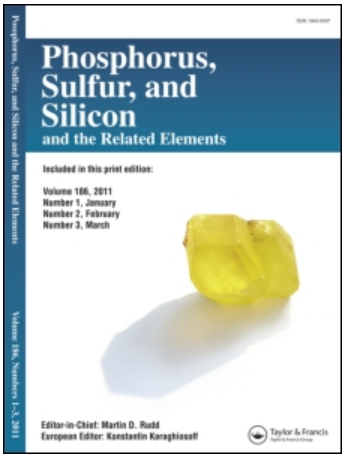

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SYNTHESIS OF PHOSPHONOINDOPROFEN

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Two synthetic routes to phosphonic analogues of indoprofen, a nonsteroidal anti-inflammatory drug, were developed by the cyclization of aniline 2 (method A) and by the Arbuzov reaction of corresponding alkylchloride 3 with triethylphosphite (method B).

Keywords Indoprofen; isoindolin-1-ones; phosphonic acids

INTRODUCTION

Indoprofen (Figure 1) is a nonsteroidal anti-inflammatory drug of the 2-arylpropionic acids (profens) family.[1] The most prominent members of this group of drugs are ibuprofen, naproxen, ketoprofen, and suprofen. Indoprofen is a highly effective drug for use in rheumatoid arthritis, osteoarthritis, and postoperative pain. It increases the production of the SMN-protein, a lack of which causes development of spinal muscular atrophy (SMA), a muscle-wasting and often life-threatening childhood disease.[2–4] However, indoprofen has serious side effects (i.e., gastrointestinal bleeding).[1–4] Therefore, it was important to study analogues of indoprofen that might be effective and well tolerated. In connection with our ongoing program on the syntheses of phosphorous analogues of bioactive and natural compounds,[5–7] we have prepared a phosphonic analogue of indoprofen, taking into account an idea that phosphonates can serve as bioisosters of carboxylic acids.[8,9] The phosphonoindoprofen **1a** was not earlier reported, though phosphonic analogues of some other profens, for example phosphonaproxen, have been described.[10,11]

RESULTS AND DISCUSSION

The diethyl phosphonoindoprofen **1b** was prepared by two methods: by cyclization of para-substituted aniline **2**[12] (method A) and by Arbuzov reaction of chloride **3**[13] with triethylphosphite (method B). The reaction of aniline **2** with methyl *ortho*-brommethylbenzoate **4**[14–19] led first to N-alkylated product **5**, which was then cyclizated

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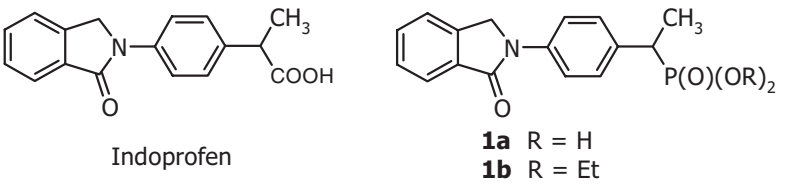
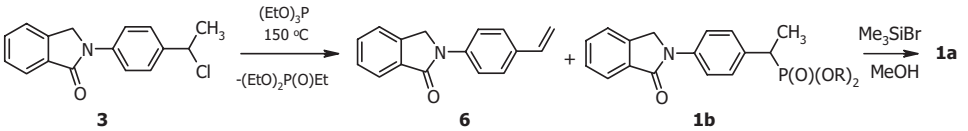


Figure 1 Structures of indoprofen and phosphonoindoprofen.

into isoindolone **1b** (Scheme 1). The conversion of **5** into phosphonoisoindolone **1b** essentially depended on the nature of the base and the solvent, and in all cases resulted in mixture of **1b** and **5.** The highest ratio of products (5:1) was obtained when initial aniline **2** was used as a base. The diethyl phosphonoindoprofen **1b** was purified by crystallization from hexane and obtained as a colorless solid in a yield of 40% (Table I).

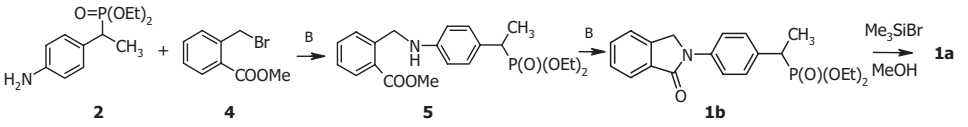


Scheme 1 Synthesis of the phosphonoindoprofen **1a** by method B.

The subsequent treatment of ester **1b** with trimethylsilylbromide and methanol provided the phosphonoindoprofen **1a** in an almost quantitative yield, which was isolated as a pale powder with a melting point of 227–228°C. This compound is slightly soluble in water, but readily soluble in organic solvents such as ethanol.

The Arbuzov reaction of *sec*-alkylchloride **3** with excess of triethylphosphite at 160 °C for 16 h led to the formation of products **1b** and **6** in 4/1 ratio.[20] Crystallization from hexane gave the pure diethyl phosphonoindoprofen **1b** in yield of 32% (Scheme 1). After treatment

Table I Synthesis of the phosphonoindoprofen **1a** by method A



Entry	Solvent	B (n-fold excess)	Temp (°C)	Time (h)	**1b*** (conversion,%)
1	DMF	K_2CO_3 (6)	75	60	75
2	DMF	K_2CO_3 (6)	100	60	75
3	DMF	Cs_2CO_3 (10)	90	60	0
4	Pyridine	Pyridine	115	16	75
5	THF	NaH (2.5)	18	16	66
6	MeOH	Et_3N (4)	65	60	25
7	*n*-PrOH	*i*-Pr_2NEt (3)	97	60	75
8	EtOH	**2** (3)	78	60	83

*According to ^1H NMR spectra.

of the ester **1b** with trimethylsilylbromide and methanol, the phosphonoindoprofen **1a** was obtained in excellent yield.

In conclusion, we have described two alternative synthetic routes to a phosphonic analogue of the nonsteroidal anti-inflammatory drug indoprofen. Both methods, A and B, were accompanied by the formation of byproducts, which were separated by crystallization. The investigation of the biological properties for phosphonoindoprofen is in progress.

EXPERIMENTAL

All commercially available reagents were used without further purification. Melting points are uncorrected. IR spectra were obtained in KBr pellets and were recorded on a Vertex 70 IR Fourier spectrometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured at 300, 100, and 80 MHz, respectively, for DMSO-d_6 solution with TMS as internal or H_3PO_4 as external standard on Varian VXR-300 and Gemini 2000 (400 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in Hz. Elemental analyses were performed in the analytical laboratory of this institute. All solvents were distilled and purified by standard procedures. Compounds **2**,[12] **3**,[13] and **4**[21] were prepared according to published methods.

Synthesis of Diethyl 1-(4-(Isoindolin-1-one-2-yl) phenyl)ethylphosphonate (Diethyl Phosphonoindoprofen) (1b)

Method A. A solution of aminophosphonate **2** (131 mg, 0.51 mmol) and methyl 2-brommethylbenzoate **4** (40 mg, 0.17 mmol) in EtOH (5 mL) was refluxed for a 60 h. After cooling, the reaction mixture was evaporated, dissolved in dichloromethane, washed with 1N HCl, dried over Na_2SO_4, and evaporated again. The residue obtained was refluxed for 5 min with hexane and filtered from insoluble impurities. **1b** crystallized upon cooling as fine colorless needles.

Yield 25 mg (40%); mp 107–108°C. IR (KBr, cm^{-1}), ν_{max}: 561, 735, 802, 820, 848, 957, 1027, 1096, 1158, 1242, 1308, 1331, 1340, 1386, 1456, 1468, 1517, 1610, 1682, 2872, 2902, 2928, 2978. Anal. calcd. for $C_{20}H_{24}NO_4P$ (373.39): C, 64.34; H, 6.48; P, 8.30. Found: C, 64.38; H, 6.50; P, 8.33. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.11 (3H, t, J 7.0 Hz, $CH_2\underline{CH_3}$), 1.22 (3H, t, J 7.0 Hz, $CH_2\underline{CH_3}$), 1.44 (3H, dd, J 18.4, 7.3 Hz, $CH\underline{CH_3}$), 3.36 (1H, m, CHP), 3.85 (2H, m, OCH_2), 3.98 (2H, m, OCH_2), 5.03 (2H, s, CH_2N), 7.39 (2H, dd, J 8.6, 2.0 Hz, Ar), 7.55 (1H, m, Ar), 7.67 (2H, m, Ar), 7.79 (1H, d, J 7.5 Hz, Ar), 7.87 (2H, d, J 8.6 Hz, Ar). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ: 15.47 (d, J 5.6 Hz), 16.06 (d, J 5.0 Hz), 16.17 (d, J 5.0 Hz), 36.40 (d, J 139 Hz), 50.32, 61.27 (d, J 5.9 Hz), 61.46 (d, J 5.9 Hz), 118.89, 122.97, 123.04, 127.91, 128.77 (d, J 6.9 Hz), 131.92, 132.30, 133.83, 137.94, 140.72, 166.30. ^{31}P NMR (80 MHz, DMSO-d_6), δ: 31.00.

Method B. A mixture of chloride **3** (0.25 g, 0.92 mmol) and triethylphosphite (1.60 mL, 9.2 mmol) was heated under reflux for a 16 h, cooled, and evaporated. The residue obtained was refluxed for 5 min with hexane and filtered from insoluble impurities. **1b** crystallized upon cooling as colorless needles.

Yield 109 mg (32%); mp 107–108°C. Analysis and spectral data were identical to **1b** obtained by method A.

Synthesis of 1-(4-(Isoindolin-1-one-2-yl)phenyl)ethylphosphonic Acid (1a) (Phosphonoindoprofen)

To a solution of the diethyl phosphonoindoprofen **1b** (15 mg, 0.04 mmol) in anhydrous dichloromethane (5 mL), Me_3SiBr (52 μL, 0.4 mmol) was added. The reaction mixture, after standing overnight, was evaporated. The residue was dissolved in aqueous dioxane (1:1) (5 mL). After 1 h standing, it was evaporated again and dried. The product was obtained as a pale solid.

Yield 13 mg (100%); mp 227–228°C. IR (KBr, cm^{-1}), ν_{max}: 545, 734, 793, 818, 838, 881, 928, 1005, 1038, 1155, 1192, 1251, 1309, 1387, 1448, 1470, 1516, 1610, 1687, 2977. Anal. calcd. for $C_{16}H_{16}NO_4P$ (317.28): C, 60.57; H, 5.08; P, 9.76. Found: C, 60.51; H, 5.10; P, 9.73. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.43 (3H, dd, *J* 17.4, 7.3 Hz, CH_3), 3.01 (1H, dq, *J* 21.8, 7.3 Hz, CHP), 5.01 (2H, s, CH_2N), 7.35 (2H, dd, *J* 8.6, 2.2 Hz, Ar), 7.55 (1H, m, Ar), 7.68 (2H, m, Ar), 7.78 (1H, d, *J* 7.3 Hz, Ar), 7.80 (2H, d, *J* 8.6 Hz, Ar). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ: 16.15 (d, *J* 5.0 Hz), 38.46 (d, *J* 132 Hz), 50.54, 119.20, 123.08, 123.17, 128.02, 128.85 (d, *J* 6.1 Hz), 131.94, 132.55, 136.32, 137.51, 140.89, 166.35. ^{31}P NMR (80 MHz, DMSO-d_6), δ: 25.80.

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