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Simple and Efficient Synthesis of New *O*,*O*-Diethyl Phosphorothioates*

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Abstract—A simple and highly effective method was developed for the synthesis of new *O*,*O*-diethyl phosphorothioates from *O*,*O*-diethyl phosphorochloridothioate and 2-chloroquinolin-3-ylmethanol derivatives in the presence of sodium hydroxide.

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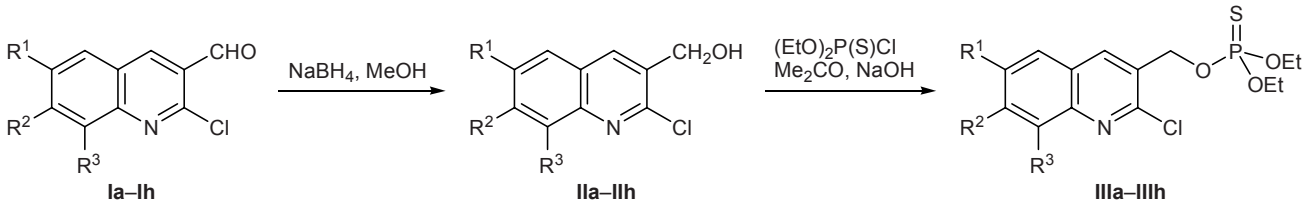
Quinolines [1] constitute an important class of heterocyclic compounds which exhibit versatile biological activity, including bactericidal [2], antitumor [3], anti-inflammatory [4], and antimalarial [5]. Such quinolines as 2-chloroquinoline-3-carbaldehyde occupy a prominent position as key intermediates for further annelation and various modifications of functional groups [6]. Organic phosphates are potent pesticides which have a variety of applications [7]. Recently, some new vinyl phosphates have been reported as potent inhibitors of phosphatase [8] and phosphodiesterase [9]. There are only a few reports on the synthesis and biological activity of their analogs possessing insecticidal [10] and antifungal [11] activity. Phosphonates [12] and α-aminophosphonates are important biologically active compounds [13] due to their structural analogy to amino acids, and they have become the subject of considerable interest. They act as peptide mimics [14], enzyme inhibitors [15], antibiotics, and pharmacological agents [16]. Phosphorothioates have found a wide range of applications in industrial, agricultural, and medicinal chemistry due to their biological and physical properties, as well as synthetic intermediates [17]. Phosphorothioate-based pesticides and analogs of biologically active phosphoric diesters were prepared [18]. In the recent years, a number of phosphorothioates have been proposed as potential chemotherapeutic agents [19] and inhibitors of some enzymes [20].

Phosphorothioates are commonly synthesized by reaction of dialkyl phosphites with sulfenyl chlorides [21], sulfenyl cyanides [22], thiosulfonates [23], disulfides [24], and sulfur [25], as well as by condensation of phosphorochloridates with thiols [26]. All these methods suffer from some disadvantages, including drastic reaction conditions and severe side reactions.

In continuation of our work related to phosphorus chemistry [27], we were interested in the synthesis of new *O*,*O*-diethyl phosphorothioates. In the present article we report on a two-step synthesis of new *O*,*O*-diethyl phosphorothioates containing highly bioactive quinoline moiety. In the first step, 2-chloroquinolin-3-ylmethanol derivatives **IIa**–**IIh** were synthe-

Scheme 1.



I–**III**, $R^1 = R^2 = R^3 = H$ (**a**); $R^1 = Me$, $R^2 = R^3 = H$ (**b**); $R^1 = R^3 = H$, $R^2 = Me$ (**c**); $R^1 = R^2 = H$, $R^3 = Me$ (**d**); $R^1 = MeO$, $R^2 = R^3 = H$ (**e**); $R^1 = R^3 = H$, $R^2 = MeO$ (**f**); $R^1 = R^2 = H$, $R^3 = Et$ (**g**); $R^1 = EtO$, $R^2 = R^3 = H$ (**h**).

* The text was submitted by the authors in English.

sized by reduction of the corresponding substituted 2-chloroquinoline-3-carbaldehydes **Ia**–**Ih** with sodium tetrahydridoborate in methanol at room temperature, and in the second step compounds **IIa**–**IIh** were converted into *O*,*O*-diethyl *O*-(2-chloroquinolin-3-yl)-methyl phosphorothioates **IIIa**–**IIIh** by treatment with *O*,*O*-diethyl phosphorochloridothioate in acetone in the presence of sodium hydroxide (Scheme 1). Phosphorothioates **IIIa**–**IIIh** were isolated in almost quantitative yield and were characterized by elemental analyses and IR, ^{1}H NMR, and mass spectra.

Thus the proposed procedure ensures synthesis of new *O*,*O*-diethyl phosphorothioates from (2-chloroquinolin-3-yl)methanol derivatives using *O*,*O*-diethyl phosphorochloridothioate in the presence of sodium hydroxide under mild conditions in a short time and with almost quantitative yields. It may be useful for combinatorial chemistry.

EXPERIMENTAL

2-Chloroquinoline-3-carbaldehydes **Ia**–**Ih** were prepared according to the procedure described previously [28] and were purified by column chromatography over silica gel (60–120 mesh). *O*,*O*-Diethyl phosphorochloridothioate was commercial product (Lancaster). Acetone, sodium tetrahydridoborate, sodium hydroxide, and methanol were purchased from S.D. Fine-Chem. All melting points were determined in open capillaries on Kumar's melting point apparatus. The ^{1}H NMR spectra were recorded on a Varian Mercury Plus spectrometer (400 MHz) from solutions in $CDCl_3$ using TMS as internal standard. The IR spectra were measured in KBr on a Perkin-Elmer FTIR instrument. The mass spectra were obtained on a Micromass Quattro II mass spectrometer (electrospray ionization). The purity of products and the progress of reactions were monitored by TLC on Merck silica gel plates.

2-Chloro-6-methylquinolin-3-ylmethanol (IIb). Sodium tetrahydridoborate, 0.2 g (5.2 mmol) was slowly added under stirring at room temperature to a solution of 1.5 g (7.2 mmol) of 2-chloro-6-methylquinoline-3-carbaldehyde (**Ib**) in 10 ml of methanol. The progress of the reaction was monitored by TLC using hexane–ethyl acetate as eluent. When the reaction was complete (10 min), the mixture was concentrated under reduced pressure, the residue was treated with ice water, and the precipitate was filtered off, washed with water, and dried in an oven at 50°C for 8.0 h. Yield 1.44 g (95.4%), mp 144–146°C. Mass spectrum, *m*/*z*: 207.8 $[M + 1]^+$, 209.9 $[M + 3]^+$.

Compounds **IIa** and **IIc**–**IIh** were synthesized in a similar way. Listed below are comp. no., yield (%), and melting point, °C: **IIa**, 95, 166–168; **IIc**, 96, 131–133; **IId**, 94, 160–162; **IIe**, 97, 129–131; **IIf**, 95, 122–124; **IIg**, 97, 120–122; **IIh**, 94, 130–132.

***O*-(2-Chloro-6-methylquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIb).** *O*,*O*-Diethyl phosphorochloridothioate, 1.5 g (7.9 mmol), was added under stirring to a solution of 1.0 g (4.8 mmol) of 2-chloro-6-methylquinolin-3-ylmethanol and 0.5 g (12.5 mmol) of sodium hydroxide in 10 ml of acetone, and the mixture was stirred until the reaction was complete (20 min; TLC, hexane–ethyl acetate, 8:2). The mixture was poured on crushed ice, and the precipitate was filtered off, washed with water, and dried in a vacuum oven at 40°C for 6.0 h. Yield 1.70 g (98.3%), mp 71–73°C. IR spectrum, ν, cm^{-1}: 2989 (C–H), 1242 (P=S), 1021 (P–O–C). ^{1}H NMR spectrum, δ, ppm: 1.31–1.40 t (6H, $CH_2C\mathbf{H}_3$, J = 8 Hz), 2.53 s (3H, 6-CH_3), 4.14–4.22 m (4H, $OC\mathbf{H}_2CH_3$), 5.27 d (2H, 3-CH_2, J = 9 Hz), 7.56 d (1H, 7-H, J = 8 Hz), 7.61 s (1H, 5-H, J = 8 Hz), 7.92 d (1H, 8-H, J = 8 Hz), 8.20 s (1H, 4-H). Mass spectrum, *m*/*z*: 360.1 $[M + 1]^+$, 362.1 $[M + 3]^+$. Found, %: C 50.12; H 5.45; N 3.75. $C_{15}H_{19}ClNO_3PS$. Calculated, %: C 50.07; H 5.32; N 3.89.

Compounds **IIIa** and **IIIc**–**IIIh** were synthesized in a similar way.

***O*-(2-Chloroquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIa).** Reaction time 25 min. Yield 95%, mp 52–54°C. IR spectrum, ν, cm^{-1}: 2992 (C–H), 1234 (P=S), 1032 (P–O–C). ^{1}H NMR spectrum, δ, ppm: 1.31–1.35 t (6H, $CH_2C\mathbf{H}_3$, J = 8 Hz), 4.14–4.22 m (4H, $OC\mathbf{H}_2CH_3$), 5.29 d (2H, 3-CH_2, J = 8 Hz), 7.56 t (1H, 6-H, J = 8 Hz), 7.72 t (1H, 7-H, J = 8 Hz), 7.84 d (1H, 5-H, J = 8 Hz), 8.00 d (1H, 8-H, J = 8 Hz), 8.28 s (1H, 4-H). Mass spectrum, *m*/*z*: 346.0 $[M + 1]^+$, 348.0 $[M + 3]^+$. Found, %: C 48.72; H 4.98; N 4.15. $C_{14}H_{17}ClNO_3PS$. Calculated, %: C 48.63; H 4.96; N 4.05.

***O*-(2-Chloro-7-methylquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIc).** Reaction time 25 min. Yield 96%, mp 53–55°C. IR spectrum, ν, cm^{-1}: 2981 (C–H), 1231 (P=S), 1028 (P–O–C). ^{1}H NMR spectrum, δ, ppm: 1.30–1.34 t (6H, $CH_2C\mathbf{H}_3$, J = 8 Hz), 2.55 s (3H, 7-CH_3), 4.13–4.20 m (4H, $OC\mathbf{H}_2CH_3$), 5.27 d (2H, 3-CH_2, J = 8 Hz), 7.39 d (1H, 6-H, J = 8 Hz), 7.72 d (1H, 5-H, J = 8 Hz), 7.78 s (1H, 8-H), 8.22 s (1H, 4-H). Mass spectrum, *m*/*z*: 360.1 $[M + 1]^+$, 362.0 $[M + 3]^+$. Found, %: C 50.18; H 5.35;

N 3.84. $C_{15}H_{19}ClNO_3PS$. Calculated, %: C 50.07; H 5.32; N 3.89.

***O*-(2-Chloro-8-methylquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIId).** Reaction time 25 min. Yield 97%, bp 164–166°C (760 mm). IR spectrum, ν, cm^{-1}: 2986 (C–H), 1223 (P=S), 1027 (P–O–C). ^1H NMR spectrum, δ, ppm: 1.31–1.39 t (6H, $OCH_2C\mathbf{H}_3$, J = 8 Hz), 2.74 s (3H, 8-CH_3), 4.13–4.21 m (4H, $OC\mathbf{H}_2CH_3$), 5.27 d (2H, 3-CH_2, J = 8 Hz), 7.42 t (1H, 6-H, J = 8 Hz), 7.55 d (1H, 7-H, J = 8 Hz), 7.64 d (1H, 5-H, J = 8 Hz), 8.22 s (1H, 4-H). Mass spectrum, *m*/*z*: 360.1 $[M + 1]^+$, 362.1 $[M + 3]^+$. Found, %: C 50.01; H 5.235; N 3.98. $C_{15}H_{19}ClNO_3PS$. Calculated, %: C 50.07; H 5.32; N 3.89.

***O*-(2-Chloro-6-methoxyquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIe).** Reaction time 20 min. Yield 97%, mp 82–84°C. IR spectrum, ν, cm^{-1}: 2983 (C–H), 1228 (P=S), 1022 (P–O–C). ^1H NMR spectrum, δ, ppm: 1.31–1.35 t (6H, $OCH_2C\mathbf{H}_3$, J = 8 Hz), 3.93 s (3H, 6-OCH_3), 4.14–4.22 m (4H, $OC\mathbf{H}_2CH_3$), 5.27 d (2H, 3-CH_2, J = 8 Hz), 7.10 d (1H, 5-H, J = 4 Hz), 7.36 d.d (1H, 7-H, J = 4, 8 Hz), 7.89 d (1H, 8-H, J = 9 Hz), 8.19 s (1H, 4-H). Mass spectrum, *m*/*z*: 376.0 $[M + 1]^+$, 378.1 $[M + 3]^+$. Found, %: C 47.85; H 5.05; N 3.78. $C_{15}H_{19}ClNO_4PS$. Calculated, %: C 47.94; H 5.10; N 3.73.

***O*-(2-Chloro-7-methoxyquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIf).** Reaction time 20 min. Yield 97%, bp 165–167°C (760 mm). IR spectrum, ν, cm^{-1}: 2987 (C–H), 1234 (P=S), 1032 (P–O–C). ^1H NMR spectrum, δ, ppm: 1.30–1.40 t (6H, $OCH_2C\mathbf{H}_3$, J = 8 Hz), 3.93 s (3H, 7-OCH_3), 4.13–4.21 m (4H, $OC\mathbf{H}_2CH_3$), 5.26 d (2H, 3-CH_2, J = 9 Hz), 7.15 d.d (1H, 6-H, J = 4, 4 Hz), 7.29 d (1H, 8-H, J = 4 Hz), 7.65 d (1H, 5-H, J = 8 Hz), 8.14 s (1H, 4-H). Mass spectrum, *m*/*z*: 376.1 $[M + 1]^+$, 378.1 $[M + 3]^+$. Found, %: C 47.76; H 4.95; N 3.66. $C_{15}H_{19}ClNO_4PS$. Calculated, %: C 47.94; H 5.10; N 3.73.

***O*-(2-Chloro-8-ethylquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIg).** Reaction time 20 min. Yield 97%, bp 183–185°C (760 mm). IR spectrum, ν, cm^{-1}: 2985 (C–H), 1220 (P=S), 1026 (P–O–C). ^1H NMR spectrum, δ, ppm: 1.23–1.41 m (9H, $OCH_2C\mathbf{H}_3$, 8-$CH_2C\mathbf{H}_3$), 3.19 q (2H, 8-CH_2, J = 8 Hz), 4.13–4.21 m (4H, $OC\mathbf{H}_2CH_3$), 5.27 d (2H, 3-CH_2, J = 8 Hz), 7.45 t (1H, 6-H, J = 8 Hz), 7.55 d (1H, 7-H, J = 8 Hz), 7.64 d (1H, 5-H, J = 8 Hz), 8.22 s (1H, 4-H). Mass spectrum, *m*/*z*: 374.1 $[M + 1]^+$, 376.1 $[M + 3]^+$. Found, %: C 51.58; H 5.76; N 3.69. $C_{16}H_{21}ClNO_3PS$. Calculated, %: C 51.41; H 5.66; N 3.75.

***O*-(2-Chloro-6-ethoxyquinolin-3-yl)methyl *O*,*O*-diethyl phosphorothioate (IIIh).** Reaction time 25 min. Yield 98%, mp 76–78°C. IR spectrum, ν, cm^{-1}: 2989 (C–H), 1227 (P=S), 1020 (P–O–C). ^1H NMR spectrum, δ, ppm: 1.31–1.34 t (6H, $OCH_2C\mathbf{H}_3$, J = 8 Hz), 1.46 t (3H, 6-$OCH_2C\mathbf{H}_3$, J = 8 Hz), 4.11–4.21 m (6H, $OC\mathbf{H}_2CH_3$), 5.26 d (2H, 3-CH_2, J = 8 Hz), 7.07 d (1H, 5-H, J = 4 Hz), 7.35 d.d (1H, 7-H, J = 4, 4 Hz), 7.88 d (1H, 8-H, J = 8 Hz), 8.15 s (1H, 4-H). Mass spectrum, *m*/*z*: 390.1 $[M + 1]^+$, 392.1 $[M + 3]^+$. Found, %: C 49.42; H 5.32; N 3.69. $C_{16}H_{21}ClNO_4PS$. Calculated, %: C 49.30; H 5.43; N 3.59.

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