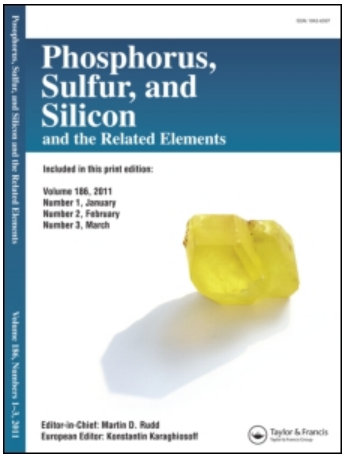

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ORGANIC PHOSPHORUS COMPOUNDS 92.[1] SYNTHESIS AND PROPERTIES OF AZETIDINE-3-PHOSPHONIC- AND 3-PHOSPHONOUS ACID

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(Dedicated to Professor R. Appel on the occasion of his 70th birthday)

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Azetidine-3-phosphonic acid, **4a**, and azetidine-3-phosphonous acid, **4b**, have been prepared by the interaction of 1-benzhydryl-3-methanesulfonato-azetidine with sodium phosphite or sodium O-ethyl-diethoxymethylphosphonite, followed by catalytic debenzhydrylation with H_2 and hydrolysis. Neither acid shows biological activity.

Key words: 3-Diethylphosphonylazetidine; 3-(O-ethyl-diethoxy-methylphosphinyl)azetidine; azetidine-3-phosphonic acid; azetidine-3-phosphonous acid; debenzhydrylation.

INTRODUCTION

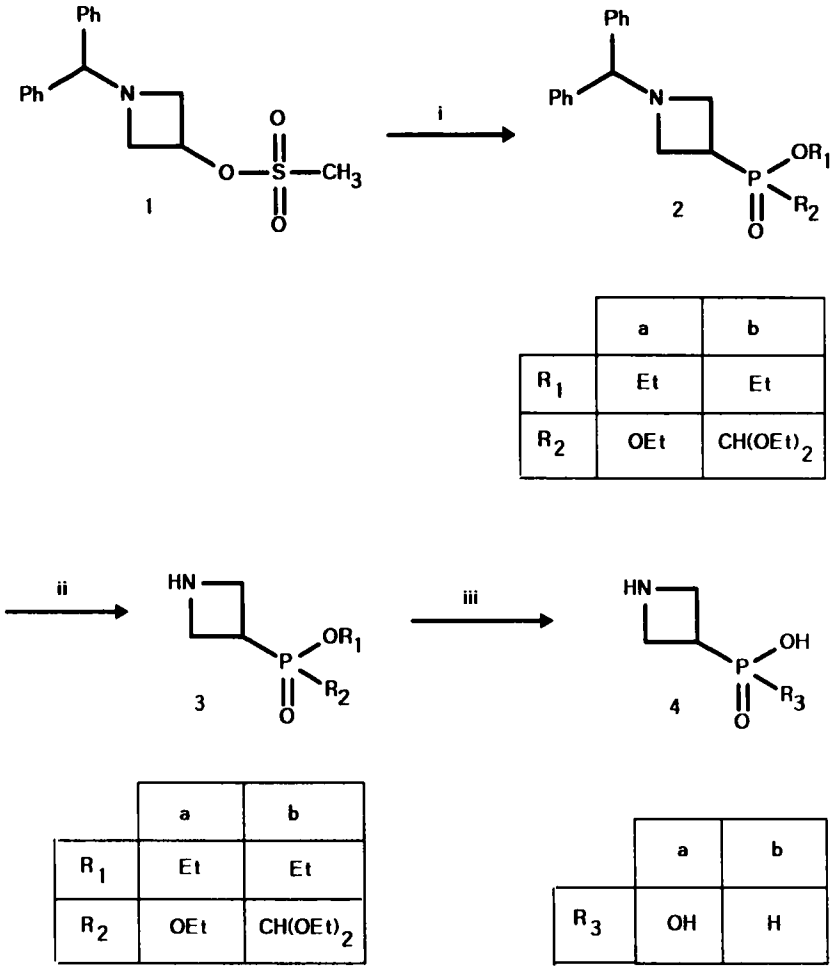
L-Azetidine-2-carboxylic acid occurs in nature[2] and has been found to inhibit the growth of E. coli cultures and various seedlings[3] and to cause abnormalities in growing embryos.[4] Azetidine-3-carboxylic acid is also known[5] and has been shown to have gameticidal properties, i.e., it sterilizes male anthers in plants.[6] Since replacement of a carboxylic acid function in biologically important molecules by a phosphorus acid often provides biologically active molecules (see e.g., References 7 and 8) it seemed of interest to synthesize azetidine-3-phosphonic and 3-phosphonous acid and determine their biological activity.

RESULT AND DISCUSSION

Interaction of 1-Benzhydryl-3-methanesulfonato-azetidine (**1**)[5] with sodium phosphite or sodium O-ethyl-diethoxy-methylphosphonite in dimethylformamide gave 1-benzhydryl-3-O,O-diethylphosphonylazetidine, **2a**, and 1-benzhydryl-3-(O-ethyl-diethoxymethylphosphinyl)azetidine **2b** in 31.6 and 40% yield, respectively. Both products could be purified by chromatography on silica-gel (Scheme). Debenzhydrylation of **2a** and **2b** with H_2 over a 5% Pd/C catalyst in ethanol proceeded at normal pressure and ambient temperature and gave **3a** or **3b** in about 60% yield.

Dealkylation of **3a** was successfully achieved with trimethylsilylbromide in chloroform solution at room temperature. Treatment of the silylester with isopropanol/propylene oxide gave azetidine-3-phosphonic acid **4a** as white crystals in 82.7% yield. The ^{31}P-chemical shift of 18.18 ppm proves its structure as a phosphonic acid.

The corresponding azetidine-3-phosphonous acid **4b** was obtained also as white



i : NaH/HP(O)OR_1R_2/DMF

ii : Pd/C,H_2,EtOH/HCl

iii : $(CH_3)_3SiBr/CHCl_3$/Propylene oxide/Isopropanol or HCl 2N / Propylene oxide/Isopropanol

Scheme

crystals in 65.8% yield by hydrolysis of **3c** with 2N HCl at reflux temperature and purification with propylene oxide/methanol.

The ^{31}P-chemical shift of 24.3 ppm with a P—H coupling constant of 525.9 Hz proves it structure as a phosphonous acid.

Biological Activity

In contrast to azetidine-3-carboxylic acid[6] the phosphonic, **4a**, and phosphonous acid analog **4b**, show no antifungal, herbicidal or gameticidal activity.

EXPERIMENTAL

Phosphorus NMR-spectra were recorded using a Bruker WP80 spectrometer at 32.28 MHz (Reference 85% H_3PO_4) and ^{1}H-NMR spectra were recorded with a Varian EM 360 spectrometer at 60 MHz or a Bruker WM 250/250 MHz spectrometer (Reference $(CH_3)_4Si$). The chemical shifts are reported in ppm, with negative values being upfield of the standard, and positive downfield.

1. *1-Benzhydryl-3-diethylphosphonylazetidine*, **2a**. To 70.1 g (0.508 mol) of diethylphosphite dissolved in 1 liter of DMF is added portionwise within one hour 12.6 g (0.508 mol) of NaH (97%). The temperature is kept between 25°and 35°C. After 2 h stirring a solution of 100 g (0.254 mol) of 1-benzhydryl-3-methanesulfonatoazetidine (**1**)[5] dissolved in 200 ml of DMF is dropwise added. The yellow solution is stirred for 26 h at 90°C, cooled to 20°C and filtered. The solvent DMF is distilled off at 20°C/1 mbar, the residue dissolved in 1 liter of ether and three times extracted with 200 ml of H_2O each. The aqueous extracts are combined and extracted twice with 150 ml of ether each. The combined etherphases are dried with Na_2SO_4 and then the ether removed on a rotor-evaporator. The residue (69.1 g of a brown oil) is chromatographed on silica gel and eluded with ethylacetate/hexane = 3:1. There is obtained 28.9 g (31.6%) of **2a**, colorless crystals, m.p. 82–84°C.

$C_{20}H_{26}NO_3P$ (359.41) calc.: C 66.84, H 7.29, N 3.90, P 8.62%
found: C 66.6, H 7.3, N 3.9, P 8.4%

^{1}H-NMR (in $CDCl_3$) δ = 1.25 (t, CH_3, 6H); 2.6–3.6 (m, —CH_2—CH—CH_2—, 5H); 4.05 (quin., OCH_2, 4H); 4.4 (s, N—CH, 1H); 7.0–7.6 (m, aryl, 10H) [ppm].

2. *1-Benzhydryl-3-(diethoxymethyl-O-ethylphosphinyl)azetidine*, **2b**. As described for **2a**, 139 g (0.708 mol) of O-ethyl-diethyoxymethylphosphonite[9] are treated with 17.5 g (0.708 mol) of NaH (97%) and 150 g (0.472 mol) of **1**. The crude product is chromatographed on silica gel and eluded with ethylacetate/hexane = 1:1. Yield 85.5 g (40.1%) of **2b**, yellow oil n^{20} = 1.5360

$C_{23}H_{32}NO_4P$ (417.49) calc.: C 66.17, H 7.73, N 3.36, P 7.42%
found: C 65.2, H 7.6, N 3.5, P 7.0%

^{1}H-NMR (in $CDCl_3$) δ = 0.95–1.45 (m, CH_3, 9H); 2.8–3.8 (m, CH_2—CH—CH_2, C—O—CH_2, 9H); 4.15 (q, P—O—CH_2, 2H); 4.48 (s, N—CH, 1H); 4.6 (d, P—CH—O), 1H, J_{PCH} 7 Hz); 6.9–7.55 (m, aryl, 10H) [ppm].

3. *3-Diethylphosphonylazetidine*, **3a**. 43.5 g (0.121 mol) of **2a**, dissolved in 400 ml of ethanol are treated at normal pressure with H_2 in the presence of 9 g of Pd/C (5%) at ambient temperature. After 62 h H_2 up-take ceased. The catalyst is filtered and the filtrate evaporated on a rotor-evaporator. The residue (36.5 g colorless oil) is flash-chromatographed on silica gel using CH_2Cl_2/CH_3OH = 95:5 as eluent. Yield of **3a**, 15.6 g (66.9%) colorless oil.

$C_7H_{16}NO_3P$ (193.10) calc.: C 43.52, H 8.35, N 7.25, P 16.03%
found: C 43.0, H 8.3, N 7.1, P 15.7%

^{1}H-NMR (in $CDCl_3$) δ = 1.30 (t, CH_3, 6H); 2.95 (s, NH, 1H); 3.1–4.4 (m, CH_2—CH—CH_2, OCH_2, 9H) [ppm].

4. *3-(O-ethyl-diethoxymethylphosphinyl)azetidine*, **3b.** 10.8 g (0.0258 mol) of **2b** are treated with H_2 in the presence of Pd/C as described for **3a**. There is obtained 3.86 g (59.6%) **3b**, a yellow oil, n^{20} = 1.4828

$C_{10}H_{22}NO_4P$ (241.26) calc.: C 47.8, H 8.83, N 5.58, P 12.33%
found: C 47.6, H 9.1, N 5.3, P 12.0%

5. *3-(O-ethyl-diethoxymethylphosphinyl)azetidine hydrochloride*, **3c**. To 41.2 g (0.0986 mol) of **2b** in 400 ml of ethanol is added 1 equiv. HCl, 8 g of Pd/C (5%) and H_2 introduced at normal pressure (after 30% conversion another 8 g and after 70% conversion again 8 g catalyst added). After H_2 up-take ceased, the mixture is filtered and from the filtrate alcohol distilled off. The residue is dissolved in H_2O, extracted three times with ether and the aqueous phase evaporated. The residue is dried over P_2O_5 to give 24.2 g (85.5%) **3c**, a resin.

$C_{10}H_{22}NO_4P \times HCl$ (287.72) calc.: C 41.75, H 8.06, N 4.87, Cl 12.32, P10.77%
found: C 39.2, H 7.9, N 4.9, Cl 12.0, P 10.5%

^{1}H-NMR (in DCl 10%) δ = 0.7–1.3 (m, CH_3, 9H); 3.1–4.4 (m, CH_2—CH—CH_2, OCH_2, 11H); 4.85 (d, $CH(OEt)_2$, 1H, J_{PCH} 7 Hz); 6.95 (s, NH × HCl, 2H) [ppm].

6. *Azetidine-3-phosphonic acid*, **4a.** A solution of 15.6 g (0.08 mol) of **3a** in 150 ml of $CHCl_3$ is treated

with 40.7 g (0.266 mol) of Me_3SiBr and the mixture stirred for 3 days at 20°C. Then $CHCl_3$ is distilled off and the residue kept at 1 mbar to remove volatile material. The residue (34.5 g yellow oil) is dissolved in isopropanol and propylene oxide added. After 12 h stirring at 20°C the precipitate is filtered and washed with ether. There is obtained 10.3 g of a white solid which still contains Br. Therefore the solid is again dissolved in 100 ml of H_2O, 40 ml of propylene oxide are added, the mixture stirred for 15 min, then evaporated at 1 mbar and the residue suspended in isopropanol/ether = 1:1. The colorless crystals are filtered and dried. There is obtained 9.1 g (82.7%) **4a**, colorless crystals, m.p. 238–240°C (dec.).

$C_3H_8NO_3P \times 0.1\ H_2O$ (138.9) calc.: C 25.9, H 5.9, N 10.0, P22.3, H_2O 1.3%
found: C 26.3, H 5.8, N 10.0, P21.7, H_2O 1.3%

^{31}P-NMR (in D_2O) δ = 18.18 ppm, J_{PCH} 11.6 Hz, J_{PCCH} 14.0 Hz

7. *Azetidine-3-phosphonous acid*, **4b.** A mixture of 21.3 g (0.074 mol) of **3c** and 250 ml of 2N HCl is refluxed for 5 h. The slightly yellow solution is extracted with ether and the aqueous phase evaporated at 30°C and 1 mbar. There is obtained 14.5 g of a yellow oil which is dissolved in 120 ml of H_2O, then 120 ml of propylene oxide and 30 ml of methanol are added and the mixture stirred for 2 h. Evaporation of the mixture yields a residue which is dried over P_2O_5. The sticky mass is suspended in isopropanol and stirred overnight to give 5.9 g (65.8%) **4b**, colorless crystals, m.p. 189°C (dec.)

$C_3H_8NO_2P \times 0.18\ H_2O$ (124.32) calc.: C 28.99, H 6.81, N 11.27, P 24.92, H_2O 2.61%
found: C 29.1, H 6.6, N 11.0, P 24.1, H_2O 2.6%

^{31}P-NMR (in D_2O) δ = 24.30 ppm; J_{PH} 525.9 Hz

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