slight increase of the urine radioactivity must be noticed for the rabbits unable to attend coprophagy. It is concomitant of the second peak in normal rabbit and may be explained by the fact that part of the soft feces can stick on the wiring of the cages and then be eaten by the rabbits in spite of their collars.

It is noteworthy that the periodicity of this damped phenomenon was in step with the nycthemeral rhythm of coprophagy in the rabbit fed ad libitum, as established by Corpet and Laplace (1976). Total radioactivity excreted by the noncoprophagous rabbit was 44.8% less than for the normal one. Based on a comparative balance study carried out over a 4-day period in both type animals, it was established that the difference observed in the urines (19.1% vs. 10.6%) was in the same range of that measured in the feces (80.2% vs. 88.7%) but opposite. If one considers these complementary observations and data, it may be stated that coprophagy contributes definitely to the recycling of [^{14}C]robenidine and that this phenomenon accounts for about 8.5% of the radioactivity ingested.

Such an evaluation must be compared with other values obtained during studies specially designed to measure the nutritional impact of coprophagy in the rabbit. By use of various tracers or collecting and then weighing separately hard and soft feces, the extent of the recycling was established to between 8% (Battaglini, 1968) and 13% (C. Dehalle, personal communication) of the dry matter ingested. The fact that robenidine is poorly absorbed can explain this very similar behavior.

CONCLUSION

From the comparative study of robenidine metabolism in rat, chicken, and rabbit, it appears that patterns are very similar qualitatively and quantitatively for birds and mammals. After breakdown of the semicarbazide function, elimination occurs in urine as a glycine conjugate of the *p*-chlorobenzylidene moiety of the molecule. However, our study did not give any data on the fate of the aminoguanidine moiety.

The pharmacokinetics of the tissue residues give the basic data necessary to fix a withdrawal period before slaughtering. Due to the longer persistence of residues in the liver, this organ may be considered as the target one for residue control.

Coprophagy was shown to result in the recycling of part of the unchanged robenidine, thus contributing to the longer persistence of liver residues when compared to those measured elsewhere in the rat.

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Pyrimidines. 23. A Structure–Activity Relationship Study of 4-Chloro-2,6-(substituted amino)pyrimidines as Pre- and Postemergence Herbicidal Agents

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Two pyrimidine analogues of the herbicide atrazine were synthesized, and their herbicidal activity was evaluated. One of these deazaatrazines, 4-chloro-2-(ethylamino)-6-(2-propylamino)pyrimidine, was found to be a highly specific preemergence herbicidal agent. It inhibits the growth of Johnson grass but is noninjurious to corn, whereas atrazine has the opposite effect in each case. In the postemergence tests, a high order of tolerance by cotton plants was noted with these pyrimidine derivatives, whereas atrazine in these tests was quite injurious to this valuable crop. Some structure–activity relationships were correlated among many of the pyrimidine analogues in both the pre- and the postemergence tests.

For centuries agricultural workers have been engaged in a battle with undesired plants in their fields. During the past 40 years, the use of herbicides has become a major tool in controlling the growth of vegetation. An examination of the present-day trend in the use of herbicides indicates that the older, inorganic herbicides and defoliants are declining in usage as more selective, more effective, and less hazardous organic agents have become available. It also reveals that among the organic agents, many heterocyclic compounds are of special value. This is illustrated by the wide use of herbicides such as atrazine [2-chloro-4-(ethylamino)-6-(2-propylamino)-*s*-triazine, 1] (Gysin and Knüsli, 1955), amitrole [amizol, 3-amino-1,2,4-triazole, 2] (Tafuro et al., 1955), and bromacil [5-bromo-3-(2-bu-

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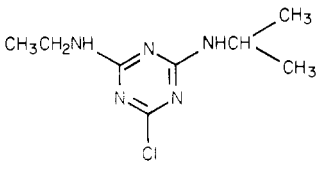

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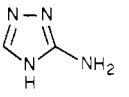

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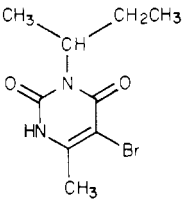

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tyl)-6-methyluracil, 3] (Bucha et al., 1962). These compounds are being used to control germinating weed grasses and broad-leaved weeds, as well as Canada thistle, cattails, leafy spurge, poison ivy, etc.

The selective inhibitory activity of many herbicides still leaves something to be desired. Atrazine, for example, can effectively kill pigweed, setaria, morning glory, etc., when applied in the field at practical concentrations. However, it is not effective against Johnson grass, a common but undesirable weed. Furthermore, atrazine is quite injurious to some economically useful crops such as cotton.

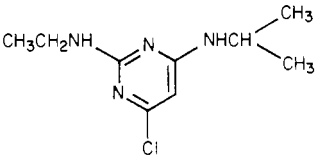
In addition to the problem of selective action, the stability of herbicides is also of serious concern. It is desirable that a herbicide be relatively stable during preparation, formulation, and storage. However, the stability should be such that after the compound exerts its herbicidal function in the soil, it would be degraded within a reasonable period of time. Otherwise, because of high residual activity, the herbicide would create environmental problems in the long run or it would render the soil denatured so that it would no longer be feasible to practice crop rotation. Thus, farmers would more or less be forced to cultivate the same type of crop every year. These problems have been repeatedly encountered by the use of atrazine or other related *s*-triazine analogues, the ring system of which is not found to occur in nature. More seriously, carcinogenicity of these *s*-triazine herbicides has been reported (Pliss and Zabeshinsky, 1970).

In light of the above, it would appear that compounds derived from naturally occurring ring systems may be more readily degraded by certain processes in the soil. Thus, the structurally related pyrimidine ring system would be a logical candidate.

Although some pyrimidine derivatives, such as bromacil (**3**), 5-alkyl (or 5*H*)-2-amino-4-chloro-6-(substituted amino)pyrimidines (Darlington, 1962; Schneider, 1970), and 2,4-(substituted amino)-6-chloropyrimidines (Gysin and Knüsli, 1958; Fusco et al., 1964), have been noted as herbicides, the deaza analogues of atrazine have never been reported. Since the pyrimidine ring has only one plane of symmetry in contrast to the three planes of symmetry possessed by the *s*-triazine ring, there are three possible isomeric substitutions (**4**–**6**) for the pyrimidine ring. The present communication reports the preparation and herbicidal activity of 4-chloro-2-(ethylamino)-6-(2-propylamino)pyrimidine (**4**) and 4-chloro-6-(ethylamino)-2-(2-propylamino)pyrimidine (**5**). In addition, a structure–activity relationship study among some related substituted aminohalopyrimidines has also been conducted.

SYNTHETIC METHODS

4-Chloro-2-(ethylamino)-6-(2-propylamino)pyrimidine (**4**) was prepared as follows: Condensation of 278 g of



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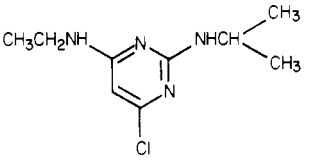

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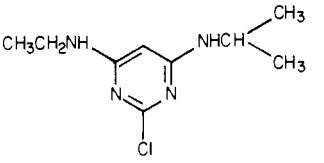

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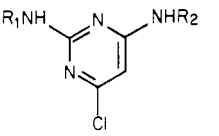
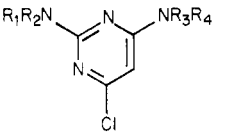
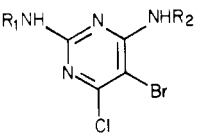


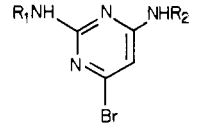
7, $R_1, R_2 = H$
8, $R_1, R_2 = CH_3$
9, $R_1, R_2 = CH_2CH_3$
10, $R_1, R_2 = CH(CH_3)_2$
11, $R_1 = CH_3$; $R_2 = (CH_2)_3CH_3$
12, $R_1 = CH_2CH_3$; $R_2 = (CH_2)_2CH_3$
13, $R_1 = CH_2CH_3$; $R_2 = CH(CH_3)CH_2CH_3$
14, $R_1 = CH_2CH_3$; $R_2 = (CH_2)_{16}CH_3$
15, $R_1 = CH_2CH_3$; $R_2 = C_5H_9$
16, $R_1 = CH_2CH_3$; $R_2 = C_6H_{11}$
17, $R_1 = CH_2CH_3$; $R_2 = CH_2C_6H_5$
18, $R_1 = CH_2CH_3$; $R_2 = CH_2CH(CH_3)_2$
19, $R_1 = CH(CH_3)_2$; $R_2 = CH_3$
20, $R_1 = CH(CH_3)_2$; $R_2 = (CH_2)_2CH_3$
21, $R_1 = CH(CH_3)_2$; $R_2 = CH_2CH(CH_3)_2$
22, $R_1 = (CH_2)_2CH_3$; $R_2 = CH(CH_3)_2$



23, $R_1, R_2, R_3, R_4 = CH_3$
24, $R_1, R_2 = CH_3$; $R_3 = H$; $R_4 = CH_2CH_3$
25, $R_1, R_2 = CH_3$; $R_3 = H$; $R_4 = (CH_2)_2CH_3$
26, $R_1, R_2 = CH_3$; $R_3 = H$; $R_4 = CH(CH_3)_2$
27, $R_1 = H$; $R_2 = CH_2CH_3$; $R_3, R_4 = (CH_2)_2CH_3$
28, $R_1 = H$; $R_2 = CH_2CH_3$; $R_3 = CH_3$; $R_4 = (CH_2)_3CH_3$



29, $R_1, R_2 = CH_3$
30, $R_1, R_2 = CH_2CH_3$
31, $R_1 = CH_2CH_3$; $R_2 = CH(CH_3)_2$
32, $R_1 = CH(CH_3)_2$; $R_2 = CH_2CH_3$



33, $R_1, R_2 = CH_2CH_3$
34, $R_1 = CH_2CH_3$; $R_2 = CH(CH_3)_2$

ethylguanidine sulfate (Schenck and Kirchhof, 1926) and 319 g of diethyl malonate in methanolic sodium methoxide gave 136 g of 4,6-dihydroxy-2-(ethylamino)pyrimidine that, on treatment with $POCl_3$, gave an 80% yield of 4,6-dichloro-2-(ethylamino)pyrimidine. The latter (24 g) was heated with 15 g of 2-propylamine in methanol at 120 °C for 12 h in a sealed container. After the usual workup, the

Table I. Preemergence Herbicidal Activity Evaluation[a]

compd	dose, lb/acre	pigweed	setaria (foxtail)	Johnson grass	morning glory	milo	corn	cotton
4	10	10	10	8Y	10	8IY	7IY	0
	2.5	10	10	8	10	0	0	0
5	10	10	10	10	10	2Y	2I	0
	2.5	8	8	2I	0	0	0	0
7	10	5	4	0	4I	0	0	0
8	5	10	10	10	8	0	0	2Y
	2.5	10	5	2I	0	0	0	0
9	10	10	10	9	10	7	0	0
	2.5	8	10	4	0	0	0	0
10	5	10	8	4	10	3I	2I	0
11	5	0	0	0	0	0	0	0
12	5	8	8	8	2I	2I	1I	2
13	5	9	0	0	0	0	0	0
14	5	0	0	0	0	0	0	0
15	5	6	2	0	0	0	0	0
16	5	9	0	0	0	0	0	0
17	5	9	3I	2I	2Y	2I	3I	2I
18	5	6	9	7	2Y	0	0	0
19	5	10	10	9	9	2I	0	0
	2.5	10	8	3	0	0	0	0
20	5	0	8	7	10	2I	0	0
21	5	6I	3I	2I	2Y	1I	2I	2I
22	5	10	3I	0	3I	0	0	0
23	10	10	10	0	2Y	0	0	
24	10	10	10	8	4I	0	0	
25	10	10	10	10	10	5	1I	
26	10	10	10	9	10	4	3I	3I
27	5	2	6I	5I	0	2I	0	0
28	5	7	2I	3I	0	0	0	0
29	5	10	0	0	0	0	3I	0
30	10	10	10	10	10	2I	2I	
	2.5	10	10	6	2I	2I	2I	0
31	5	9	2I	0	0	0	0	0
32	10	10	10	7I	5I	0	0	0
	2.5	10	10	4Y	0	0	0	0
33	5	2	0	0	0	0	0	0
34	5	10	7	2	8	0	0	0
atrazine	5	10	10	1	10	2I	5I	10
	2.5	10	10	0	10	1I	2Y	10
	1.25	10	10	0	10	0	1Y	10

[a] I = growth inhibited. Y = yellowing.

product was treated with concentrated H_2SO_4 in ether to give 26 g of the sulfate salt of **4**: mp 119–121 °C; λ_{max}^{EtOH} 222 (ε 25 000) and 278 nm (ε 7500). The other deaza analogue of atrazine, 4-chloro-6-(ethylamino)-2-(2-propylamino)pyrimidine (**5**), was prepared in a similar manner from 2-propylguanidine sulfate (Crowther et al., 1948) via 4,6-dihydroxy-2-(2-propylamino)pyrimidine and 4,6-dichloro-2-(2-propylamino)pyrimidine. The sulfate salt of **5** had a melting point at 140–141 °C and λ_{max}^{EtOH} 221 (ε 26 500) and 284 nm (ε 7500). Other substituted aminohalopyrimidines were prepared by analogous methods.

HERBICIDAL ACTIVITY EVALUATION

Preemergence Herbicidal Evaluation. For determination of herbicidal activity of candidate materials by a soil preemergence evaluation, flats (11 in. × 13 in.) are planted with the desired crops to a depth of 0.5 in. The crops employed are pigweed, setaria (foxtail), Johnson grass, morning glory, milo, corn, and cotton. In the interest of uniformity, care is employed in using a consistent amount of soil in the bottom of the flats, in the use of a template in the marking of the seed rows, in the amount of seeds used, and particularly in the amount of soil placed on top of the seeds. The chemicals are screened at a dosage range of 2.5–10 lb of active ingredient/acre. Candidate materials are suspended in water, and 250 mL of such a suspension is uniformly distributed over such flats. The flats are immediately transferred to the greenhouse and covered for a period of 3 days so that additional watering is not required until some of the plants have begun to make their appearance above ground.

When it is assured that all emergence has occurred, emergence counts are made on all crops. At the end of 14–16 days, a phytotoxicity reading is made on the various crops. The herbicidal activity is indicated not only by the stand of the crop but also by the extent of damage to the emerged seedlings (see Table I; test data of atrazine are also included for comparison). Phytotoxicity data are recorded on a scale of 0–10, 0 indicating no injury and 10 indicating that the plants were killed (a value of 8 being the lower limit of activity).

Discussion. In the preemergence tests, both the deazaatrazines **4** and **5** are superior to atrazine in that the deaza compounds are injurious to Johnson grass but do not inhibit the growth of corn, whereas atrazine has the opposite effects. Compound **4** is more potent and selective as a herbicidal agent. Among related pyrimidines tested, compounds **9**, **19**, **25**, and **30** possess a similar activity profile but are of somewhat less potency. Others are either much less active or nonselective. Bulky alkylamine substituents usually resulted in drastic reduction of herbicidal activity or were totally inactive, especially when the linear alkyl chain length is longer than three carbons, as illustrated by compounds **11** and **14**.

Postemergence Herbicidal Evaluation. The crops employed in this study were pigweed, setaria, Johnson grass, milo, morning glory, oats, wheat, red kidney beans, corn, and cotton. Weed species are approximately 2 in.

Table II. Postemergence Herbicidal Activity Evaluation[a]

compd	dose, lb/acre	pigweed	setaria	Johnson grass	morning glory	milo	oats	wheat	red kidney beans	corn	cotton
4	5	10	10	10	10	10	10	10	10	10	0
	2.5	10	10	10	10	10	9	7	9	9	0
5	5	10	10	10	10	10	10	7	10	9	0
7	5	0	0	0	0	0	0	0	0	0	0
8	5	10	9	6	8	4	5	1	5	5	3Y
9	5	9	9	10	10	9	10	10	10	10	6
10	5	10	10	9	10	10	10	10	10	10	0
11	5	10	10	9	10	5	10	10	10	3	4Y
12	5	10	10	10	10	10	10	10	10	10	0
13	5	10	10	7	10	6	10	10	10	4	4Y
14	5	1	0	0	0	0	0	0	2	0	0
15	5	10	10	9	10	7	7	10	10	3	8
16	5	10	6	0	10	1	7	7	7	0	4
17	5	9	9	2	10	0	5	4	5	0	2Y
18	5	10	10	10	10	10	10	10	10	8	1
19	5	3	9	1	10	2	7	2	4	2I	3
20	5	10	10	3	10	10	10	10	10	10	0
21	5	10	9	0	10	10	10	10	10	8	0
22	5	8	5	4	3	1	7	0	4	0	0
23	5	5	6	3	10	5	4	2	4	3	0
24	5	1	4	1	7	1	3	0	5Y	0	0
25	5	4	4I	4	4	2	3	2	5	2I	0
26	5	10	10	9	10	1	10	10	10	5	0
27	5	5	8	9	10	2I	10	9	10	2I	4Y
28	5	10	10	8	10	5I	9	3	4	3I	0
29	5	8	6	5	9	0	2	0	4	1I	0
30	5	9	7	2	10	1	9	6	5	4	0
31	5	4	7	4	3	2	2Y	1	3	0	0
32	5	9	10	5	5	2	8	8	9	0	0
33	5	5	10	2	10	2I	7	10	7	3I	7
34	5	10	10	3	10	1	10	10	10	0	5Y
atrazine	2.5	10	10	1	10	3I	10	10	10	0	10
	2	10	10	0	10	0	10	9	10	0	10

[a] I = growth inhibited. Y = yellowing.

in height at time of spraying, corn about 4 in., and wheat and oats 3 in. Red kidney beans used for the present evaluation are approximately 3 weeks old.

Chemicals are dissolved in appropriate solvents and diluted with water to obtain the desired final spray suspension. Candidate materials are screened at 5 lb/acre (active ingredient) calculated on a broadcast basis. (When these materials are used on the basis of a band treatment, the dosage per acre would actually be on the order of one-third of that indicated; e.g., a 2.5 lb/acre broadcast application would correspond to approximately 0.8 lb/acre on a band treatment basis.)

The plants are normally scored for phytotoxicity 10–12 days after spray application (see Table II). Phytotoxicity ratings are based upon a scale of 0–10, 0 indicating no injury and 10 indicating that the plants were killed. Again, a value of 8 is considered as the lower limit of herbicidal activity.

Discussion. In the post emergence tests, the deaza analogues **4** and **5** as well as other pyrimidine analogues **9**, **10**, **12**, and **18** possess greater herbicidal activity than atrazine on Johnson grass, milo, and corn. Atrazine is quite injurious to cotton whereas the pyrimidines in general have no effect on this valuable crop. The alkyl groups substituted on the amino nitrogen functions are again of importance to herbicidal activity; unsubstituted amine (compound **7**) or an amine group containing a long straight chain (compound **14**) possesses no herbicidal activity. Compounds containing methylamino groups are usually nonselective and display irregular activity. The preferred alkyl substituents are ethyl, propyl, and 2-propyl. It is of interest to note that compounds **16** and **34** possess an activity profile similar to that of atrazine with the exception that they are less inhibitory to cotton.

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