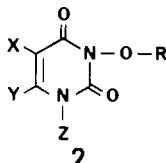
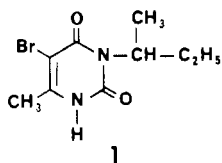


3-Alkoxyuracil Derivatives. 1. Herbicidal Activity

Ailsa L. Cossey¹ and John N. Phillips*

The herbicidal activities of a series of 3-alkoxyuracil derivatives have been evaluated, pre- and post-emergence, against a variety of plant species. 3-Alkoxy-5-bromo-6-methyluracils containing three to four carbon atoms in the alkoxy group have been shown to be potent nonselective preemergent herbicides. They appear to act by inhibiting photosynthesis and are comparable in effectiveness to the uracil herbicide, bromacil. When applied postemergence, they are less effective, though more selective, than bromacil.

The substituted uracils bromacil (1) (5-bromo-3-sec-



butyl-6-methyluracil), isocil (5-bromo-6-methyl-3-isopropyluracil), terbacil (3-*tert*-butyl-5-chloro-6-methyluracil), and lenacil (3-cyclohexyl-5,6-trimethyleneuracil) can be regarded as cyclic ureas belonging to the *N*-phenylamide group of herbicidally active photosynthetic inhibitors—a group which includes the anilide, phenylurea, and phenylcarbamate herbicides (Buchel, 1972). Although the uracils have found widespread use as herbicides, e.g., bromacil for general weed control in industrial and non-cropland situations, terbacil for annual weed control in citrus and sugarcane, and lenacil for weed control in sugar beet (Hoffman, 1972; Kearney and Kaufman, 1975), relatively little data of a structure-activity nature has been reported.

The facile synthesis of 3-hydroxyuracils from hydroxyurea and β -keto esters (Cossey and Phillips, 1970) provided starting materials which could be readily transformed into alkoxy analogues of the uracil herbicides. A series of 3-alkoxyuracil derivatives (2) was accordingly synthesized and formed the basis of a study in which molecular structure was related to herbicidal effectiveness.

EXPERIMENTAL SECTION

Materials. Bromacil was purified by extracting a commercial formulation, Hyvar X (Du Pont), with chloroform. The extract was filtered and concentrated, and the solid residue crystallized from ethanol to give a microcrystalline white solid, mp 157 °C.

The uracil derivatives set out in Table I were synthesized from appropriately substituted 3-hydroxy- or 3-alkoxyuracils by one of three typical procedures, exemplified by A, B, and C below. The table records the starting material employed in each synthesis, the type of procedure involved, and the melting point of the product. In all cases the observed mass of the molecular ion (M^+) as determined by high-resolution mass spectroscopy using an AE1-MS9 mass spectrometer was in close agreement with the calculated value. Proton NMR spectra determined on a Varian A-60A spectrometer were also consistent with assigned structures. The typical synthetic procedures employed are illustrated by the following syntheses.

(A) *5-Bromo-3-hydroxy-6-methyluracil* (4). 3-Hydroxy-6-methyluracil (Cossey and Phillips, 1970) (3) (0.1 mol) was suspended in water (200 mL), bromine (0.1 mol) added dropwise with shaking, and the mixture warmed on a steam bath for 30 min. When the mixture was cooled, the product precipitated and was crystallized from ethanol to give colorless plates: mp 263–265 °C; yield 80%. Anal. Calcd for $C_5H_5BrN_2O_3$ [M^+ = 219.94835 (found: 219.94831)]: C, 27.1; H, 2.26; Br, 36.2. Found: C, 26.97; H, 2.38; Br, 36.7.

(B) *5-Bromo-3-ethoxy-6-methyluracil* (6). 5-Bromo-3-hydroxy-6-methyluracil (4) (0.05 mol) was dissolved in water (200 mL) containing sodium carbonate (0.025 mol). Ethyl bromide (0.2 mol) was added, and the reaction mixture stirred and refluxed for 17 h. When the mixture was cooled, the product (6) separated out and was crystallized from acetone to give colorless needles: mp 219–221 °C; yield 84%. Anal. Calcd for $C_7H_9BrN_2O_3$ [M^+ = 247.97965 (found: 247.98044)]: C, 33.70; H, 3.62; N, 11.20. Found: C, 33.66; H, 3.55; N, 11.31. *Note:* Alkylation with long-chain ($>C_8$) alkyl halides was generally carried out in ethanol in the presence of 1 equiv of sodium ethoxide.

(C) *6-Methyl-3-propoxy-5-thiocyanatouracil* (28). Sulfuryl chloride (0.01 mol) was added to lead thiocyanate (0.01 mol) dispersed in methylene chloride (25 mL) and stirred for 30 min, and the mixture filtered into a 25-mL methylene chloride solution of 6-methyl-3-propoxyuracil (26) (0.01 mol) and stirred overnight at room temperature. The solution was concentrated, methanol (25 mL) added, and the yellow residue filtered off. Water added to the filtrate precipitated the product (28) which was crystallized from ethanol to give a pale yellow solid: mp 145–146 °C; yield 60%. For $C_9H_{11}N_3O_3S_1$, M^+ = 214.05212 (found: 214.05182).

Herbicidal Assay. Pre- and postemergent herbicidal activities of compounds were evaluated by using *Pisum sativum* (cv. Victory Freezer) peas, *Sinapis alba* mustard, *Linus usitatissimum* linseed, and *Hordeum vulgare* (cv. Cape) barley. In addition, preemergent activity was also assessed on *Zea mays* (cv. Fitzroy) maize and *Lolium perenne* (cv. New Zealand Perennial) ryegrass, and post-emergent activity on *Polygonum convolvulus* buckwheat and *Beta vulgaris* sugar beet.

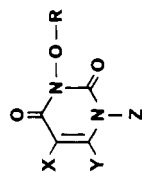
Seeds were sown in rows (one species per row; two rows per pan) on the surface of 4 cm of moist, steam-sterilized soil (University of California, Mixture II) contained in aluminum pans (20 × 10 × 7 cm³).

Preemergent herbicidal activity was assayed by dispersing an acetone solution (10 mL) of the test compound in fine sand (50 g), allowing the acetone to evaporate, distributing the sand as an even layer over the soil surface on which the seeds had been placed, and covering with 1 cm of soil. The plants were grown in a glasshouse (24 ± 3 °C) under fluorescent lights (16 000 lx at the surface; 16-h

CSIRO, Division of Plant Industry, Canberra City, A.C.T. Australia.

¹Deceased.

Table I. Structures, Chemical Properties, and Herbicidal Activities of 3-Alkoxyuracils



compd no. ^a	R	X	Y	Z	mp, °C	synthesis ^b		herbicidal activity ^c												T ₉₀ ^d kg ha ⁻¹		
						SM	proc	preemergence						postemergence								
								M	P	L	B	Ma	R	M	P	'Sb	L	B	Bw			
1	H	H	CH ₃	H	253-254	*	3	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.125
3	H	Br	CH ₃	H	263-265	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	>16
4	CH ₃	Br	CH ₃	H	201-202	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	>16
5	CH ₃	Br	CH ₃	H	219-221	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	2
6	C ₂ H ₅	Br	CH ₃	H	218-220	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.25
7	C ₂ H ₅ Cl ^e	Br	CH ₃	H	177-179	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.25
8	n-C ₃ H ₇	Br	CH ₃	H	196-199	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.25
9	i-C ₃ H ₇	Br	CH ₃	H	156-158	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.25
10	C ₃ H ₃ ^f	Br	CH ₃	H	218-220	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.25
11	C ₃ H ₃ ^g	Br	CH ₃	H	167-168	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
12	n-C ₄ H ₉	Br	CH ₃	H	160-161	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
13	s-C ₄ H ₉	Br	CH ₃	H	197-198	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
14	i-C ₄ H ₉	Br	CH ₃	H	155-156	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
15	n-C ₄ H ₁₁	Br	CH ₃	H	162-163	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
16	n-C ₆ H ₁₃	Br	CH ₃	H	152-153	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
17	n-C ₈ H ₁₇	Br	CH ₃	H	152-154	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
18	n-C ₈ H ₁₅	Br	CH ₃	H	153-154	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
19	n-C ₈ H ₁₉	Br	CH ₃	H	143-145	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
20	n-C ₁₀ H ₂₁	Br	CH ₃	H	137-140	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
21	n-C ₁₁ H ₂₃	Br	CH ₃	H	143-145	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
22	n-C ₁₂ H ₂₅	Br	CH ₃	H	144-146	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
23	n-C ₁₃ H ₂₇	Br	CH ₃	H	142-144	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
24	n-C ₁₄ H ₂₉	Br	CH ₃	H	134-137	*	4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
25	n-C ₁₆ H ₃₃	Br	CH ₃	H	191-193	*	3	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
26	n-C ₃ H ₇	H	CH ₃	H	154-155	*	3	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
27	n-C ₃ H ₇	H	CH ₃	H	145-146	*	3	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
28	n-C ₃ H ₇	SCN	CH ₃	H	121-123	*	26	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
29	n-C ₃ H ₇	SCN	CH ₃	H	178-179	*	27	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
30	H	H	n-C ₃ H ₇	H	235-236	*	30	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
31	H	Br	n-C ₃ H ₇	H	136-138	*	31	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
32	n-C ₃ H ₇	Br	n-C ₃ H ₇	H	118-120	*	31	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
33	n-C ₃ H ₇	Br	n-C ₃ H ₇	H	170-171	*	31	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
34	H	H	CH ₃	CH ₃	206-208	*	34	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
35	H	Br	CH ₃	CH ₃	95-96	*	35	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
36	n-C ₃ H ₇	Br	CH ₃	CH ₃	68-69	*	35	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5
37	n-C ₃ H ₇	Br	CH ₃	CH ₃		*	35	++	++	++	++	++	++	++	++	++	++	++	++	++	++	0.5

^a All compounds showed satisfactory agreement between the mass of the molecular ion observed by high-resolution mass spectroscopy and the calculated mass. ^b Starting material (SM) and typical synthetic procedure (proc) given or referenced (*). ^c Herbicidal activity against mustard (M), peas (P), sugar beet (Sb), linseed (L), barley (B), maize (Ma), ryegrass (R), and buckwheat (Bw). ++, <10% plant survival at 1 kg ha⁻¹; +, <10% plant survival at 8 kg ha⁻¹; no rating, >90% plant survival at 8 kg ha⁻¹. ^d Phytotoxicity on ryegrass. Rate in kg ha⁻¹ giving <10% survival of ryegrass 6 weeks after sowing. ^e C₂H₄Cl = 2-chloroethyl. ^f C₃H₅ = allyl. ^g C₃H₃ = propargyl.

photoperiod) with daily overhead watering. The application rate of the compound corresponded to 1 or 8 kg ha⁻¹. Postemergent herbicidal activity was assayed by spraying 14-day-old seedlings, grown in untreated soil as described above, with 50 mL of a 50% acetone solution of the test compound, the concentration being such as to give an equivalent surface application rate of 1 or 8 kg ha⁻¹. Herbicidal effectiveness of a compound was evaluated in terms of plant survival, 4 weeks after sowing. Treatments in which less than 10% of the plants survived 1 or 8 kg ha⁻¹ applications of compound were rated ++ or +, respectively.

Preliminary studies indicated that alkoxyuracil derivatives were relatively nonselective as preemergent herbicides among the species studied, and ryegrass was chosen as a typical species for a more detailed phytotoxicity evaluation. Compounds were soil incorporated as described above at rates equivalent to 16, 8, 4, 2, 1, 0.5, and 0.25 kg ha⁻¹, and their effects on ryegrass, grown under the standard conditions, assessed 6 weeks after sowing. Preemergent phytotoxicity on ryegrass was expressed in terms of the lowest application rate in kg ha⁻¹ (T_{90}) giving less than 10% plant survival 6 weeks after sowing.

RESULTS AND DISCUSSION

The herbicidal activity of the various 3-alkoxyuracil derivatives applied, pre- or postemergence at 1 or 8 kg ha⁻¹, on the plant species assayed, are set out in Table I in terms of ++ and + ratings. Where no ratings are recorded in Table I, >90% of plants survived and grew normally at 8 kg ha⁻¹. Table I also includes T_{90} values for bromacil and the unbranched 3-alkoxy-5-bromo-6-methyluracils.

Significant herbicidal activity was confined for the most part to those compounds structurally similar to bromacil, i.e., 5-bromo-6-methyluracils having a 3-alkoxy group in place of the 3-*sec*-butyl substituent. Activity was associated with alkoxy groups containing two to six carbon atoms ($n = 2-6$), with optimum activity centered around the C₃ and C₄ derivatives (see Table I). The most active, the 3-propoxy compound (8), was a convenient reference material with which the effects of structural modification on herbicidal effectiveness in this series could be compared.

The phytotoxicity associated with compound 8 was largely retained when the propoxy group was replaced by ethoxy (6), 2-chloroethoxy (7), isopropoxy (9), butoxy (12), or *sec*-butoxy (13) but somewhat reduced when replaced by isobutoxy (14), amyloxy (15) and hexyloxy (16). Compounds in which hydroxy (4), methoxy (5), or long-chain ($n > 6$) alkoxy (17-25) groups substituted for the propoxy group were inactive at 8 kg ha⁻¹. Phytotoxicity was also

reduced or lost when unsaturation was introduced into the propoxy side chain as in the double-bonded allyloxy (10) or triple-bonded propargyloxy (11) derivatives.

Replacement of the 5-bromo substituent in 8 by hydrogen (26) or a thiocyanato group (28) or of the 6-methyl substituent by a 6-propyl group (32), or methylation of the 1-nitrogen atom (36), led to loss of herbicidal activity at 8 kg ha⁻¹ against all species tested, except for compounds 28 and 32 on mustard. As Table I shows, the more herbicidally effective alkoxyuracils were comparably active to bromacil when applied preemergence and, like bromacil, were relatively nonselective between the species studied. When applied postemergence, however, the alkoxyuracils showed a greater degree of selectivity. Thus mustard, barley, and sugar beet were sensitive to the 3-propoxy derivative (8) at 1 kg ha⁻¹, while peas, linseed, and buckwheat were tolerant at 8 kg ha⁻¹. However, all test species were controlled by bromacil at 8 kg ha⁻¹ and all, except peas and barley, at 1 kg ha⁻¹.

The phytotoxic symptoms observed with preemergently applied alkoxyuracil derivatives were similar to those shown by bromacil treatments. Plants germinated normally, but in the second week after emergence, chlorosis of the leaves and desiccation of the shoot tissue, particularly in meristematic regions, became apparent and was followed by progressive desiccation of the whole plant over a period of 1-2 weeks. These symptoms were characteristic of herbicides which inhibited photosynthesis and exerted their toxic effect by starving the plant of photosynthetic assimilates. Bromacil has been shown to be such a photosynthetic inhibitor (Hilton et al., 1964), and it is likely that the alkoxyuracil derivatives behave similarly.

ACKNOWLEDGMENT

We thank Dr. R. L. N. Harris for helpful discussions and acknowledge the skilled experimental assistance of C. M. Foster (chemical synthesis) and A. E. Geissler (herbicidal assay).

LITERATURE CITED

- Buchel, K. H. *Pestic. Sci.* 1972, 3, 89.
- Cossey, A. L.; Phillips, J. N. *Chem. Ind. (London)* 1970, 58.
- Hilton, J. L.; Monaco, T. J.; Moreland, D. E.; Genter, W. A. *Weeds* 1964, 12, 129.
- Hoffman, C. E. *Pestic. Chem., Proc. Int. IUPAC Congr. Pestic. Chem., 2nd, 1971* 1972, 5, 65.
- Kearney, P. C.; Kaufman, D. D. "Herbicides", 2nd ed.; Marcel Dekker: New York, 1975; p 294.

Received for review April 7, 1980. Revised January 5, 1981.
Accepted February 23, 1981.