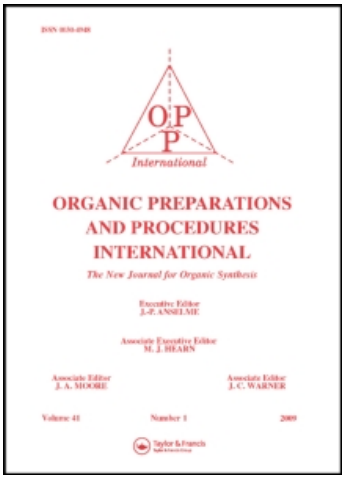

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PREPARATION OF SOME PHOSPHOLIPID-TARGETED METRONIDAZOLE DERIVATIVES

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(dd, $^2J_{CF}$ = 16.2 Hz, $^3J_{CF}$ = 7.3 Hz, 4C, Arom.), 151.4 (dd, $^1J_{CF}$ = 256 Hz, $^4J_{CF}$ = 4 Hz, 2C, CF), 163.0 (s, 4C, COOH); ^{19}F NMR: δ 119.3 (s, 2F). IR (nujol): 1730, 1700 (C=O), 1490, 1440 (Arom.) cm^{-1}. *Anal.* Calcd for $C_{10}H_4F_2O_8$: C, 41.40; H, 1.39; F, 13.10. Found: C, 41.45; H, 1.40; F, 13.20

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PREPARATION OF SOME PHOSPHOLIPID-TARGETED METRONIDAZOLE DERIVATIVES

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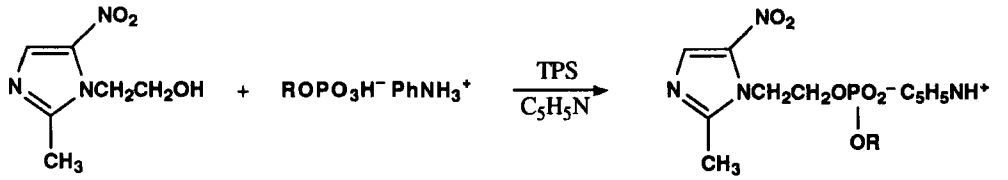
Nitroimidazoles such as metronidazole (**1**) are used clinically against a variety of anaerobic infections and are in trials in cancer therapy.[1] Efforts to improve the effectiveness of the drug have involved directing the nitroimidazole to an important biological target *via* structural modifications. In one approach, a DNA intercalating group, the phenanthridinium ion, was attached to the substrate's side-chain.[2] Interactions potentially also occur at the cell membrane, and to probe the effect of directing to this target, we decided to prepare phosphatidyl derivatives of nitroimidazoles by appropriate substitution in the side chain. Our approach involved the preparation of mixed phosphoric diesters, (RO)(R'O)PO_2H, which is a notoriously difficult task.[3] The present paper describes the synthetic methodology developed for the preparation of phosphoric diesters **2** derived from **1** and simple primary alcohols.

Since anilinium salts of monoalkyl phosphates **3** are readily available,[4] we used those

compounds as substrates in condensation reactions with **1**. Review of condensation methods indicated that 2,4,6-triisopropylbenzenesulfonyl chloride (TPS),[5] applied successfully to the synthesis of glycerophospholipids,[6] should be a reagent of choice.



1 **3** **2**

a) R = C_2H_5; b) R = n-C_8H_{17}; R = n-$C_4H_9CH(C_2H_5)CH_2$

Although the reaction conditions are very simple, isolation of pure **2** can present some problems. The best yields were obtained with the initial molar ratio of monophosphate: metronidazole:TPS = 1:2:3, hence unreacted substrates had to be separated from the desired product. When pyridine was used as a solvent, the anilinium ion introduced in **3** was converted quantitatively into 2,4,6-triisopropylbenzenesulfonanilide (**4**), and the diphosphate esters were obtained as their pyridinium salts **2**. The excess of **1**, by-product **4**, pyridinium 2,4,6-triisopropylbenzenesulfonate (formed from the excess of TPS upon aqueous work-up), and product **2** were separated and recovered with good yields by column chromatography. The results of the synthesis are listed in the Table.

TABLE. Pyridinium Alkyl 2-(2'-Methyl-5'-nitroimidazoyl)ethyl Phosphates (**2**)

R	R_f[a]	Yield (%)	δ_P	Formula	Elemental Analysis[b] Calcd (%)			Found (%)		
					C	H	N	C	H	N
2a	0.05	87	-0.80	$C_{13}H_{19}N_4O_6P$	43.58	5.35	15.64	42.04	5.91	15.15
				(**2a**•H_2O)	41.49	5.62	14.89			
2b	0.26	79	4.02	$C_{19}H_{31}N_4O_6P$	51.58	7.06	12.66	51.12	7.30	12.24
				(**2b**•H_2O)	49.56	7.22	12.17			
2c	0.17	62	3.80	$C_{19}H_{31}N_4O_6P$	51.58	7.06	12.66	49.94	7.21	12.45
				(**2c**•H_2O)	49.56	7.22	12.17			

a) $CHCl_3$/MeOH (3:1, v/v); b) Since all the products are hygroscopic, calculated values for their monohydrates are also given

EXPERIMENTAL SECTION

Metronidazole (**1**) and TPS were purchased from Aldrich and were used as supplied. Anilinium alkylphosphates **3** were prepared as described before.[4] Dry pyridine was obtained by heating under reflux over KOH pellets, distilling, and storing over KOH pellets. Silica gel 60 (0.063-0.200 mm) and TLC plastic plates 60 F_{254} (Merck) were used for column and thin-layer chromatography. ^1H NMR spectra were recorded on a Varian XL 400 MHz spectrometer, and ^{31}P NMR spectra on a Varian XL 200 MHz spectrometer in CD_3OD; chemical shifts are given relative to TMS and 85% phosphoric acid.

Preparation of Phosphorodiesters (2). General Procedure.- Compound **1** and dry salt **3** (molar ratio 2:1) were dissolved in dry pyridine (18 mL per mmol of **3**) and to this solution was added dropwise a solution of TPS (three mol-equivalents) in pyridine (5 mL per mmol of TPS) at room temperature with occasional cooling. The solution was left at room temperature for 5-7 hrs, water (*ca.* 10 vol% of the pyridine used) was added, and the solution was left for another few hours. The solution was evaporated under reduced pressure on a rotary evaporator, and the residual amounts of pyridine and water were removed by lyophilization. The remaining orange, viscous syrup (crude yield 100%) was dissolved in a minimum volume of chloroform and subjected to column chromatography using chloroform as first eluting solvent. Fraction 1: **4** (85-90%), mp. 158-160°. ^{1}H NMR ($CDCl_3$): δ 1.18 (6 H, d, J = 7.1 Hz, 2xMe of *p-i*Pr), 1.30 (12 H, d, J = 7.2 Hz, 4 x Me of *o-i*Pr), 2.87 (1H, septet, J = 7.1 Hz, CH of *p-i*Pr), 4.10 (2 H, septet, J = 7.2 Hz, 2 x CH of *o-i*Pr), 6.80-7.40 (8 H, m, H_{arom}, NH). *Anal.* Calcd for $C_{21}H_{29}NO_2S$: C, 70.15; H, 8.13; N, 3.89. Found: C, 70.04; H, 8.02; N, 4.01.

The eluting solvent was changed to $CHCl_3$/MeOH (3:1, v/v) and the following fractions were collected.

Fraction 2: Unreacted **1** (46-52%), mp. and mixed mp. 159-161°.

Fraction 3: Pyridinium 2,4,6-triisopropylbenzenesulfonate (60-65%), ^{1}H NMR (DMSO-d_6): δ 1.09 (6 H, d, J = 7.0 Hz, 2 x Me of p-iPr), 1.21 (12 H, d, J = 7.1 Hz, 4 x Me of o-iPr), 4.00-4.95 (3 H, m, 3 x CH of iPr), 6.84 (2 H, s, 3-H, 5-H), 8.02-9.13 (5 H, m, pyridinium protons).

Fraction 4: pyridinium alkyl 2-(2'-methyl-5'-nitroimidazoyl)ethyl phosphate (**2**). ^{1}H NMR spectra of **2** corresponded to those of **1** and **3**, but as a result of the condensation, the signal of the OCH_2 in **1** (δ_H 4.36, t, J=5.2 Hz) was shifted downfield (δ_H *ca* 4.6) and increased its multiplicity due to the coupling with the phosphorus nuclei. For example, for **2a**, ^{1}H NMR ($CDCl_3$): δ 1.16 (3 H, t, J = 7.0 Hz, Me of POEt), 2.58 (3 H, s, C_{arom} Me), 3.80 (2H, t, J = 7.1 Hz, NCH_2), 4.23 (2 H, quint, $J_{HH} = J_{HP}$ = 7.0 Hz, CH_2 of POEt), 4.65 (2 H, quart, $J_{HH} = J_{HP}$ = 7.1 Hz, OCH_2 of $POCH_2CH_2N$), 8.07 (1 H, s, H_{arom} of nitroimidazole moiety), 8.12 (2 H, t, J = 5.4 Hz, 3-H_{arom}, 5-H_{arom} of pyridinium ion), 8.66 (1 H, t, J = 5.4 Hz, 4-H_{arom} of pyridinium ion), 8.89 (2 H, d, J = 5.4 Hz, 2-H_{arom}, 6-H_{arom} of pyridinium ion). The ^{1}H NMR spectra of **2b** and **2c** were analogous to that of **2a**, except for the signals resulting from the presence of the *n*-octyl or 2-ethylhexyl group instead of the ethyl group. For other data, see TABLE.

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4-PIPERIDINOPYRIDINE AS AN EFFECTIVE CATALYST FOR THIONE-THIOL REARRANGEMENT OF XANTHATES

Submitted by (11/08/91)

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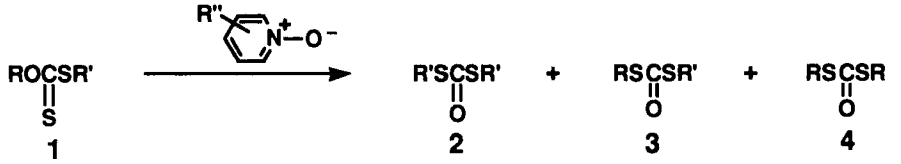
A short synthesis of thiols from alcohol under neutral non-aqueous conditions would be very attractive to synthetic chemists.[1] Thus, combination of the catalytic thione-thiol rearrangement of *O,S*-dialkyl dithiocarbonates (xanthates, **1**) and aminolysis of the rearranged products with ethanolamine serves as an efficient method for the generation of thiols,[2] in which all of the reactions and work-up can be carried out in a single distilling flask. In this context, we reported that pyridine *N*-oxides bearing electron-donating substituents are useful catalysts for the rearrangement of *O,S*-dialkyl xanthates (**1**) to *S,S*-dialkyl dithiocarbonates (**2, 3, 4**).[3]



a) R = Et, R' = Me **b**) R = *n*-Pr, R' = Me **c**) R = *n*-Bu, R' = Me **d**) R = *i*-Pr, R' = Me

Based on these results,[3] we considered that the parent pyridines bearing electron-donating groups might also show similar catalytic activity because they have a high-lying highest occupied molecular orbital (HOMO) with the large HOMO coefficient and a negative net charge on the pyri-