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Some Methyl 2,5- and 5,6-Dihalonicotinates

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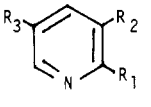
The preparation of the methyl esters of eight dihalonicotinic acids is described. The esters were synthesized either by the methanolysis of their respective acid chlorides or by treatment of the appropriate acid with diazomethane in ether. Experimental and spectral data for the methyl dihalonicotinates are presented.

We have previously reported the synthesis of a series of 2,5- and 5,6-dihalonicotinic acids of potential medicinal interest (*1-5*). As an extension of that work, we now wish to report the preparation and characterization of the methyl esters (I-VIII) of eight of the aforementioned acids.



	R_1	R_2	R_3
I	Cl	Br	CO_2CH_3
II	Cl	F	CO_2CH_3
III	Cl	CO_2CH_3	Br
IV	Cl	CO_2CH_3	Cl
V	Br	Cl	CO_2CH_3
VI	Br	Br	CO_2CH_3
VII	Br	CO_2CH_3	Br
VIII	Cl	CO_2CH_3	I

We found that two standard esterification procedures could be employed. Conversion of the acid to the acid chloride followed by rapid treatment of the latter with methanol proved to be a successful procedure in those instances attempted. Alternatively, direct methylation of the acid with diazomethane in ether was employed in some cases. As indicated in Table I several of the esters were prepared by both methods.

Elemental analyses (C, H, N) for the methyl dihalonicotinates in agreement with theoretical values were obtained and submitted for review as supplementary material. (See paragraph at end of text regarding supplementary material.) Experimental and physical data for the esters reported herein are presented in Table I.

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 337 spectrophotometer with samples prepared as KBr disks. Proton nuclear magnetic resonance spectra were obtained in deuteriochloroform on a Jeolco C-60 HL instrument with tetramethylsilane as internal standard.

Acid Chloride Method. Typical Procedure. A mixture of 5-bromo-6-chloronicotinic acid (*1*) (1.2 g, 0.005 mol) and thionyl chloride (5 mL) was stirred magnetically under gentle reflux for 1 h. The excess thionyl chloride was then removed under reduced pressure (rotary evaporator) leaving the crude acid chloride as a heavy yellow oil. The oil was dissolved immediately in dry benzene (10 mL), and anhydrous methanol (5 mL) was added. The resulting solution was heated under gentle reflux for 1 h. Evaporation of the volatile solvents afforded the

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Table I. Experimental and Spectral Data for Methyl Dihalonicotinates

cmpd	yield,[a] %	mp,[a] °C	method used[b]	IR ν,[c] cm⁻¹	proton NMR,[d] ppm H_4	H_6	CH_3
I	86	76-77	(A) B	1718, 1418, 1362, 1300, 1274, 1205, 1020, 844, 758, 649	8.53 d	8.95 d	4.00 s
II	80	87-88	A	1727, 1592, 1418, 1309, 1282, 1183, 1093, 760, 590	8.03 dd	8.83 d	3.98 s
III	49	48-49	A (B)	1709, 1427, 1403, 1294, 1266, 1111, 1047, 769, 645	8.30 d	8.60 d	3.99 s
IV	42	42-43	(A) B	1704, 1425, 1401, 1292, 1258, 1111, 1042, 766, 649, 587	8.15 d	8.47 d	4.01 s
V	73	68-69	B	1715, 1572, 1412, 1355, 1299, 1266, 1183, 1099, 1015, 755	8.33 m	8.93 m	4.00 bs
VI	89	90-91	B	1718, 1412, 1355, 1299, 1258, 1183, 1099, 1005, 755	8.50 m	8.93 m	4.03 s
VII	89	48-49	B	1712, 1437, 1403, 1383, 1292, 1258, 1105, 1026, 763, 641	8.30 m	8.65 m	4.07 s
VIII	83	75-76	B	1705, 1439, 1399, 1282, 1235, 1183, 1105, 1036, 769, 645	8.50 m	8.78 m	4.10 bs

[a] After recrystallization from aqueous ethanol. [b] A indicates the acid chloride method; B indicates the diazomethane method. Where both methods are indicated, the one in parentheses gave the reported (and highest) yield. [c] Only the most intense absorption bands are reported. [d] Signals were observed in the correct area ratio. s = singlet, d = doublet, m = ill-defined multiplet, bs = broad singlet, dd = doublet of doublets.

crude methyl ester as a yellow-white solid. The crude ester was stirred with a 15% sodium carbonate solution (20 mL) at room temperature for 15 min, filtered, and recrystallized from aqueous ethanol to yield 1.09 g of pure methyl 5-bromo-6-chloronicotinate (I) as white fluffy needles.

Diazomethane Method. Typical Procedure. A freshly prepared solution of diazomethane in ether was slowly added at room temperature to a solution of 2,5-dibromonicotinic acid (*1*) (1.0 g, 0.00356 mol) in anhydrous ether (45 mL) until the yellow color of diazomethane persisted and nitrogen evolution ceased. The ether was allowed to evaporate slowly in the hood draft overnight, affording the crude methyl ester as a white solid. The solid was stirred with a 15% sodium carbonate solution (30 mL) for 15 min, filtered, and recrystallized from aqueous ethanol to yield 0.93 g of pure methyl 2,5-dibromonicotinate (VII) as white fluffy needles.

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Supplementary Material Available: Elemental analyses (C, H, N) for the methyl dihalonicotinates (1 page). Ordering information is given on any current masthead page.

Solubility of Organic Substances in Liquid Xenon

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The solubility of various organic substances in liquid xenon at 60-95-atm pressure and temperatures of 0-40 °C is described. Large organic neutral species dissolve readily; attempts to dissolve ion pairs or free ions failed.

The importance of solvation on proton transfers continues to be a matter of lively interest (*1*). A low-dielectric solvent that does not selectively solvate either anions or cations and is transparent at visible and infrared wavelengths would lend itself to spectrophotometric comparisons with other nonaqueous solvents, such as acetonitrile, dimethyl sulfoxide, and methanol, frequently used by kineticists. There is a considerable literature describing the use of liquid xenon as a solvent (*2*), particularly for simple substances such as CO_2 and CH_3OH dissolved in liquid xenon at low pressures and cryogenic temperatures. Liquid xenon is an attractive solvent to work with because it is either a liquid or a supercritical fluid at easily accessible pressures (60-95 atm) and temperatures (0-40 °C) and because the method of preparing solutions by pressurizing pure gas in a sealed system makes it easy to prepare very pure solutions.

Experimental Methods

Xenon gas with 1 ppm impurity levels was obtained from Cryogenic Rare Gas Laboratories, Inc., Newark, NJ. The materials to be studied were placed in the observation cell, a stainless-steel vessel with three sapphire windows that was constructed from designs reported in the literature (*3*). Valves

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