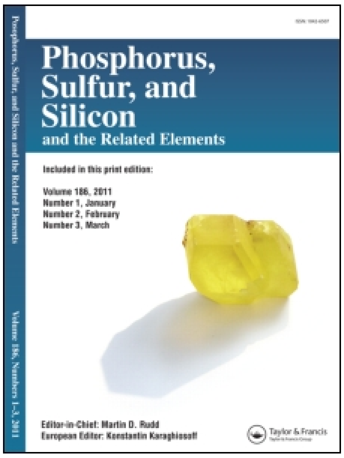

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α-HETEROSUBSTITUTED PHOSPHONATE CARBANIONS. XVIII.[1] A NOVEL ENTRY TO INDOLES

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α-HETEROSUBSTITUTED PHOSPHONATE CARBANIONS. XVIII.[1] A NOVEL ENTRY TO INDOLES

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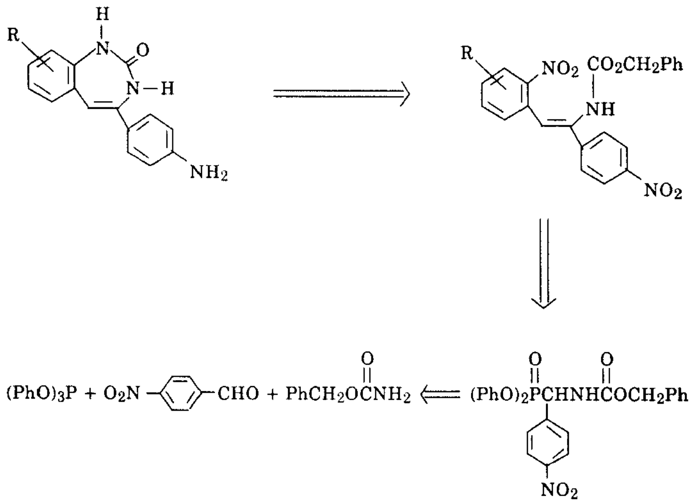
A convenient and novel ring closure method to substituted 2-arylindoles via diphenyl 1-(carbobenzyloxyamino)-1-(4-nitrophenyl)methanephosphonate carbanion is described.

Key words: α-Heterosubstituted phosphonate carbanions; diphenyl 1-(carbobenzyloxyamino-1-(4-nitrophenyl)methanephosphonate, α-(carbobenzyloxyamino-β-(2-nitroaryl)-4-nitrostyrene, indole.

INTRODUCTION

In earlier papers we described the synthesis of a number of heterocyclic systems such as indoles,[2] benzo[a]furans,[3] and quinolines[4] by utilizing α-heterosubstituted phosphonate carbanions as tools. In continuation of this research, we recently synthesized naphthyridines, benzoquinolines, phenanthridines and various higher condensed heterocycles[5] using the same anionic species. The synthesis of heterocyclic systems utilizing the Wittig reaction, that is by the use of phosphorus ylids, has been reported. Thus, Zimmer reported the synthesis of pyrido[1,2-*a*] indoles and pyrrolo[1,2-*a*] indoles by a ringclosure reaction of the ylid derived of 2-succinimido- or 2-glutarimidobenzaldehydes.[6] A similar reaction was also described by W. Flitsch.[7] Corre[8] and coworkers synthesized benzofurans using the ylid obtained from esters of bromomethylphenol. The Aza-Wittig reaction was utilized for ringclosures to prepare thieno[2,3-*c*]pyridines,[9] thieno[3,2-*c*]pyridines[9] and furo[3,2-*c*]pyridines.[9] The synthesis of a number of 1H pyrrolo[1,2-*a*] benzimidazoles, 10H-pyrrolo[1,2-*a*]perimidines and imidoazo[2,1-*a*]isoindoles was achieved by Zimmer.[10]

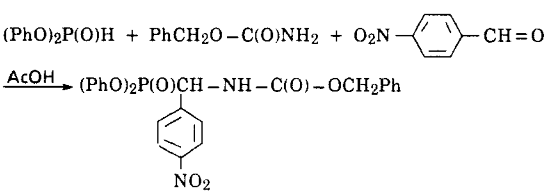
In search for new ways to broaden the scope of α-heterosubstituted phosphonate carbanions for the synthesis of heterocycles, it appeared that the pharmacological interesting 1,3-benzodiazepine-2-one system could be obtained by employing a carbanion derived of diphenyl 1-(carbobenzyloxyamino-1-(4-nitrophenyl)methanephosphonate (**1**). A retrosynthetic approach to the formation of this 7-membered heterocycle is outlined in Scheme I. It was envisioned that reduction of the intermediate vinylcarbamate substituted styrene to the corresponding diamino compound and its subsequent intramolecular condensation with the benzoyl ester carbonyl group would yield the desired class of compounds. The synthesis of the required carbamoylphosphonate went smoothly according to a method previously reported.[11]



SCHEME I

RESULTS AND DISCUSSION

The phosphonate **1** was obtained according to Equation (1). It exhibited a chemical



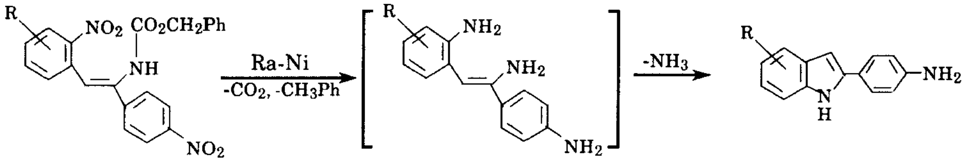
1

(1)

shift of 14.33 (δ, DMSO) which is in the expected range of this type of compounds with an electron withdrawing group linked to the NH-moiety.[12] Compound **1** then was condensed in a methanolic potassium hydroxide solution with the appropriate *o*-nitrobenzaldehyde to give the intermediate α-(carbobenzyloxyamino)-β-(2-nitroaryl)-4-nitrostyrenes **2a–2c** in good yields. However, contrary to our expectations the Raney nickel catalyzed hydrogenation did not yield the desired 1,3-diazepine-2-ones but rather substituted 2-(4-aminophenyl) indoles **3a–3c** (Scheme II).

The reaction seems to proceed as outlined in Scheme II, because in one run involving **2c** the intermediate triamine, identified by its ^{1}H-NMR spectrum, could be isolated. By refluxing it in toluene in the presence of a trace of potassium hydroxide, it smoothly ringclosed to **3c**.

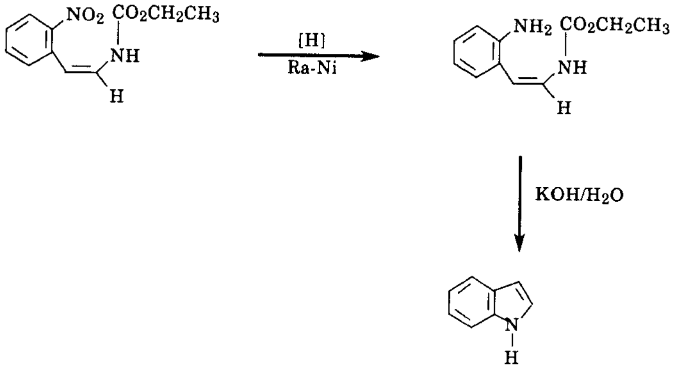
This indole synthesis is reminiscent to one published by Weerman[13] some eighty years ago, in which he got indole in 6% yield by alkali promoted hydrolysis of the ethyl ester according to a sequence outlined in Scheme III.



2a R=H
2b R=7-OMe
2c R=5,6-O-CH2-O-

3a R=H
3b R=7-OMe
3c R=5,6-O-CH2-CH2

SCHEME II



SCHEME III

EXPERIMENTAL

Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected. 1H-NMR spectra were obtained using a Varian EM360A spectrometer with tetramethylsilane as the internal standard. Infrared spectra were recorded on a Perkin-Elmer Model Number 197 spectrophotometer. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona. All solvents were reagent grade. The tetrahydrofurane (THF) was dried over 5 Å molecular sieves. The ethyl alcohol used was of analytical grade. The Raney nickel, no. 28, was purchased from the Davison Chemical Company.

Diphenyl 1-(carbobenzyloxyamino)-1-(4-nitrophenyl)methanephosphonate (**1**). Into a 250 ml flask equipped with a mechanical stirrer was charged *p*-nitrobenzaldehyde (0.15 mole), benzylcarbamate (0.10 mole), diphenyl phosphite (0.10 mole) and 150 ml of glacial acetic acid. The mixture became slightly exothermic when a solid started precipitating. After 4 hrs the mixture was heated on a steambath for 1 hr resulting in a clear solution. Upon cooling, a solid crystallized from this solution; it was removed by filtration and washed with cold methanol. The phosphonate, m.p. 166–168°C (chloroform/methanol) was obtained in a yield of 74%. IR (KBr) 3250 (m), 1710 (s), 1590 (m), 1520 (s), 1480 (s), 1340 (s), 1250 (s), 1200 (s), 1180 (s), 1160 (s), 940 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ 5.18 (s, 2H), 5.72 (dd, 1H, J = 10, 24 Hz), 6.52–8.4 (m, 20H); ^{31}P-NMR (DMSO) δ 14.33.

Anal. Calcd. for $C_{27}H_{23}N_2O_7P$: C, 62.55; H, 4.47; N, 5.40.
Found: C, 62.63; H, 4.49; N, 5.55.

α-(Carbobenzyloxyamino)-β-(2-nitroaryl)-4-nitrostyrenes. General Procedure: The phosphonate **1** (0.02 mole) was dissolved in 200 ml of dry THF, blanketed with nitrogen and cooled to −78°C. To this solution was added 22 ml of 1 M KOH/MeOH in a dropwise manner. After 30 min, the substituted 2-nitrobenzaldehyde (0.02 mole) in 30 ml of THF was added dropwise. The resulting solution was allowed to slowly return to ambient temperature overnight. About 40 ml of water was added, and this solution was evaporated to leave an oil. The organics were extracted into chloroform, washed with a saturated saline solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent produced a residue that was crystallized in an appropriate solvent.

α-(Carbobenzyloxyamino)-β-(2-nitrophenyl)-4-nitrostyrene (**2a**). m.p. 144–146°C (isopropanol), yield 62%. IR (KBr) 3250 (m), 1680 (s), 1590 (m), 1500 (s), 1340 (s), 1260 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ 5.02 (s, 2H), 6.44 (broad singlet, exchanges with D_2O, 1H), 6.88 (s, 1H), 7.13–8.5 (m, 13H).

Anal. Calcd. for $C_{22}H_{17}N_3O_6$: C, 62.97; H, 4.08; N, 10.01.
Found: C, 63.05; H, 4.16; N, 10.16.

α-(Carbobenzyloxyamino)-β-(3-methoxy-2-nitrophenyl)-4-nitrostyrene (**2b**). m.p. 186–189°C (ethyl acetate), yield 44%. IR (KBr) 3240 (m), 1690 (s), 1600 (m), 1510 (s), 1340 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$/DMSO, d_6/TMS) δ 3.92 (s, 3H), 5.07 (s, 2H), 6.36 (s, 1H), 6.9–9.1 (m, 13H).

Anal. Calcd. for $C_{23}H_{19}N_3O_7$: C, 61.47; H, 4.26; N, 9.35.
Found: C, 61.48; H, 4.28; N, 9.16.

α-(Carbobenzyloxyamino)-β-(4,5-methylenedioxy-2-nitrophenyl)-4-nitrostyrene (**2c**). m.p. 184–187°C (ethyl acetate/isopropanol). IR (KBr) 3250 (m), 1680 (s), 1600 (m), 1510 (s), 1480 (s), 1350 (s), 1320 (s), 1270 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$/DMSO, d_6/TMS) δ 5.1 (s, 2H), 6.3 (s, 2H), 7.1–9.26 (m, 13).

Anal. Calcd. for $C_{23}H_{17}N_3O_8$: C, 59.61; H, 3.70; N, 9.07.
Found: C, 59.45; H, 3.71; N, 8.97.

General Procedure for the Raney Nickel Reduction. The appropriate type **2** compound (4.3 mmole) in 100 ml of anhydrous ethanol was charged into a Parr bottle containing about 1 gram of Raney nickel that had been twice washed with anhydrous ethanol. The Parr bottle was pressurized to 30 psi with hydrogen and shaken for 18 hrs. After removal of the catalyst by filtration through filter aid, the product was isolated by concentration of the filtrate at reduced pressure. The residue was recrystallized in an appropriate solvent. If the uncyclized triamine was isolated as in the case of **3c**, cyclization to the desired indole was affected in refluxing toluene in an inert atmosphere with a catalytic amount of potassium hydroxide.

2-(4-Aminophenyl)indole (**3a**). m.p. 205–208°C (ethyl acetate), yield 84%. IR (KBr) 3400 (m), 3320 (m), 1620 (s), 1610 (m), 1500 (s), 1460 (m), 1440 (m), 1300 (m) cm^{-1}; ^{1}H-NMR (DMSO, d_6/TMS) δ 5.3 (broad singlet, exchanges in D_2O, 2H), 6.52–7.9 (m, 9H), 11.3 (broad singlet, exchanges in D_2O, 1H); mass spectrum, m/e (relative intensity) 208 (M^+, 100), 180(29), 104(21), 89(19), 32(40), 28(86).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45.
Found: C, 81.09; H, 6.61; N, 13.40.

2-(4-Aminophenyl)-7-methoxyindole (**3b**). m.p. 145–146°C (ethyl acetate/hexane), yield 81%. IR (KBr) 3400 (m), 3330 (m), 1620 (s), 1510 (s), 1500 (s), 1250 (s), 1300 (s) cm^{-1}; ^{1}H-NMR ($CDCL_3$/DMSO, d_6/TMS) δ 3.93 (s, 5H, 2 exchange in D_2O), 6.4–7.61 (m, 8H), 9.22 (broad singlet, exchanges with D_2O, 1H).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76.
Found: C, 75.81; H, 6.03; N, 11.50.

2-(4-Aminophenyl)-5,6-methylenedioxyindole (**3c**). m.p. 208–210°C (ethyl acetate/hexane), yield 45%. IR (KBr) 3410 (m), 1610 (m), 1460 (s), 1340 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$/DMSO, d_6/TMS) δ 5.02 (broad singlet, exchanges with D_2O, 2H), 5.93 (s, 2H), 6.4–7.7 (m, 7H), 11.05 (broad singlet, exchanges in D_2O, 1H); mass spectrum (analyzed as its acetamide), m/e (relative intensity) 294 (M+, 100), 89(95), 85(50).

α-(Carbobenzyloxyamino)-β-(4,5-methylenedioxy-2-aminophenyl)-4-aminostyrene. m.p. decomposes with charring over a wide temperature range. IR (KBr) 3360 (m), 1700 (s), 1610 (s), 1600 (s), 1470 (s), 1330 (s), 1270 (s), 1230 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ 3.4 (broad singlet, 2H), 4.88 (s, 1H), 5.62 (s, 2H), 5.86–7.32 (m, 16H).

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