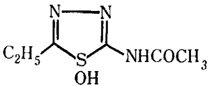
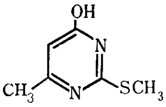
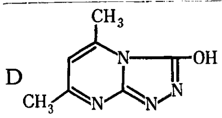
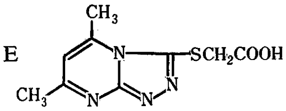
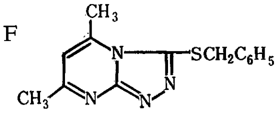
Table 6. Summarized results on biological activities.

Compound		Herbicidal	Growth regulatory	Sporicidal	Anti-bacterial	Fungicidal	to Soil microbes
III		−	+	+	−	−	−
VII		+	−	++	++	++	++
IX		−	−	−	−	−	−
X		+	−	−	−	−	−
XIV		−	−	−	−	−	−
A		+	−	−	−	−	−
B		+	−	−	−	+	−
C		+	−	−	−	−	−
D		+	+	−	−	+	−
E		+	+	++	−	−	−
F		−	+	+	−	−	−

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