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ALKYL ESTERS OF 2-[5-CHLORO(BROMO)-6-METHOXY-4-METHYLPYRIMIDINYL-2-OXY] ALKANOIC ACIDS

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The reaction of a mixture of formaldehyde and sodium cyanide or of lactic acid nitrile with trimethyl(6-methoxy-4-methylpyrimidinyl-2)ammonium chloride give the 2-(6-methoxy-4-methylpyrimidinyl-2-oxy)alkanoic acid nitriles. They were subsequently converted to the corresponding alkyl esters by a Pinner reaction and then to their 2-(5-halo-6-methoxy-4-methylpyrimidinyl-2-oxy) derivatives using N-halosuccinimides.

Keywords: halosuccinimides, pyrimidinyloxyalkanoic acid nitriles and esters, cyanomethylating mixture.

As heterocyclic analogs of the 2,4-dichlorophenoxyalkanoic acids which show high herbicidal activity, we have previously synthesized *sym*-triazinyloxyacetic acids and their derivatives and several of them proved to be plant growth regulators [1]. In this connection there is also interest in the analogous pyrimidine derivatives reported above.

This report is concerned with the synthesis of the methyl and ethyl esters of 2-[5-chloro(bromo)-6-methoxy-4-methylpyrimidinyl-2-oxo]alkanoic acid **1a-f** *via* the corresponding nitriles **2a,b**. The latter were prepared by the action of a mixture of sodium cyanide and formaldehyde or of lactic acid nitrile on the previously reported trimethyl(6-methoxy-4-methylpyrimidinyl-2)ammonium chloride (**3**) [2]. They were converted to the esters **4a-c** by a Pinner reaction. Regioselective halogenation of compounds **4a-c** using N-halosuccinimides (HS) then gave the 5-halo derivatives **1a-f** (Table 1).

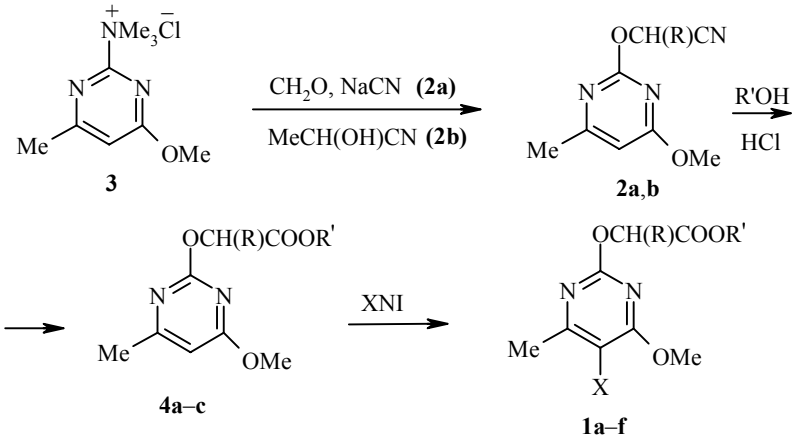

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TABLE 1. Characteristics of Compounds **1a-f**, **4a-c**

Compound*	R	R'	X	Empirical formula	Found, % / Calculated, %				mp, °C	^{1}H NMR spectrum (DMSO-d_6), δ, ppm	Yield, %
					C	H	N	Hal			
1a	H	Me	Cl	$C_9H_{11}ClN_2O_4$	44.14 / 43.81	4.27 / 4.46	11.53 / 11.36	14.69 / 14.41	56-57	4.95 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.65 (3H, s, OCH_3); 2.45 (3H, s, CH_3)	84
1b	H	Me	Br	$C_9H_{11}BrN_2O_4$	37.47 / 37.11	4.00 / 3.78	9.79 / 9.62	27.70 / 27.49	82-84	4.40 (2H, s, OCH_2); 3.78 (3H, s, OCH_3); 3.65 (3H, s, OCH_3); 2.40 (3H, s, CH_3)	72
1c	H	Et	Cl	$C_{10}H_{13}ClN_2O_4$	45.83 / 46.07	5.17 / 4.99	10.51 / 10.75	14.00 / 13.63	78-80	4.95 (2H, s, OCH_2); 4.25 (2H, q, $\underline{CH_2}CH_3$); 4.00 (3H, s, OCH_3); 2.45 (3H, t, CH_3); 1.30 (3H, t, $CH_2\underline{CH_3}$)	69
1d	H	Et	Br	$C_{10}H_{13}BrN_2O_4$	39.59 / 39.34	4.02 / 4.26	9.40 / 9.18	26.47 / 26.23	102-104	4.90 (2H, s, CH_2); 4.17 (2H, q, $\underline{CH_2}CH_3$); 3.92 (3H, s, OCH_3); 2.40 (3H, s, CH_3); 1.20 (3H, t, $CH_2\underline{CH_3}$)	76
1e	Me	Me	Cl	$C_{10}H_{13}ClN_2O_4$	46.34 / 46.07	5.22 / 4.99	11.01 / 10.75	13.90 / 13.63	60-62	5.18 (1H, q, CH); 3.97 (3H, s, OCH_3); 3.65 (3H, s, OCH_3); 2.40 (3H, s, CH_3); 1.60 (3H, d, $CHCH_3$)	80
1f	Me	Me	Br	$C_{10}H_{13}BrN_2O_4$	39.06 / 39.34	3.99 / 4.26	9.36 / 9.18	26.49 / 26.23	61-63	5.20 (1H, q, CH); 3.98 (3H, s, OCH_3); 3.70 (3H, s, OCH_3); 2.45 (3H, s, CH_3); 1.60 (3H, d, $CHCH_3$)	77
4a	H	Me		$C_9H_{12}N_2O_4$	51.27 / 50.94	6.04 / 5.66	12.97 / 13.20		60-62	6.20 (1H, s, Het); 4.45 (2H, s, OCH_2); 3.80 (3H, s, OCH_3); 3.65 (3H, s, OCH_3); 2.45 (3H, s, CH_3)	72
4b	H	Et		$C_{10}H_{14}N_2O_4$	52.84 / 53.10	6.38 / 6.19	12.70 / 12.39			6.10 (1H, s, Het); 4.90 (2H, s, OCH_2); 3.60 (3H, s, OCH_3); 2.35 (3H, s, CH_3); 4.20 (2H, q, $\underline{CH_2}CH_3$); 1.32 (3H, t, $CH_2\underline{CH_3}$)	70
4c	Me	Me		$C_{10}H_{14}N_2O_4$	53.35 / 53.10	6.47 / 6.19	12.08 / 12.39			6.20 (1H, s, Het); 5.10 (1H, q, CH); 3.95 (3H, s, OCH_3); 3.60 (3H, s, OCH_3); 2.40 (3H, s, CH_3); 1.60 (3H, d, $CH\underline{CH_3}$)	80

* Compound **4b** n_D^{20} = 1.4750, **4c** n_D^{20} = 1.4970.

EXPERIMENTAL

IR spectra were recorded for suspensions in vaseline oil on a UR-20 instrument and ^{1}H NMR spectra on a Mercury-300 (300 MHz) spectrometer. Monitoring of the course of the reaction and the purity of the materials obtained was carried out using TLC on Silufol-254 plates in the system acetone-hexane, 1:2.

Parameters for compounds **1a-f** and **4a-c** are given in Table 1.

(6-Methoxy-4-methylpyrimidinyl-2-oxy)acetonitrile (2a) was obtained as described in [3] using the cyanomethylating mixture (NaCN + 36% CH_2O) and compound **3**.

2-(6-Methoxy-4-methylpyrimidinyl-2-oxy)propiononitrile (2b). A solution of NaOH (0.44 g, 0.011 mol) in water (2 ml) was added portionwise to compound **3** (2.2 g, 0.01 mol) in lactic acid nitrile (2.8 ml, 0.04 mol) at 0°C. The mixture was stirred for 1 h at 0°C and 30 min at 20-22°C. Water (10 ml) was added to the reaction mixture and the resultant oil was extracted with ether (2 × 10 ml) and the extract dried over $MgSO_4$. After distillation of the ether and the excess of starting nitrile at 83-84°C (15 mm Hg), the residue was redistilled in vacuo to give compound **2b** (1.35 g, 70%); bp 122-124°C (2 mm Hg). IR spectrum, ν, cm^{-1}: 2260 (C≡N), 1585, 1560, 1505 (C=N, C=C), 1165, 1120 (C–O–C). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 6.20 (1H, s, Het); 5.20 (1H, q, OCH); 3.90 (3H, s, OCH_3); 2.45 (3H, s, CH_3); 1.60 (3H, d, $CHCH_3$). Found, %: C 56.2; H 5.9; N 21.9. $C_9H_{11}N_3O_2$. Calculated, %: C 55.9; H 5.7; N 21.8.

Alkyl Esters of 2-(6-Methoxy-4-methylpyrimidinyl-2-oxy)alkanoic Acids (4a-c). Dry hydrogen chloride was passed to saturation point through a solution of the nitrile **2a,b** (0.01 mol) and the corresponding absolute alcohol (0.013 mol) in absolute ether (15 ml) with cooling in an ice salt mixture. The reaction mixture was held for 1 day in the fridge and diluted with absolute ether (15 ml). The resultant imino ester hydrochloride was filtered off and left for 1 day in a desiccator over H_2SO_4. The hydrochloride was then dissolved in water (5 ml) and neutralized using $NaHCO_3$ to pH 7. The product **4a** was filtered off; products **4b,c** were extracted with ether (2 × 10 ml), the extract dried over $MgSO_4$, and the ether distilled off to give a yellow, oily residue.

Alkyl Esters of 2-(5-Halo-6-methoxy-4-methylpyrimidinyl-2-oxy)alkanoic Acids (1a-f). A mixture of the ester **4a-c** (0.01 mol) and bromosuccinimide (1.8 g, 0.01 mol) or chlorosuccinimide (1.34 g, 0.01 mol) in chloroform (10 ml) was refluxed for 3 to 3.5 h. After distillation of solvent the residue was triturated with warm water (3 ml) and the precipitated product **1a-f** was filtered, washed on the filter with water (3 ml), and recrystallized from heptane.

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