INDOLE DERIVATIVES

LXXVI.* SYNTHESIS OF TRIS(1-BENZYL-5-INDOLINYL)PHOSPHINE OXIDE AND INDOLE-5-PHOSPHONIC ACID DERIVATIVES

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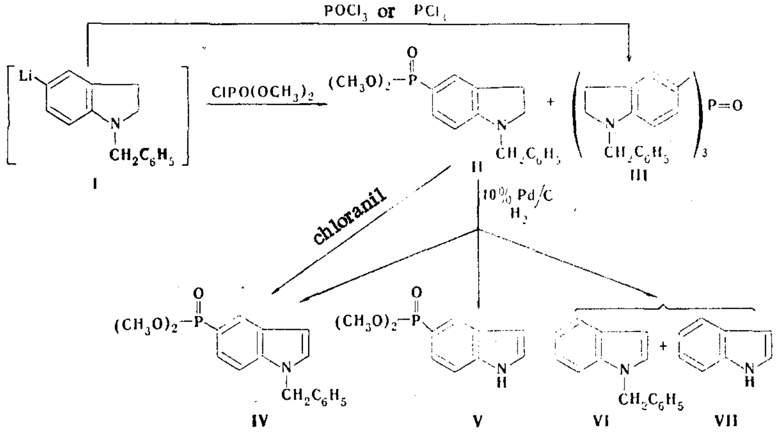
UDC 547.751'241.07

Tris(1-benzyl-5-indolinyl)phosphine oxide, the structure of which was confirmed by alternative synthesis, is formed as a side product along with the previously described dimethyl-1-benzylindoline-5-phosphonate in the reaction of 1-benzyl-5-lithioindoline with dimethyl chlorophosphate. Dimethyl 1-benzylindole-5-phosphonate was obtained by the dehydrogenation of dimethyl 1-benzylindoline-5-phosphonate with chloranil. The catalytic dehydrogenation of this same indoline is accompanied by debenzylation, which leads to dimethyl indole-5-phosphonate, and by splitting of the P–C bond.

We have previously established [2] that dimethyl 1-benzylindoline-5-phosphonate (II) is formed in the reaction of 1-benzyl-5-lithioindoline (I) with dimethyl chlorophosphate. Continuing our study of this reaction, we have isolated tris(1-benzyl-5-indolinyl)phosphine oxide (III) as a side product.

This sort of interaction of an organolithium derivative with dimethyl chlorophosphate was previously observed in similar reactions [3,4]. The addition of I to $ClPO(OCH_3)_2$ leads to predominant condensation with the acid chloride. Increasing the dilution and the time of addition of I also prevents the occurrence of the side reaction.



We obtained oxide III by alternative synthesis by condensation of I with phosphorus oxychloride via the method in [5]. We also observed the formation of III in an attempt to obtain tris(1-benzyl-5-indolinyl)-phosphine by condensation of I with phosphorus trichloride via the method in [6], which may explain the ease of oxidation characteristic for triarylphosphines.

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*See [1] for communication LXXV.

D. I. Mendeleev Moscow Chemical-Engineering Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 498-501, April, 1972. Original article submitted March 22, 1971.

The dehydrogenation of ester II occurs when it is heated with chloranil in xylene, but dimethyl 1-benzylindole-5-phosphonate (IV) is formed in low yields (about 30%), which is common on dehydrogenation with quinones [7]. We were unable to debenzylate indole IV by refluxing in xylene with a palladium catalyst or with sodium metal in liquid ammonia.

The best results in the catalytic dehydrogenation of indoline II are obtained when it is refluxed with 10% palladium on carbon in xylene in a stream of hydrogen for 4 h. The dehydrogenation is accompanied by debenzylation, and a rather easily separable mixture of dimethyl indole-5-phosphonate (V) (38% yield) and benzyl derivative IV (14% yield) is formed. The reductive cleavage of the C−P bond to form 1-benzylindole (VI) and indole (VII), which is quite rare for compounds of pentavalent phosphorus [8], also occurs in the course of this reaction. This process becomes especially appreciable as the reaction time increases. In a control experiment (heating I under the same conditions without a palladium catalyst), we observed that cleavage of the C−P bond does not occur; i.e., this process apparently occurs only under reducing conditions.

A difficult-to-separate mixture of II, IV, V, and other reaction products is formed on heating with a palladium catalyst in xylene without a stream of hydrogen in the presence of a hydrogen acceptor – cinnamic acid – or with Raney nickel in alcohol (in a stream of hydrogen or without it). When indoline II is heated with palladium on carbon in an autoclave at 140° and a hydrogen pressure of 40 atm, only slight dehydrogenation and debenzylation occur, and cleavage of the C−P bond becomes appreciable.

Dimethyl 1-acetylindoline-5-phosphonate [2] is not dehydrogenated when it is refluxed with a palladium catalyst in xylene; however, hydrolysis of its acetamido group in both acid (5 and 15% hydrochloric acid) and alkaline (5% KOH, Na_2CO_3, or $NaHCO_3$ solutions) media is accompanied by hydrolysis of the phosphonic acid ester.

Thus catalytic dehydrogenation with simultaneous debenzylation of II proved to be the most convenient method for obtaining the organophosphorus derivative of indole (V).

The following signals can be observed in the PMR spectra of indoles IV and V: the spectrum of IV has a doublet at 3.652 ppm (6H, J_{P-H} = 12 Hz), while that of V has a doublet at 3.687 ppm (6H, J_{P-H} = 13 Hz) from the methyl protons of the phosphonic acid ester; the spectrum of IV has a singlet at 5.265 ppm (2H) from the benzyl CH_2 group. In addition, complex multiplets from the aromatic protons at 6.59-8.06 and 6.56-8.06 ppm, respectively, are observed for IV and V.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the compounds were obtained with a UR-10 spectrometer. The PMR spectra of deuteromethanol solutions were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1306 spectrometer with direct inlet of the sample into the source.

Tris(1-benzyl-5-indolinyl)phosphine Oxide (III). A) The reaction mass obtained after condensation of I (obtained from 40 g (0.14 mole) of 1-benzyl-5-bromoindoline (VIII) and 3.82 g (0.55 g-atom) of lithium in 600 ml of absolute ether via the method in [2]) with 27.81 g (0.19 mole) of dimethyl chlorophosphate in 700 ml of absolute ether was worked up as previously described in [2]. The ether extract (2 liters)was dried with Na_2SO_4 at −15°. After 12 h, the ether solution was filtered and evaporated to give 12.5 g of a green oil. Additional extraction of the drying agent with methylene chloride (five 200-ml portions) and evaporation gave another 20.02 g of oil. The combined residues (32.52 g) were placed on a column filled with 438 g of silica gel and eluted with chloroform to give, successively, 7.81 g (27%) of amines (primarily 1-benzylindoline), 15.8 g of II, 3.48 g of a mixture of reaction products, and 2.4 g of III. Subsequent chromatography of the mixture of condensation products on silica gel with elution by chloroform gave 2.8 g of II and 0.3 g of III. A total of 18.6 g (58%) of II and 2.7 g of III as a dark-brown oil were obtained. Two crystallizations from benzene−hexane with treatment with carbon gave 1.65 g (7.3%, based on the 1-benzyl-5-bromoindoline entering into the reaction) of III with mp 204-215° (dec.). UV spectrum: λ_{max} 292 nm, log ε 4.88 (in dioxane). IR spectrum: 1275 cm^{-1} (P=O). Found: C 80.8; H 6.3; N 6.1; P 4.3%. $C_{45}H_{42}N_3OP$. Calculated: C 80.4; H 6.3; N 6.3; P 4.5%.

B) A solution of 0.77 g (5.5 mmole) of $POCl_3$ in 25 ml of ether was added dropwise at 0-5° in the course of 20 min to a filtered ether solution of I [from 4.32 g (15 mmole) of VIII and 0.42 g (0.06 g-atom) of lithium in 100 ml of absolute ether]. An abundant amount of a precipitate formed during the addition. The mixture was stirred for 1 h at room temperature, decomposed with water, and made alkaline with 5% KOH to pH 10. The ether layer was separated, washed with water, and dried with Na_2SO_4. The ether-insoluble residue was extracted with chloroform, and the chloroform extract was washed with water and dried with Na_2SO_4. The ether and chloroform extracts were evaporated, and the combined residues (3.54 g) were placed on a column filled with 100 g of silica gel and eluted with chloroform to give, successively, 1.41 g (45%) of amines, 0.22 g of crude III, and 1.22 g of III with slight admixtures of more polar reaction products. Two crystallizations from benzene–hexane with treatment with activated charcoal gave 0.75 g (40%, based on the VIII entering into the reaction) of III with mp 207-218° (dec.).

C) A solution of 1.02 g (0.074 mole) of PCl_3 in 5 ml of ether was added dropwise with ice-cooling in the course of 10 min to a filtered solution of I [from 8.64 g (0.03 mole) of VIII and 0.84 g (0.12 g-atom) of lithium in 100 ml of absolute ether], and the mixture was stirred at about 20° for 30 min and refluxed for 30 min. It was then cooled, 15 ml of 10% hydrochloric acid was added, and the ether was removed by vacuum distillation. A total of 80 ml of concentrated hydrochloric acid was added to the residue, the mixture was stirred for 1.5 h, and 1 g of activated charcoal was added. The mixture was filtered, and the charcoal was washed with 20 ml of concentrated hydrochloric acid. The filtrate was diluted with stirring with 1.2 liter of water containing ice, and the precipitate (5.6 g) was removed by filtration and placed on a column containing 150 g of silica gel and eluted with chloroform to give 2.86 g of III as a yellow oil. Crystallization from benzene–hexane gave 1.89 g (28% based on VIII) of a product with mp 204-215° (dec.).

Samples of III obtained by methods A-C did not depress the melting points of one another and had identical IR spectra.

Dimethyl 1-Benzylindole-5-phosphonate (IV). A mixture of 1.6 g (5 mmole) of II, 1.5 g (6 mmole) of chloranil, and 10 ml of xylene was refluxed for 4 h and filtered. The precipitate was washed with 30 ml of hot benzene, and the filtrate was placed in a separatory funnel and washed successively with 30 ml of 5% Na_2CO_3 solution and water until it gave a neutral reaction. The benzene extract was dried with Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was placed on a column filled with 100 g of Al_2O_3 and eluted with chloroform to give 0.53 g (33%) of IV as a light-brown oil with mp 89-90° (from ether). The product was quite soluble in benzene, ether, and chloroform and only slightly soluble in hexane and water. UV spectrum: λ_{max}, nm (log ε): 235 (4.75), 285 (3.72) (in alcohol). IR spectrum: 1240 (P=O) and 1030 cm^{-1} (P–O–C). PMR spectrum: doublet at 3.65 ppm (6H, OCH_3, $J_{P,H}$ = 12 Hz), singlet at 5.26 ppm (2H, $N-CH_2$), and multiplet at 6.59-8.06 ppm (aromatic protons). Found: C 64.5; H 6.0; N 4.6; P 9.6%; M (mass-spectroscopy) 315. $C_{17}H_{18}NO_3P$. Calculated: C 64.8; H 5.9; N 4.4; P 9.8%; M 315.

Dimethyl Indole-5-phosphonate (V). A mixture of 8.0 g (25.2 mmole) of II, 8.0 g of 10% palladium on carbon, and 80 ml of xylene was refluxed in a stream of hydrogen for 4 h and filtered. The catalyst was washed with 120 ml of hot benzene and twice with 50-ml portions of hot chloroform. The filtrates were combined and the solvent was evaporated. The residue was dissolved in 150 ml of hot benzene, and the solution was evaporated to ~30 ml. Hexane (10 ml) was added, and 1.73 g of V was filtered away from the solution after 12 h at ~0°. Another 0.31 g of V was obtained by treatment of the mother liquor with charcoal and evaporation to ~20 ml. The combined reaction products were recrystallized from benzene–hexane to give 1.63 g (29%) of V with mp 141.5-143°. The mother liquors were combined and evaporated, and the residue (2.95 g) was placed on a column containing 200 g of Al_2O_3 and eluted successively with 5 : 1 and 1 : 1 benzene–chloroform mixtures to give, initially, 0.03 g (0.6%) of 1-benzylindole (VI), 0.06 g (2%) of indole (VII), 1.10 g (14%) of IV with mp 89-90° (from ether), 0.13 g of a mixture of IV and V, and 0.50 g (9%) of V. A total of 2.13 g (38%) of dimethyl indole-5-phosphonate (V) was obtained. Compound V was soluble in alcohol and chloroform, less soluble in benzene, ether, and water, and only slightly soluble in hexane. UV spectrum: λ_{max}, nm (log ε): 228 (4.77), 280 (3.64) (in alcohol). IR spectrum: 1235 (P=O), 1030 (P–O–C), and 3200 cm^{-1} (N–H). PMR spectrum: doublet at 3.69 ppm (6H, OCH_3, $J_{P,H}$ = 13 Hz), and a multiplet at 6.56-8.06 ppm (aromatic protons). Found: C 53.6; H 5.7; N 6.3; P 13.7%; M (by mass spectrometry) 225. $C_{10}H_{12}NO_3P$. Calculated: C 53.3; H 5.4; N 6.2; P 13.8%; M 225.

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