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LETTERS TO THE EDITOR

Synthesis of 5-[3-(Diphenylphosphinoyl)propyl]-2-thiobarbituric Acid

A. N. Reznikov and N. K. Skvortsov

St. Petersburg State Technological Institute,
Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: orgphos@yandex.ru

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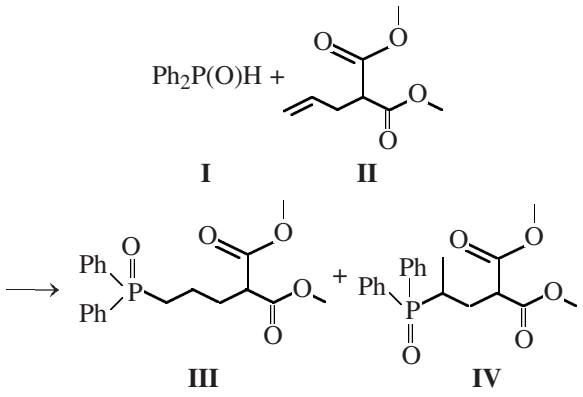
2-Thiobarbituric acids are widely used for the synthesis of diverse pyrimidine derivatives [1–3] possessing antiphlogistic, anesthetic, anticonvulsive, bactericidal, cytostatic, antitumor, and antiviral activities. 5-Phosphinoylalkyl-2-thiobarbituric acids that combine in their molecules two active fragments, a phosphorus-containing group and a pharmacogenic easily modified 2-thioxodihydropyrimidine-4,6-(1*H*,5*H*)-dione groups are interesting as valuable intermediates in the synthesis of biologically active compounds. The main method of synthesis of 5-substituted 2-thiobarbituric acids is condensation of 2-substituted diethyl malonates with thiourea in the presence of base [4]. However, malonic acid derivatives with phosphoruscontaining substituents form a poorly studied class of compounds. The syntheses of diethyl 2-[2-(diphenylphosphinoyl)ethyl]malonate and diethyl 2,2-bis[2-(diphenylphosphinoyl)ethyl]-malonate by adding diethyl malonate to diphenyl(vinyl)phosphine oxide [5] and of diethyl 2-[3-(diethoxyphosphinoyl)propyl]malonate from diethyl phosphite, 1,3-dibromopropane, and diethyl malonate [6] have been described. We suggest that phosphorylation of unsaturated derivatives of malonic esters provides a more promising synthetic approach to such compounds.

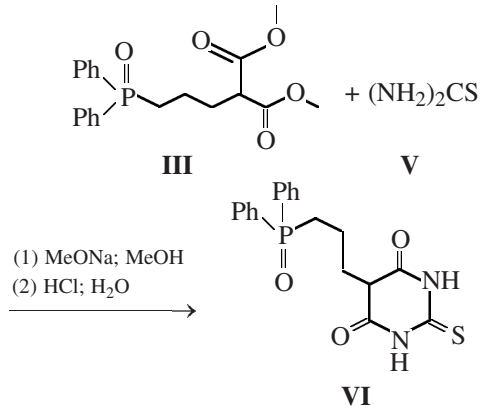
Earlier we reported the catalytic hydrophosphorylation of dialkyl 2-allylmalonates with diakyl phosphites, leading to phosphorylated malonates [7, 8]. By contrast, the reaction of diphenylphosphine oxide with dialkyl 2-allylmalonates results in dealkoxycarbonylation [8].

Continuing these investigations, we reacted diphenylphosphine oxide (**I**) with dimethyl 2-allylmalonate (**II**) under conditions of radical initiation by UV illumination or by adding 2,2'-azobisisobutironitrile (AIBN) to an equimolar mixture of the reagents. Reaction selectivity was monitored by ^{1}H and ^{31}P NMR spectroscopy. It was found that this reaction proceeds with high conversion (over 95%) and regioselectivity (90.1%) to form dimethyl 2-[3-(diphenylphosphinoyl)propyl]malonate (**III**) (δ_P 31.3 ppm). The yield of isomeric product **IV** (δ_P 30.7 ppm) is 9.9%.



Malonate **III** reacts with thiourea (**V**) in the presence of sodium methylate to give 5-[3-(diphenylphosphinoyl)propyl]-2-thiobarbituric acid (**VI**).

Compound **VI** forms sodium and ammonium salts readily soluble in water. The ^{1}H NMR spectrum of compound **VI** contains multiplets of methylene groups in the phosphinoylalkyl substituent and a broad singlet of the NH group in the region characteristic of 2-thiobarbituric acids [9]. The phosphorus chemical shift of compound **VI** is specific of phosphine oxides. The presence in the ^{13}C NMR spectrum of this com-



pound of a singlet at 92.82 ppm, characteristic of the carbon atom at a double bond, as well as a signal of the carbon atom bound to hydroxyl (170.62 ppm) points to partial enolization of compound **VI** dissolved in DMSO.

The IR spectrum of compound **VI** has much in common with the spectrum of 2-thiobarbituric acid [10, 11]. Besides, strong bending bands of aromatic C–H bonds [δ(C–H) 696, 715, 722, 731, 748 cm^{-1}] are observed.

Dimethyl 2-[3-(diphenylphosphinoyl)propyl]-malonate (III). Dimethyl 2-allylmalonate (0.852 g) and diphenylphosphine oxide (0.950 g) were illuminated under an inert atmosphere with unfiltered light of a DRT-400 lamp for 4 h. The reaction product was isolated by column chromatography. Yield 1.72 g (98.0%).

Dimethyl 2-allylmalonate (0.999 g), diphenylphosphine oxide (1.166 g), and AIBN (22 mg) were heated under argon for 3 h, and then 6 mg of AIBN was added additionally. The reaction product was isolated by column chromatography. Rf 0.55 (methanol–ethyl acetate, 1 : 10). Yield 1.94 g (90.0%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.66 m (2H, CH_2), 2.00 m (2H, CH_2), 2.27 m (2H, CH_2P), 3.34 t (1H, CH, $^3J_{HH}$ 7.5 Hz), 3.67 s (6H, CH_3), 7. 46 m (6H, Ph), 7.70 m (4H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δC, ppm: 19.58 s (CH_2), 29.15 d (CH_2, $^2J_{CP}$ 52.7 Hz), 30.03 s (CH_2), 51.14 s [*C*H$(COOMe)_2$], 52.46 s (CH_3O), 128.64 d (Ph, *m*-C, $^3J_{CP}$ 13.2 Hz), 130.70 d (Ph, *o*-C, $^2J_{CP}$ 8.6 Hz), 131.75 s (Ph, *p*-C), 133.72 s (Ph, C_i), 169.37 s [*C*(O)O]. ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.3 ppm.

5-[3-(Diphenylphosphinoyl)propyl]-2-thiobarbituric acid (VI). To a solution of sodium methylate prepared from 0.263 g of sodium and 3 ml of methanol, 2.14 g of dimethyl 2-[3-(diphenylphosphinoyl)-propyl]malonate in 10 ml of methanol was added, and 0.443 g of thiourea was added to the resulting yellow solution. The reaction mixture was refluxed for 4 h, methanol was then removed in a vacuum. The nonvolatile residue was dissolved in 15 ml of water, and the solution was filtered and acidified with conc. HCl to ®H 2. The precipitate that formed was dissolved in 1.02 g of 25% aqueous ammonia and 10 ml of water, the solution was filtered, and the filtrate was acidified with a solution of 1.66 g of conc. H_2SO_4 in 3 ml of water. The precipitate that formed was filtered off, dried, and recrystallized from ethanol. Yield 1.22 (55.2%), mp 248°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.57 m (2H, CH_2), 2.35 m (4H, $2CH_2$), 7.52 m (6H, Ph), 7.75 m (4H, Ph), 11.98 br.s (2H, 2NH). ^{13}C NMR spectrum, δ_C, ppm: 20.15 s (CH_2), 21.83 d (CH_2, $^3J_{CP}$ 7.30 Hz), 26.27 d (CH_2, $^2J_{CP}$ 69.7 Hz), 92.82 s (C= tautomeric form), 128.72 d (Ph, *m*-C, $^3J_{CP}$ 12.1 Hz), 130.40 d (Ph, *o*-C, $^2J_{CP}$ 9.4 Hz), 131.96 s (Ph, *p*-C), 132.87 s (Ph, C_i), 160.83 s (*C*=O), 170.62 s (*C*–OH tautomeric form), 173.10 s (C=S). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 33.1. IR spectrum, cm^{-1}: 425 m, 472 m, 511 s, 544 s, 586 m, 632 w, 672 s, 696 s, 716 s, 722 s, 732 s, 748 s, 785 m, 817 m, 865 m, 884 m, 924 m, 937 m, 997 m, 1022 m, 1057 m, 1071 m, 1078 s, 1089 s, 1123 s, 1144 s, 1175 s, 1184 s, 1210 s, 1247 s, 1290 s, 1328 s, 1354 s, 1391 m, 1436 s, 1482 m, 1548 s, 1562 s, 1605 s, 1651 s, 1721 m, 1978 w, 2180 m, 2243 m, 2620 m, 2858 s, 2896 s, 2925 s, 3013 s, 3057 s, 3421 m.

The ^{1}H, ^{13}C and ^{31}P NMR spectra were registered on Brucker NW 400 and AC 200 instruments in $CDCl_3$ and $(CD_3)_2SO$ at 400.14 (^{1}H), 50.33 (^{13}C), and 81.01 (^{31}P) MHz. All data are represented in ppm relatively to TMS (^{1}H) and 85% H_3PO_4 (^{31}P). No additional reference compounds were used, the frequencies were tied to the signal of the deuterated solvent.

The IR spectra were registered on a Shimadzu FTIR-8400S instrument (4000–500 cm^{-1}) from KBr pellets.

Chromatography was performed on silica gel 60 of chromatographic grade, methanol from Merck, AIBN of pure grade, sodium of analytical grade, and thiourea, HCl and ethyl acetate of chemical grade. Dimethyl 2-allylmalonate was prepared by the procedure in [12] and diphenylphosphine oxide, by the procedure in [13].

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