ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 4, pp. 518–520. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © D.A. Tatarinov, A.V. Bogdanov, B.I. Buzykin, V.F. Mironov, 2014, published in Zhurnal Organicheskoi Khimii, 2014, Vol. 50, No. 4, pp. 529–531.

Pfitzinger Reaction of Dialkyl(aryl)(2-methyl-4-oxopent-2-yl)phosphine Oxides

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Received January 14, 2014

Abstract—New phosphorus-containing derivatives of quinoline-4-carboxylic acid were synthesized by the Pfitzinger reaction from isatin and dialkyl(aryl)(2-methyl-4-oxopent-2-yl)phosphine oxides.

DOI: 10.1134/S1070428014040137

Derivatives of quinolinecarboxylic acids exhibit a broad spectrum of biological activity. Quinoline-4-carboxylic acid amides and hydrazides display antimicrobial [1], antitubercular, anti-inflammatory, and analgesic activity [2–5]. Some derivatives were found to possess antiproliferative activity [6].

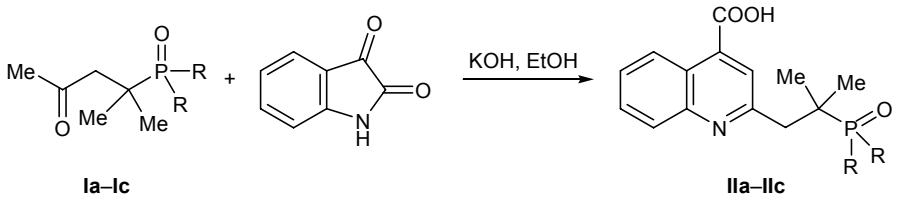
In recent years, quinoline derivatives containing a phosphonate or phosphine oxide fragment have been reported [7, 8] and shown to exhibit biological activity, e.g., anti-inflammatory [9]; some compounds are nucleoside analogs and are active against human immunodeficiency virus [10]. Nevertheless, no quinoline-4-carboxylic acid derivative with a phosphorus-containing substituent on C^2 has been reported so far.

We have recently shown that conjugation of Isoniazid with the anti-acidotic drug Dimephosphon, dimethyl (2-methyl-4-oxopent-2-yl)phosphonate [11], or its P,C-analogs, dialkyl(2-methyl-4-oxopent-2-yl)-phosphine oxides [12], considerably reduces the toxicity without affecting the therapeutic effect [13, 14]. Therefore, it seemed reasonable to synthesize quinoline-4-carboxylic acid derivatives containing a dialkyl-(or aryl)phosphorylalkyl substituent in the 2-position.

In the present article we describe the synthesis of new phosphorus-containing quinoline-4-carboxylic acid derivatives by the Pfitzinger reaction of isatin with dialkyl(aryl)(2-methyl-4-oxopent-2-yl)phosphine oxides. Unlike the procedure reported in [15] where the reactions of isatins were carried out using a large excess of volatile carbonyl compounds, we used equimolar amounts of isatin and oxoalkylphosphine oxides **I** (Scheme 1). The yields of quinolines **IIa**–**IIc** were 50–70%, and the reaction mixtures contained some amounts of unreacted isatin and aldolization products of initial phosphorus-containing ketone **I**. Pure quinolinecarboxylic acids **IIa**–**IIc** were isolated by recrystallization from acetone. The reaction involves exclusively the methyl group neighboring to the carbonyl group with formation of only one regioisomer, which may be rationalized by the effect of steric factor on the Pfitzinger reaction [15].

The product structure was determined by spectral methods. The MALDI mass spectra of **IIa**–**IIc** displayed peaks corresponding to the protonated molecular ions $[M + H]^{+\cdot}$. Their ^1H NMR spectra contained upfield signals from protons of the methyl groups in

Scheme 1.



Ia–Ic **IIa–IIc**

R = Ph (**a**), Et (**b**), Bu (**c**).

the α-position with respect to phosphorus (doublets at δ 1.2–1.3 ppm, $^3J_{PH}$ = 15.3–15.7 Hz). The signal from protons in the 2-CH_2 group appeared as a doublet in a weaker field (δ 3.2–3.4 ppm, $^3J_{PH}$ = 7.2–8.0 Hz). The position and multiplicity of signals from the alkyl or aromatic groups on the phosphorus atom in the ^{1}H NMR spectra of compounds **II** were identical to those observed for previously described phosphine oxides **I** [12]. Signals from protons in the quinoline fragment were typical of 2-substituted quinoline-4-carboxylic acids.

Phosphorus-containing quinoline-4-carboxylic acids **IIa–IIc** attract interest as potential biologically active compounds. In addition, the presence in their molecules of phosphine oxide and carboxy groups makes these compounds promising as complexing agents.

EXPERIMENTAL

The ^{1}H and ^{31}P–{^{1}H} NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 and 161.0 MHz, respectively, from solutions in $CDCl_3$ using the residual proton signal of the solvent as reference. The IR spectra were measured on a Bruker Vector-22 instrument from samples dispersed in mineral oil or films placed between KBr plates. The MALDI mass spectra were obtained on a Bruker Daltonics UltraFlex III TOF/TOF mass spectrometer in the linear mode (Nd:YAG laser, λ 355 nm). The data were processed using FlexAnalysis 3.0 program (Bruker Daltonics), positive ions were detected, samples were deposited onto a metal target, and 2,5-dihydroxybenzoic acid was used as matrix.

Compounds **IIa–IIc** were synthesized according to the procedure described in [16]. A mixture of 1 g (6.8 mmol) of isatin and 1.9 g (33.9 mmol) of potassium hydroxide was dissolved in a mixture of 5 mL of ethanol and 10 mL of water, the mixture was stirred for 5 min at 20°C, 6.8 mmol of phosphine oxide **Ia–Ic** was added, and the mixture was heated for 8 h under reflux with stirring. The mixture was then cooled to 20°C and acidified to pH ~5–6 with 10% aqueous HCl. Compound **IIa** separated from the solution and was filtered off. Compounds **IIb** and **IIc** were extracted into methylene chloride (3×30 mL), the combined extracts were dried over sodium sulfate and evaporated on a rotary evaporator, and the residue was recrystallized from acetone and dried at 100°C under reduced pressure (10 mm).

2-[2-(Diphenylphosphoryl)-2-methylpropyl]-quinoline-4-carboxylic acid (IIa). Yield 2.3 g (79%), white powder, mp 217–219°C. IR spectrum, ν, cm^{-1}: 3365, 3060, 2962, 2926, 2855, 2716, 2521, 2467, 1967, 1921, 1702, 1592, 1462, 1437, 1370, 1340, 1316, 1264, 1237, 1212, 1188, 1159, 1136, 1115, 1089, 1027, 1000, 932, 853, 801, 772, 754, 723, 707, 637, 577, 558, 540, 519. ^{1}H NMR spectrum, δ, ppm: 1.22 d (6H, CH_3, $^3J_{PH}$ = 15.7 Hz), 3.21 d (2H, CH_2, $^3J_{PH}$ = 8.0 Hz), 7.40–7.56 m (7H, *m*-H, *p*-H, 6-H), 7.64 m (1H, 7-H, $^3J_{HH}$ = 7.4 Hz), 7.69 s (1H, 3-H), 7.94 d (1H, 8-H, $^3J_{HH}$ = 8.9 Hz), 7.99 br.d.d (4H, *o*-H, $^3J_{HH}$ = 8.4, $^3J_{PH}$ = 8.3–8.5 Hz), 8.69 d (1H, 5-H, $^3J_{HH}$ = 8.4 Hz). ^{31}P–{^{1}H} NMR spectrum: δ_P 37.2 ppm. Mass spectrum (MALDI): *m*/*z* 430 $[M + H]^{+\cdot}$. Found, %: C 72.61; H 5.56; N 3.25; P 7.19. $C_{26}H_{24}NO_3P$. Calculated, %: C 72.72; H 5.63; N 3.26; P 7.21. *M* 429.0.

2-[2-(Diethylphosphoryl)-2-methylpropyl]-quinoline-4-carboxylic acid (IIb). Yield 1.3 g (57%), yellow powder, mp 211–212°C. IR spectrum, ν, cm^{-1}: 3368, 3069, 3040, 2976, 2959, 2922, 2885, 2720, 2422, 1925, 1691, 1587, 1506, 1466, 1422, 1404, 1392, 1356, 1338, 1311, 1265, 1238, 1212, 1189, 1162, 1119, 1036, 1006, 981, 967, 913, 850, 808, 774, 760, 701, 656, 636, 555, 509, 479, 432. ^{1}H NMR spectrum, δ, ppm: 1.29 d (6H, CH_3, $^3J_{PH}$ = 15.4 Hz), 1.35 d.t (6H, $PCH_2C\mathbf{H}_3$, $^3J_{HH}$ = 7.3, $^3J_{PH}$ = 16.0 Hz), 1.85 m (2H, PCH_2, part *A* of *ABMX*$_3$ spin system), 2.02 m (2H, PCH_2, part *B* of *ABMX*$_3$ spin system), 3.43 d (2H, CH_2, $^3J_{PH}$ = 7.6 Hz), 7.61 d.d.d (1H, 6-H, $^3J_{HH}$ = 8.3, 6.9, $^4J_{HH}$ = 1.2 Hz), 7.71 d.d.d (1H, 7-H, $^3J_{HH}$ = 8.3, 6.9, $^4J_{HH}$ = 1.3 Hz), 8.08 s (1H, 3-H), 8.11 d (1H, 8-H, $^3J_{HH}$ = 8.2 Hz), 8.93 d (1H, 5-H, $^3J_{HH}$ = 7.8 Hz). ^{31}P–{^{1}H} NMR spectrum: δ_P 63.5 ppm. Mass spectrum (MALDI): *m*/*z* 334 $[M + H]^{+\cdot}$. Found, %: C 64.83; H 7.31; N 4.23; P 9.27. $C_{18}H_{24}NO_3P$. Calculated, %: C 64.85; H 7.26; N 4.20; P 9.29. *M* 333.0.

2-[2-(Dibutylphosphoryl)-2-methylpropyl]-quinoline-4-carboxylic acid (IIc). Yield 1.25 g (47%), light yellow powder, mp 158–160°C. IR spectrum, ν, cm^{-1}: 3422, 3063, 3038, 2959, 2932, 2872, 2964, 2426, 1938, 1695, 1590, 1556, 1507, 1411, 1369, 1337, 1310, 1259, 1243, 1191, 1164, 1114, 1050, 1027, 1004, 968, 906, 850, 815, 801, 768, 745, 730, 716, 695, 637, 551, 509, 473. ^{1}H NMR spectrum, δ, ppm: 0.97 t [6H, $P(CH_2)_3C\mathbf{H}_3$, $^3J_{HH}$ = 7.3 Hz], 1.29 d (6H, CH_3, $^3J_{PH}$ = 15.3 Hz), 1.48 m [4H, $P(CH_2)_2C\mathbf{H}_2$], 1.64–2.07 m (8H, $PC\mathbf{H}_2C\mathbf{H}_2$), 3.45 d (2H, CH_2, $^3J_{PH}$ = 7.2 Hz), 7.62 m (1H, 6-H, $^3J_{HH}$ = 7.6 Hz), 7.74 m (1H, 7-H, $^3J_{HH}$ = 7.5 Hz), 8.10 s (1H, 3-H), 8.14 d (1H, 8-H, $^3J_{HH}$ =

7.5 Hz), 8.93 d (1H, 5-H, $^{3}J_{HH}$ = 8.4 Hz). $^{31}P–\{^{1}H\}$ NMR spectrum: δ_P 61.6 ppm. Mass spectrum (MALDI): *m*/*z* 390 $[M + H]^{+\cdot}$. Found, %: C 67.79; H 8.32; N 3.58; P 7.92. $C_{22}H_{32}NO_3P$. Calculated, %: C 67.85; H 8.28; N 3.60; P 7.95. *M* 389.0.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 12-03-97042r_povolzh'e) and by the Academy of Sciences of Tatarstan Republic.

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