Synthesis and Nematocidal Activity of 2-Pyridyl Alkanesulfonates

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A series of halo-2-pyridyl alkanesulfonates was prepared by treatment of a 2-pyridinol with an alkanesulfonyl chloride in the presence of a base. Some of these compounds were highly active against root-knot nematodes in greenhouse tests. The most active was 3,5-dichloro-2-pyridyl methanesulfonate, which gave control at 4.5 lb. per acre. These sulfonate esters are relatively stable on storage at room temperature, but hydrolyze readily in aqueous base.

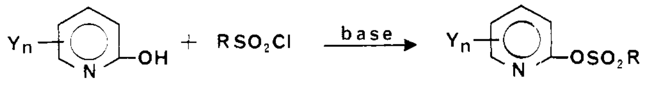
The nematocides which have been introduced in the last few years differ from the fumigants which were previously the only materials available to the grower. Fumigants are relatively volatile halogenated hydrocarbons which diffuse readily through the soil because of their high vapor pressure. The newer nematocides are nonvolatile and depend upon water to move them through the soil. A discussion of these newer nematocides was published recently (Perry, 1967).

In 1964, McBeth *et al.* described a new nonfumigant nematocide, 2,4-dichlorophenyl methanesulfonate, which, although not highly toxic to root-knot nematodes, gave good control against this pest. It was suggested that the material was a very slow killer and might be acting as a nematode repellent. It occurred to us that certain analogs might have even greater activity against nematodes.

The literature contains very few references to sulfonate esters of pyridinols. 2-Pyridyl alkanesulfonates have not been reported previously, and 3-pyridyl methanesulfonate is the only alkanesulfonate which has been described. It was prepared as a cholinesterase inhibitor by Ginsburg (1962), who treated 3-pyridinol with methanesulfonyl chloride, employing 2,6-lutidine as the hydrogen chloride acceptor. A recent U.S. patent (De Selms, 1968) claims, but does not give the physical properties of, 2-nitro-3-pyridyl alkanesulfonates. Trichloro- and tetrachloro-4-pyridyl alkanesulfonates were claimed as herbicides in a U.S. patent (Martin, 1966) without giving physical properties. A few pyridyl esters of aromatic sulfonic acids have been reported. For example, the tosylates of 2- and 3- pyridinol were prepared by treatment with *p*-toluenesulfonyl chloride in pyridine, while the unstable 4-pyridinol derivative was made using the sodium salt in ether (Cavallito and Haskell, 1944). The 4-nitrobenzenesulfonate of 2-pyridinol was prepared via the sodium salt (Adams *et al.*, 1949).

We report a series of 2-pyridyl alkanesulfonates, many of which have been found to be effective against the root-knot nematode in greenhouse tests.

These esters were prepared (Table I) by treating substituted 2-pyridinols with the appropriate alkanesulfonyl chloride in the presence of various bases in non-aqueous (pyridine, triethylamine, sodium carbonate slurry with butanone) and in aqueous systems (sodium hydroxide, potassium hydroxide).



Chlorination of 2-pyridyl methanesulfonate is a poor route to the chlorinated pyridyl ester. In one synthesis, 2-pyridyl methanesulfonate was chlorinated at 25° C. in chloroform, and gas chromatographic analysis showed the following products: 2% 5-chloro-, 3% 3,5-dichloro-2-pyridyl methanesulfonate, and 13% 3,5-dichloro-2-pyridinol.

2-Pyridyl alkanesulfonates are stable at room temperature. Storage for long periods of time, especially at elevated temperature (40°), will, however, lead to gradual decomposition. This is a hydrolytic phenomenon inasmuch as 3,5-dichloro-2-pyridinol and methanesulfonic acid are found as the decomposition products of XII (see Table I). The rate of hydrolysis is highly dependent upon pH. With dilute solutions (0.01*M*) of XII in buffered 50% aqueous methanol at pH 5.8, 7.0, and 10.0, the number of days required for complete hydrolysis at 25° were >36, 16, and 1, respectively. The rate of hydrolysis of XII was followed by observing the decrease in UV absorption, λ_{max} 276 mμ (ϵ 3680), and the concomitant increase in absorption of the hydrolysis product, 3,5-dichloro-2-pyridinol, λ_{max} 320 mμ (ϵ 6470).

NEMATOCIDAL ACTIVITY

Greenhouse tests were carried out at Boyce Thompson Institute, Yonkers, N. Y., using soil infected with root-knot nematodes, *Meloidogyne incognita*, prepared as follows: 125 cc of air-dried soil plus sand mixture (2:1) is infested with a stock of root-knot nematodes prepared 7–10 days previously (at the rate of 6–7 g of chopped galls per gallon of soil). A 10-ml. aliquot of the chemical and surfactant (Triton X-100; Rohm & Haas Co.) at a weight ratio of 3.5:1 at 37 lb. per acre or less (14:1 and 7:1 at 150 and 75 lb. per acre, respectively) is poured onto the surface, and the containers are capped and shaken vigorously 1 hour later. The samples are incubated for 5 to 7 days, shaken again, and then 4 cucumber seeds are placed on the surface of the soil and covered with 1/2 inch of sand. After 3 to 4 weeks, the roots are examined for galls and the response is rated. The results of the tests obtained in this study are given in Tables II and III.

Some of the mono- and dihalo-2-pyridyl alkanesulfonates were quite active, while the unhalogenated compound had little if any activity. The dichloro compound (XII) was considerably more active than the dibromo compound (XI). Introduction of a methyl group in the 6-position led to the complete loss of nematocidal activity of the 3,5-dihalo compounds (XVIII, XIX) but not of the 5-bromo-2-pyridyl methanesulfonate (X). With a given chloropyridinol, the activity decreased as the alkanesulfonate chain length was increased. When methanesulfonate was replaced by chloromethanesulfonate, there was less activity, except with the 5-chloro-2-pyridyl esters (IV, V).

Compound XII was the most active of the series in green-

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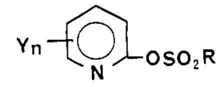
Table I. Physical and Analytical Data for 2-Pyridyl Alkanesulfonates



Compound No.	Pyridinol Yn	R	Yield, %	Method[a]	M.P., ° C.	Analyses					
						Carbon		Hydrogen		Nitrogen	
						Calcd	Found	Calcd	Found	Calcd	Found
I	. . .	CH_3	39	A	54–55	41.61	42.10	4.08	4.14	8.09	8.19
II	5-Br[c]	CH_3	81	B	68–69	28.59	28.41	2.40	2.48	5.56	5.42
III	3-Cl[d]	CH_3	64	B	73.5–75	34.72	34.64	2.91	3.15	6.75	6.71
IV	5-Cl[e]	CH_3	59	A	117–119 (0.01)[b]	34.71	34.50	2.91	3.17	6.75	7.16
V	5-Cl	$ClCH_2$	12	B	46–47.5	29.77	29.41	2.08	2.19	5.79	5.60
VI	6-Cl[f]	CH_3	35	A	34–35	34.72	35.15	2.91	3.16	6.75	6.54
VII	6-Cl	C_4H_9	47	A	126–131 (0.02)[b]	43.30	43.37	4.81	4.97	5.61	5.94
VIII	6-Cl	$C_6H_5CH_2$	39	A	102–103	50.80	50.73	3.55	3.60	4.94	. . .
IX	6-Cl	$ClCH_2$	29	B	41–43	29.77	29.52	2.08	2.45	5.79	5.58
X	5-Br-6-CH_3[g]	CH_3	69	B	60.5–62	31.59	31.26	3.03	2.89	5.26	5.04
XI	3,5-Br_2[c]	CH_3	58	B	76–77	21.77	21.82	1.52	1.46	4.23	4.07
XII	3,5-Cl_2[h]	CH_3	88	E	63–64	29.77	29.54	2.08	2.01	5.79	5.59
XIII	3,5-Cl_2	C_2H_5	25	F	135–137 (0.1)[b]	32.83	33.00	2.76	2.75	5.47	5.51
XIV	3,5-Cl_2	C_3H_7	66	A	36–37	35.57	35.48	3.35	3.30	5.18	5.03
XV	3,5-Cl_2	C_4H_9	53	A	158–162 (0.01)[b]	38.01	38.12	3.90	4.00	4.93	4.77
XVI	3,5-Cl_2	$ClCH_2$	25	C	129–139 (0.03)[b]	26.06	26.04	1.47	1.51	5.07	5.01
XVII	3-Br-5-Cl[i]	CH_3	89	E	82.5–84	25.15	25.20	1.76	1.86	4.89	4.60
XVIII	3,5-Br_2-6-CH_3[g]	CH_3	53	D	87–87.5	24.37	24.60	2.05	2.16	4.06	4.06
XIX	3,5-Cl_2-6-CH_3[d]	CH_3	35	B	49–50	32.83	32.92	2.76	2.75	5.47	5.38

[a] All prepared by treating the pyridinol with one equivalent of alkanesulfonyl chloride, with the following variations: A = with one molar quantity of sodium carbonate in refluxing butanone; B = RSO_2Cl in an organic solvent added to a solution of the pyridinol in an equivalent of 3–4% sodium hydroxide at 25° and then stirred for 15 min.; C = as in B, except that 3% potassium hydroxide is used; D = as in B, except that 1% potassium hydroxide is used; E = triethylamine, 20% excess, used as the base in toluene, at 25° for 1 hour; F = like B, except for 1 hour. [b] Boiling point ° C. (mm.). [c] Chichibabin and Tyashelowa, 1920. [d] Cava and Bhattacharyya, 1958. [e] Kabachnik, 1937. [f] Aldrich Chemical Company. [g] Adams and Schrecker, 1949. [h] Chichibabin and Egorov, 1928. [i] See text.

Table II. Greenhouse Nematocidal Activity of Halo-2-pyridyl Alkanesulfonates

Compound No.	Effectiveness[a] against Root-Knot Nematode *Meloidogyne incognita* at Lb./acre 150	75	37	18
Standard 2,4-Cl_2-$C_6H_3O_3SCH_3$			4, 4	3, 2
I	2, 2			
II	4, 4	4,[b] 3[b]	1, 1	
III		3,[b] 2[b]		
IV	4, 5	5, 5	4, 4	2, 2
V	3, 4	5, 5	5, 5	3, 2
VI	5, 5	5, 4	4, 4	
VII	3, 3			
VIII	3, 2			
IX	3, 3			
X	3, 4	4, 4	2, 2	
XI	3, 4	4, 4	2, 2	
XII	5, 5	5, 5	5, 5	5, 5
XIII	5, 5	5, 5	4, 4	
XIV	4, 3	5, 3	2, 1	
XV	3, 4			
XVI	3, 3			
XVII	4, 4	2, 1		
XVIII	1, 1			
XIX	1, 1			

[a] Rating key: 1 = severe galling (equal to control); 2 = moderate galling; 3 = light galling; 4 = very light galling; 5 = no galling, 100% effective. [b] Tested at 100 lb. per acre. Each value is the rating for an individual pot. Many additional tests for XII are not recorded.

house tests. It was as active, or more so, than all of the commercial nematocides tested (Table III). However, field experiments with XII have shown that larger quantities were needed for good control than were required in the greenhouse. Instability in soil and limited movement appear to be the causes of poor field performance.

SYNTHESES OF COMPOUNDS

Pyridinols. The pyridinols prepared in this study have all been described in the literature (references and melting points are given in the footnotes of Table I), with the exception of 3-bromo-5-chloro-2-pyridinol. The preparation of this material, as well as its precursor, the corresponding 2-amino compound, is given below.

2-Amino-3-bromo-5-chloropyridine. Bromine, 124.5 grams (0.78 mole), was added, with stirring and cooling below 35°, to a solution of 2-amino-5-chloropyridine, 100.0 grams (0.78 mole), in an approximately equimolar quantity of 10% sulfuric acid, 800 grams. After all of the bromine had been added, the mixture was heated on a steam bath for 1 hour, cooled, and allowed to stand in a refrigerator overnight. The mixture was neutralized with 10% sodium hydroxide and the solids were removed by filtration, dried, treated with boiling trichloroethylene, and filtered hot. A yellow solid, 86.3 grams (53%), mp. 81–84°, crystallized from the cooled solution. The analytical sample was purified by recrystallization from 2-propanol, mp. 82–84°.

Anal. Calcd for $C_5H_4BrClN_2$: C, 28.95; H, 1.94; N, 13.50. Found: C, 28.74; H, 1.96; N, 13.32.

3-Bromo-5-chloro-2-pyridinol. Sodium nitrite, 57.5 grams (0.83 mole), was added in small portions at 0° to a solution of 2-amino-3-bromo-5-chloropyridine, 86.3 grams (0.42 mole), in 6*N* sulfuric acid, 580 ml. A large volume of foam resulted, and it was necessary to add water to keep the mixture fluid. The mixture was stirred first at 25° for 1 hour and then on the steam bath for another hour, cooled, and neutralized with dilute sodium hydroxide. The resultant solids were removed by filtration, dried, and recrystallized from 2-propanol, yielding 52.7 grams (61%) of product, mp. 171.5–174°. Additional recrystallization from 2-propanol raised the melting point to 172–174°.

Anal. Calcd for $C_5H_3BrClNO$: C, 28.81; H, 1.45; N, 6.72. Found: C, 28.33; H, 2.03; N, 6.50.

Table III. Greenhouse Nematocidal Activity of Compound XII Compared with Commercial Nematocides

No.	Compound[b]	Effectiveness[a] against *Meloidogyne incognita* at Lb./acre 18	9	4.5
1	3,5-Dichloro-2-pyridyl methanesulfonate (XII)	5, 5, 5	5, 4, 4	2, 4, 3
2	1-Chloro-2,3-dibromopropane (Nemagon)	3, 3	1, 1	. . .
3	2,4-Dichlorophenyl methanesulfonate (SD7727)	3, 2, 2	2, 2, 2	1, 1, 1
4	*O,O*-Diethyl *O-p*-(methylsulfinyl) phenyl phosphorothioate (Dasanit)	5, 5, 5	5, 4, 3	1, 3, 2
5	3,5-Dimethyl-1,3,5-2*H*-tetrahydro-thiadiazine-2-thione (Mylone)	5, 5	3, 3	
6	*O*-Ethyl *S,S*-dipropyl phosphorodithioate (Mocap)	3, 4, 5	2, 2, 3	1, 1, 1
7	*S*-Methyl *N*-(methylcarbamoyloxy) thioacetimidate (Lannate)	4, 3, 3	2, 3, 1	1, 1
8	2-Methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (Temik)	5, 5, 5	5, 5, 4	3, 2, 4
9	Phenyl *N,N'*-dimethylphosphorodiamidate (Nellite)	3, 3, 4	2, 2, 3	. . .
10	Tetrachlorothiophene (Penphene)	4, 4, 4	3, 3, 4	1, 2, 2

[a] Rating key: See Table II footnotes. [b] Sources of materials: 1, International Minerals & Chemical Corp.; 2, Shell Chemical Co.; 3, Shell Chemical Co.; 4, Chemagro Corp.; 5, Union Carbide Corp.; 6, Mobil Chemical Company; 7, Du Pont; 8, Union Carbide Corp.; 9, Dow Chemical Co.; 10, Pennsalt Chemicals Corp.
Each value is the rating for an individual pot.

2-Pyridyl Alkanesulfonates. A total of 19 compounds were synthesized by one of the 6 methods described (Table I). An example of each of the major variations used is described below:

2-Pyridyl Methanesulfonate (Compound I, Method A). A mixture of 2-pyridinol, 28.5 grams (0.30 mole), methanesulfonyl chloride, 34.4 grams (0.30 mole), and anhydrous sodium carbonate, 31.8 grams (0.30 mole), with dried butanone, 300 ml, was stirred and heated at reflux for 4 hours and the hot mixture filtered. The filtrate was evaporated under reduced pressure, leaving an oil which slowly crystallized. The crude material was pressed on a porous plate to remove adherent oil, leaving a white solid, 20.4 grams (39%), mp. 52.5–55°. The analytical sample was purified by recrystallization from ethyl acetate and then from a butanone and hexane mixture to mp. 54–55°.

5-Bromo-2-pyridyl Methanesulfonate (Compound II, Method B). 5-Bromo-2-pyridinol, 20.4 grams (0.117 mole), was dissolved in 1.0 equivalent of 3% sodium hydroxide solution, and to this solution was added methanesulfonyl chloride, 13.5 grams (0.117 mole), in trichloroethylene, 150 ml. The addition was carried out in seven minutes at 21–26°, while maintaining the pH at 10 to 11 by the addition of excess 10% sodium hydroxide solution (13 ml.). The mixture was stirred for another 15 minutes at 25° to complete the reaction, the layers were separated, and the organic layer was washed twice with 25-ml. portions of 5% sodium hydroxide solution and then with water until neutral. Evaporation of the trichloroethylene gave a white solid which had a light oily appearance. Pressing on a porous plate removed the oil, yielding 23.8 grams (81%), mp. 68–69°.

3,5-Dichloro-2-pyridyl Methanesulfonate (Compound XII, Method E). Methanesulfonyl chloride, 57.2 grams (0.50 mole), dissolved in toluene, 100 ml., was added in 15 min. at 25° to a solution of 3,5-dichloro-2-pyridinol, 82.0 g. (0.50 mole), in a mixture of triethylamine, 61.3 g. (0.60 mole), and toluene, 200 ml. The mixture was stirred for 1 hour at 25°, filtered, and the triethylamine hydrochloride washed on the filter with fresh toluene, 200 ml., allowing the washings to combine with the reaction mixture filtrate. Excess triethylamine and some toluene were removed under vacuum, some fresh toluene was replaced, and the solution washed twice with 50-ml. portions of 4% sodium hydroxide, twice with 500-ml. portions of 1% acetic acid, and then with water until neutral. The volatiles were removed completely by stirring under water aspirator vacuum (24 mm.) to 96°, to yield an oil which crystallized. As crystallization began, cyclohexane, 100 ml., was added gradually with stirring and the slurry filtered after 15 minutes. The dried solids weighed 106.8 grams (88%) and had mp. 61–62.5°. The analytical sample, mp. 63–64°, was purified by recrystallization from 2-propanol.

ACKNOWLEDGMENT

The authors are indebted to Philip J. Kotz, Linda J. Hogan, and Raymond P. Mariella, Jr., for assistance in the syntheses of compounds and to L. W. Ferrara and his staff for most of the analytical work.

LITERATURE CITED

Adams, R., Hine, J., Campbell, J., *J. Am. Chem. Soc.*, **71**, 387–90 (1949).
Adams, R., Schrecker, A. W., *J. Am. Chem. Soc.*, **71**, 1186–95 (1949).
Cava, M. P., Bhattacharyya, N. K., *J. Org. Chem.* **23**, 1287–9, 1614–6 (1958).
Cavallito, C. J., Haskell, T. H., *J. Am. Chem. Soc.*, **66**, 1927 (1944).
Chichibabin, A. E., Egorov, A. F., *J. Russ. Phys. Chem. Soc.*, **60**, 683–90 (1928).
Chichibabin, A. E., Tyashelowa, V. S., *J. Russ. Phys. Chem. Soc.*, **50**, 483–92 (1920).
DeSelms, R. C. (to Chevron Research Co.), U.S. Patent **3,409,624** (Nov. 5, 1968).
Ginsburg, S., *J. Med. Pharm. Chem.*, **5**, 1364–7 (1962).
Kabachnik, M. I., *J. Gen. Chem.* (*U.S.S.R.*), **7**, 1749–53 (1937).
Martin, R. T. (to Dow Chemical Co.), U.S. Patent **3,249,419** (May 3, 1966).
McBeth, C. W., White, L. V., Ichikawa, S. T., *Plant Disease Reptr.*, **48**, 634–5 (1964).
Perry, V. G., *Agr. Chem.*, **22**, 36–7, (October 1967).

Received for review June 6, 1969. Accepted October 3, 1969.