Convenient Preparation of Methyl 10-(1,3,2-Oxazaphospholidin-2-one)undecanoate and Methyl 10-(1,3,2-diazaphospholidin-2-one)undecanoate

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Synthesis and spectral studies of methyl 10-(1,3,2-oxazaphospholidin-2-one)undecanoate and methyl 10-(1,3,2-diazaphospholidin-2-one)undecanoate are reported. These fatty products were obtained in excellent yields when methyl 10-hydroxyundecanoate was reacted with phosphorus oxychloride, and the resultant intermediate was treated with aminoethanol and ethylenediamine in two different reactions.

KEY WORDS: Aminoethanol, ethylenediamine, methyl 10-hydroxyundecanoate, phosphorus oxychloride.

Organophosphorus compounds have achieved considerable interest in recent times. The role of organophosphorus compounds in the life processes of living organisms is well established (1). Phosphorus products are also highly effective for controlling agricultural pests, as herbicides and defoliants (1). In industry, they are used as plasticizers for polymers, hardeners for photomaterials and films, admixtures for increasing the incombustibility of compounds, extractants and as additives in lubricants (1).

Alkyl lysophospholipids inhibit the growth of tumor cell invasion and metastasis and enhance the tumoricidal capacity of macrophages (2). Some fatty acid derivatives have shown antileukemic activity (3). Zidovudine, formerly named AZT and a pioneer anti-AIDS drug, is also a phosphorus-containing product (4,5). The broad-spectrum applications of phosphorus products have stimulated attempts to synthesize new fatty phosphorus chemicals.

We focused our efforts on the synthesis of cyclic systems that contain nitrogen and oxygen atoms along with phosphorus. Nitrogen- and oxygen-containing cyclic compounds are well-known for a variety of biological activities. Here, we report the synthetic modifications of methyl 10-hydroxyundecanoate that showed such cyclic systems at C_{10}. This study is a part of our continuing search for structurally new C_{10} fatty acid products (6,7).

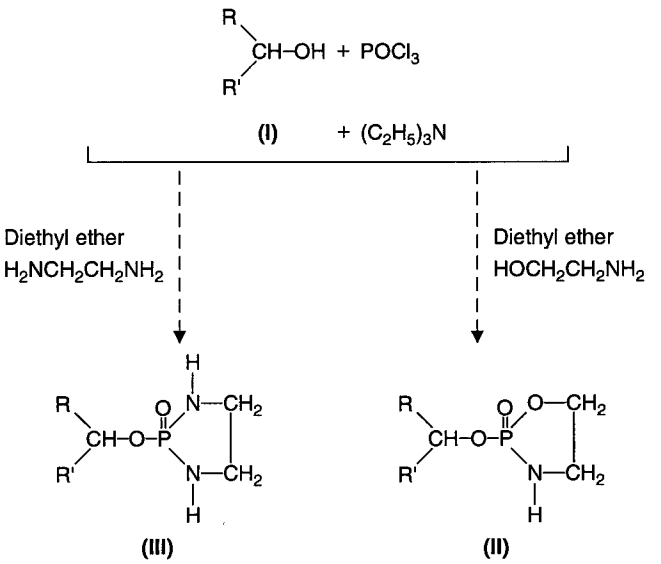
MATERIALS AND METHODS

Similar methods were used as reported earlier (6,7). The 10-hydroxyundecanoic acid (m.p. 49.5°C) was prepared from 10-undecenoic acid (commercial grade; Aldrich Chemical Co., St. Louis, MO) by a previously known method (8). Its carboxylic group was converted to the methyl ester by CH_3OH/H^+. Infrared was measured neat and nuclear magnetic resonance in $CDCl_3$ on a Shimadzu 408 spectrophotometer (Kyoto, Japan) and on a Varian A 60 MHz spectrometer (Palo Alto, CA), respectively. Mass spectra were recorded on a JEOL JMS-D 300 mass spectrometer at 70 eV (JEOL, Ltd., Tokyo, Japan).

Reactions of methyl 10-hydroxyundecanoate (I) and phosphorus oxychloride with aminoethanol and ethylenediamine (Scheme 1): Fatty alcohol (I) was added to a solution of phosphorus oxychloride and triethylamine, under nitrogen, in dry diethyl ether at 0°C. The reaction was stirred for 30 min. To this, triethylamine and amine reactant was added at room temperature. The reaction mixture was stirred for 5 h. Its completion and formation of the major product was monitored by thin-layer chromatography. The reaction mixture was filtered, washed with water and dried over anhydrous sodium sulfate. Purification of the major product was carried out by column chromatography (silica gel) with petroleum ether (PE) as eluent.

Product (II): I (1 g; 4.62 mmol), phosphorus oxychloride (0.65 mL; 6.93 mmol), triethylamine (0.42 mL; 3 mmol + 0.56 mL; 4 mmol = 0.98 mL; 7 mmol); diethyl ether (25 mL); aminoethanol (423 mg; 6.93 mmol); column chromatography (PE, 90:10, vol/vol). Oily product (II), which failed several attempts of crystallization; yield, 80%. Analysis: $C_{14}H_{28}O_5NP$: C, 52.38%; H, 8.79%; N, 4.36%; found: C, 52.3%; H, 8.7%; N, 4.3% theoretical.

Product (III): I (1 g, 4.62 mmol); phosphorus oxychloride (0.65 mL; 6.93 mmol); triethylamine (0.42 mL; 3 mmol + 0.56 mL; 4 mmol = 0.98 mL; 7 mmol); diethyl ether (25 mL); ethylene diamine (416 mg; 6.93 mmol); column chromatography (PE, 85:15, vol/vol). Oily product (III), which failed several attempts of crystallization; yield, 77%. Analysis: $C_{14}H_{29}O_4N_2P$; C, 52.59%; H, 9.15%; N, 8.79%; found: C, 52.5%; H, 9.1%; N, 8.7%, theoretical.



SCHEME 1

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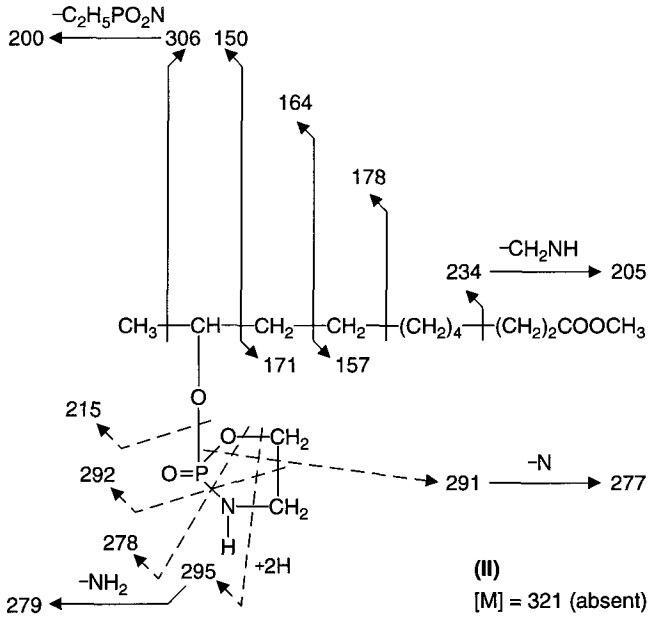
RESULTS AND DISCUSSION

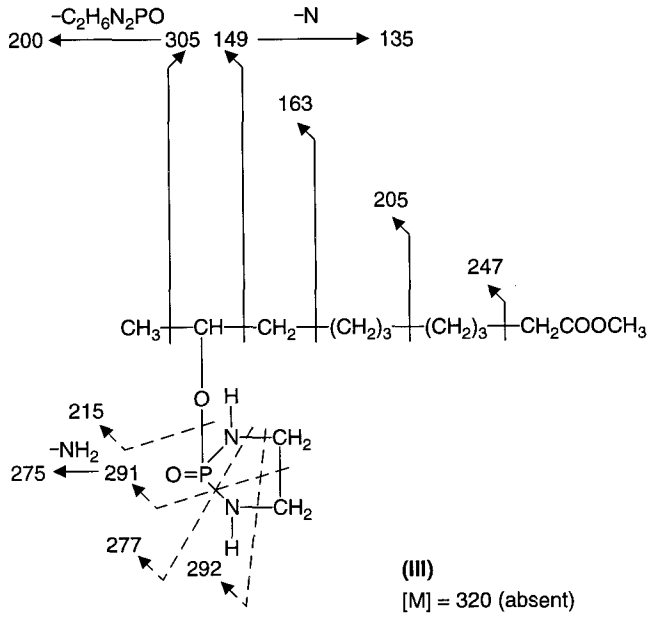
Methyl 10-hydroxyundecanoate (**I**), on treatment with $POCl_3$, $(C_2H_5)_3N$ and aminoethanol, gave a light-yellow, viscous reaction mixture, which on purification over a silica-gel column afforded an oily product (**II**). Presence of P and N atoms in **II** was revealed by infrared (IR) bands at 3350 (NH stretching), 1240 (NH-CH_2), 1260 (P=O) and 1155 cm^{-1} (P-O-alkyl). Other significant bands were at 1730 (-$COOCH_3$) and 1370 (OCH_2). The NMR spectrum showed diagnostic signals, a triplet at δ 5.4 (1H, HN-CH_2, D_2O exchangeable), a broad multiplet at 4.2-3.85 (3H, CH_2N, signal of methine proton, CHO, partly merged with the signal of CH_2N protons), a triplet at 3.4 (2H, -OCH_2) and a doublet at 1.45 (3H, CH_3-CH, J = 7 Hz). Usual fatty acid ester signals were observed at 3.65 *s*(3H, $COOCH_3$), 2.35*t* (2H, α to ester carbonyl) and 1.3 *br s* (fatty methylene chain). Appearance of one D_2O exchangeable signal (δ 5.4) for one proton (NH) is an indication for the cyclic nature of the compound. These data characterized **II** as methyl 10-(1,3,2-oxazaphospholidin-2-one)undecanoate.

Mass spectroscopy studies (Scheme 2) have further confirmed the cyclic nature of product (**II**). The molecular ion at *m/z* 321 was absent. However, the structure-revealing peaks present were at *m/z* 306 (highest ion peak) and 150, which resulted from cleavage α to oxygen at C_{10}. Cleavage β to oxygen at C_{10} was present at 164. These fragments confirm the position of the ring substituent at the C_{10} carbon.

Similarly, methyl 10-hydroxyundecanoate (**I**), on treatment with ethylenediamine, afforded an oily product (**III**) after silica-gel column chromatography. The IR spectrum was identical as that of **II**, except for the broadening of the band centered at 3350 cm^{-1} (NH stretching). This is due to the presence of two NH groups. Significant bands were at 1735 ($COOCH_3$), 1240 (-HN-CH_2), 1255 (P=O) and 1150 cm^{-1} (P-O-alkyl). Two NMR signals indicated the cyclic nature of **III**. A D_2O-exchangeable broad multiplet centered at δ 5.3 was observed for two protons



SCHEME 2



SCHEME 3

(2 × HN), and another signal was observed as a singlet at δ 3.4 for two methylene groups sandwiched between two nitrogen atoms in the cyclic system. Beside these, there were a doublet at δ 1.6 for terminal methyl protons, a multiplet at 4.1 (CH-O, J = 7 Hz), a singlet at 3.65 (-$COOCH_3$), a triplet at 2.35 (-CH_2-$COOCH_3$) and a broad singlet at 1.3 (fatty chain). These observations characterized **III** as methyl 10-(1,3,2-diazaphospholidin-2-one)undecanoate.

The mass spectrum showed no molecular ion at *m/z* 320. But structure-confirming fragment ions were at *m/z* 305 (highest ion peak) and 149, which came from cleavage α to the oxygen at C_{10} carbon (Scheme 3). Cleavage β to the oxygen at C_{10} was also observed from *m/z* 163.

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