A Novel Synthesis of Quinazoline Derivatives with Triethyl Phosphite (1)

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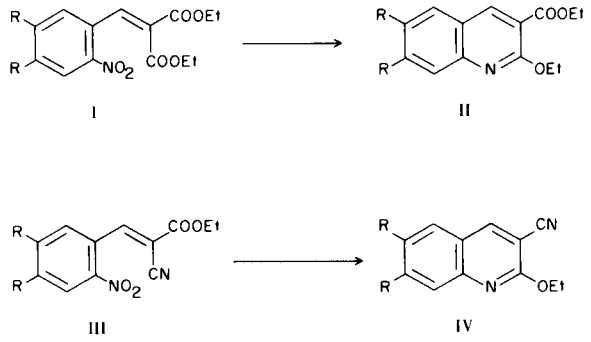
Received June 7, 1971

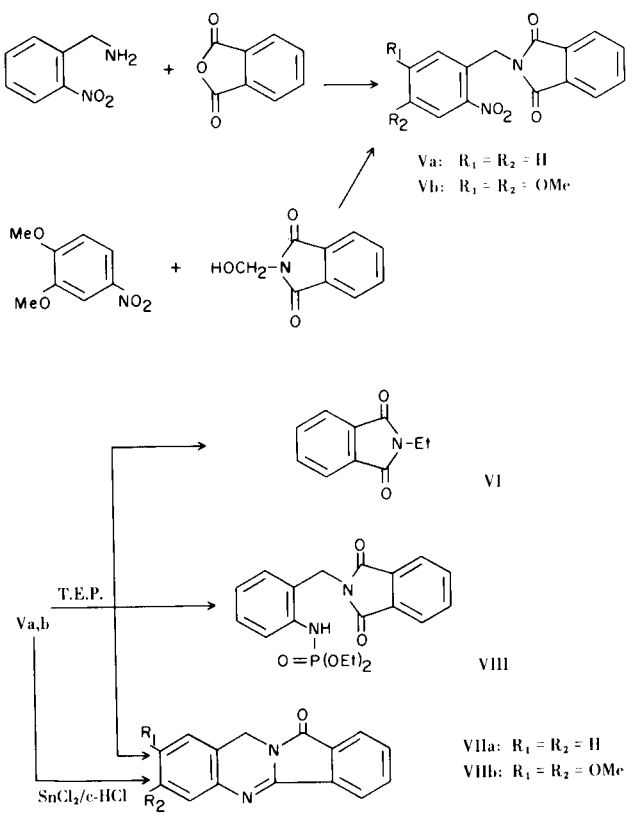
Recently, many researchers have been investigating the reduction of aromatic nitro compounds with triethyl phosphite (3-11). We reported that compounds such as 4,5-disubstituted 2-nitrobenzylidenemalonate (I), in which carbonyl and nitro groups are *cis*-oriented in relation to each other, react with triethyl phosphite to give the quinoline derivatives (II) in excellent yield (11). Furthermore, we allowed ethyl 3,4-disubstituted benzylidenecyanoacetates (III), whose ethoxycarbonyl group was *trans*-oriented to the benzene ring, to react with triethyl phosphite to give the quinoline derivatives (IV) in excellent yield (16). We herein report the reaction of the *N*-(2-nitrobenzyl)phthalimide derivatives (Va) and (Vb) with triethyl phosphite.

CHART 1



N-(2-Nitrobenzyl)phthalimide (Va) (1 mole), obtained by heating 2-nitrobenzylamine with phthalic anhydride, was heated with triethyl phosphite (5 moles) to give a mixture of three compounds; *N*-ethylphthalimide (VI), the isoindoloquinazoline (VIIa), and the phosphoramide derivative (VIII). The same treatment of the *N*-(4,5-dimethoxy-2-nitrobenzyl)phthalimide (Vb), obtained from 4-nitroveratrol and *N*-hydroxymethylphthalimide by Downes' method (15), also gave *N*-ethylphthalimide (VI) and the isoindoloquinazoline derivative (VIIb). Microanalysis of VI verified this composition, and the ir spectrum showed absorptions characterizing phthalimide. The nmr spectrum showed signals characteristic of the ethyl group and aromatic protons. Furthermore, the compound VI was identical with an authentic specimen (13) by mixed melting point. The structures of the compounds VIIa and VIIb, formed by removal of three oxygen atoms from the starting materials, were supported by ir spectra, in which the absorption due to the nitro and one of the imide carbonyl groups disappeared. Microanalysis also verified their compositions, and nmr spectra supported the structural assignment. Furthermore, these spectral data were completely superimposable on those of an authentic sample which was synthesized *via* the routes reported by Gabriel (14) and Downes (15). The compound VIII, formed by the nucleophillic attack of triethyl phosphite on the nitrene, showed the corresponding molecular ion peak in the mass spectrum, and microanalysis of the compound VIII verified

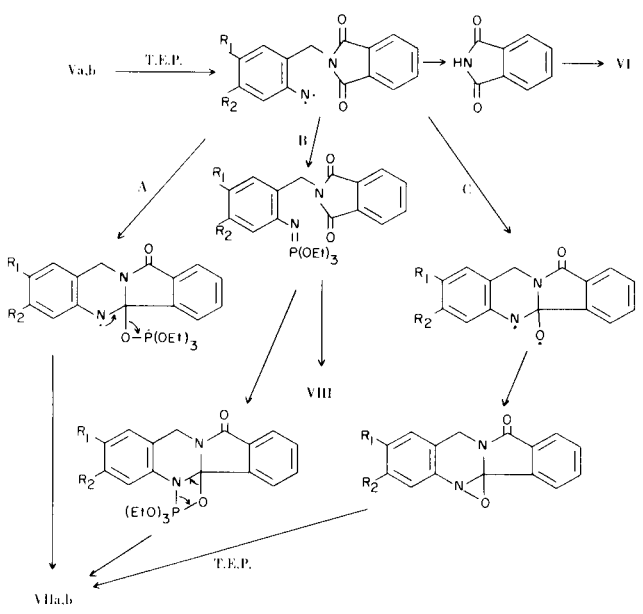
CHART 2



its composition. The ir spectrum showed the absorptions due to NH and phthalimide C=O and P-C-O stretching. The nmr spectrum showed the signals of an ethoxy group, NH, and the aromatic protons.

Perhaps the simplest mechanism to explain the formation of *N*-ethylphthalimide (VI), the isoindoloquinazolines (VIIa, b) and the phosphoramide (VIII) involves initial reduction of the nitro group and formation of the nitrene, followed by one of the routes A, B, and C as shown in Chart 3.

CHART 3



EXPERIMENTAL

Ir spectra were measured with a Hitachi EPI-3 recording spectrophotometer, nmr spectra with a Hitachi R-20 spectrometer, with tetramethylsilane as internal standard, and mass spectra with a Hitachi RMU 7 mass spectrometer.

N-(2-Nitrobenzyl)phthalimide (Va).

To a solution of 1.9 g. of the hydrochloride of *o*-nitrobenzylamine (17) in 10 ml. of water was added 5 ml. of 5% sodium hydroxide solution. The precipitated amine was then extracted with a small amount of benzene. The extract was washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated under a current of nitrogen to give the amine, to which was added 1.5 g. of phthalic anhydride. The mixture was fused for 10 minutes at *ca.* 160°. After cooling, the crystals were recrystallized from benzene to afford 16 g. (57%) of Va as yellowish-brown needles, m.p. 217-218°; ν max (chloroform) 1780, 1720 (C=O), 1530, 1345 cm^{-1} (NO_2); δ (deuteriochloroform) 5.21 (2H, singlet, benzylic protons), 7.10-8.10 ppm (8H, multiplet, aromatic protons).

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 63.91; H, 3.63; N, 10.16.

Reaction of *N*-(2-Nitrobenzyl)phthalimide (Va) with Triethyl Phosphite.

A solution of 2.1 g. of compound Va and 6.3 g. of triethyl phosphite was heated under reflux at 160-170° for 20 hours under a current of nitrogen and the mixture was evaporated at 100° (3 mm.) in order to remove a lower boiling substance. The residue was chromatographed on silica gel and eluted with benzene. The solvent was removed from the first benzene eluate to leave 0.4 g. (40.4%) of *N*-ethylphthalimide (VI) as pale yellow needles, m.p. 74-77° [lit., m.p. 77-79° (12)] (from dilute ethanol); ν max (chloroform) 1780, 1715 cm^{-1} (C=O); δ (deuteriochloroform) 1.29 (3H, triplet, J = 6.5 Hz, CH_3CH_2-), 3.75 (2H, quartet, J = 6.5 Hz, CH_3-CH_2-), 7.50-8.10 ppm (4H, multiplet, aromatic protons).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.64; H, 5.54; N, 8.21.

Removal of the solvent from the second benzene eluate gave 0.4 g. (21%) of 10,12-dihydroisoindolo[1,2-*b*]quinazolin-12-one (VIIa) as yellow needles, m.p. 182-184° (from ethanol); ν max (chloroform) 1730 (C=O), 1655 cm^{-1} (C=N); δ (deuteriochloroform) 4.93 (2H, singlet, C_{10}-H), 7.00-8.15 ppm (8H, multiplet, aromatic protons).

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.51; H, 4.24; N, 11.88.

Elution with chloroform gave 0.9 g. (32.9%) of diethyl *N*-(*o*-benzylphthaloylphenyl)phosphoramidate (VIII) as pale yellow granules, m.p. 146-148° (from benzene-hexane); ν max (chloroform) 3400 (NH), 1780, 1720 (C=O), 1020, 970 cm^{-1} (P-O-C); δ (deuteriochloroform) 1.04 (6H, triplet, J = 6.5 Hz, 2 x CH_3CH_2O-), 3.75, 3.98 (each 2H, two quartets, J = 6.5 Hz, 2 x CH_3CH_2O-), 4.55 (2H, singlet, benzylic protons), 5.48 (1H, broad doublet, NH), 6.20-8.00 ppm (8H, multiplet, aromatic protons); m/e 388 (M^+, 100%).

Anal. Calcd. for $C_{19}H_{20}N_2O_5P$: C, 58.76; H, 5.45; N, 7.21. Found: C, 58.30; H, 5.59; N, 7.26.

Reaction of *N*-(4,5-Dimethoxy-2-nitrobenzyl)phthalimide (Vb) with Triethyl Phosphite.

The same treatment of 3.4 g. of compound Vb with 8.3 g. of triethyl phosphite gave 0.1 g. (6%) of *N*-ethylphthalimide (VI) as pale yellow needles, the spectral data of which were completely identical with those of an authentic sample as above. Then 0.5 g. (17%) of 10,12-dihydro-7,8-dimethoxyisoindolo[1,2-*b*]quinazolin-12-one (VIIb) was obtained as yellowsih-green needles, m.p. 245-246° (from ethanol); ν max (chloroform) 1725 (C=O), 1650 (C=N); δ (deuteriochloroform) 2.87, 3.89 (each 3H, two singlets, 2 x OCH_3), 4.87 (2H, singlet, C_{10}-H), 6.55-8.10 ppm (6H, multiplet, aromatic protons).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 68.95; H, 4.71; N, 9.67.

Acknowledgment.

We thank President A. Yamaguchi and Mr. T. Sogabe, Nippon Chemipha Co. Ltd., for their encouragement, and Miss A. Kawakami, Miss C. Yoshida, Miss Y. Tadano, and Mr. T. Ohuchi for nmr and mass spectral determinations, and for microanalyses.

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