

The Synthesis of Pseudorutaecarpine with Triethyl Phosphite (I)

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Pseudorutaecarpine was synthesized by nitrene reaction of 3-(2-nitrobenzyl)-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-9-one (IV).

Rutaecarpine, the indole alkaloid from *Evodia rutaecarpa*, was originally investigated by Asahina and his co-workers who suggested the structure I (3,4). By treatment of the compound IV, which was obtained by condensation of *o*-nitrobenzaldehyde (III) with desoxyvasicinone (II) (5) at 140°, with triethyl phosphite, followed by rearrangement of the nitrene V as an intermediate through route A, we hoped to obtain rutaecarpine (I).

Meanwhile, we reported a modified synthesis of several compounds by application of this reaction (10-16). Furthermore, Sundberg and his co-workers reported that the β,β' -disubstituted *o*-nitrostyrene derivatives (VII) underwent ring closure with rearrangement to give indole derivatives (VIII) through a nitrene intermediate (17). We now report a simple synthetic method of a rutaecarpine-like compound by this reaction.

CHART 1

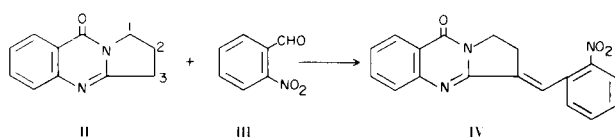
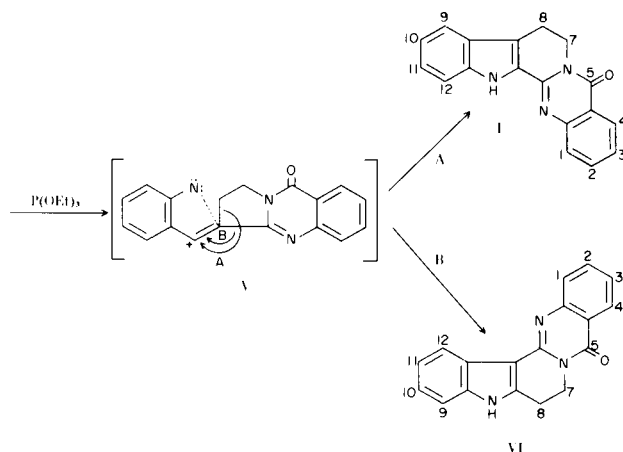
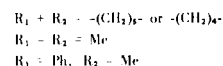
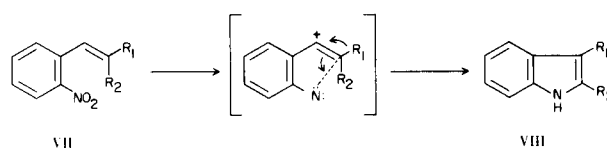
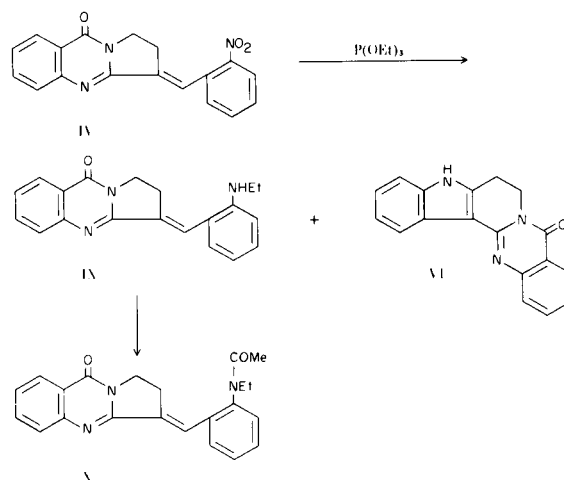


CHART 2



Heating compound IV with two equimolar amounts of triethyl phosphite at 170° for 20 hours in a current of nitrogen afforded two compounds after chromatographic

CHART 3



The reaction of aromatic nitro compounds with triethyl phosphite was investigated by Cadogan and his co-workers, and this reaction has been applied to the synthesis of indole derivatives. The reaction mechanism has been attributed to the participation of a nitrene (6-9).

separation on silica gel. The first compound had the molecular formula $C_{20}H_{19}N_3O$ (from mass spectrometry and microanalysis). In the infrared spectrum, the absorption band due to the nitro group disappeared and the band attributable to NH group appeared at 3150 and 3300 cm^{-1} . Furthermore, the nuclear magnetic resonance spectrum showed one ethyl group and one exchangeable proton (NH group). Treatment of this compound with acetic anhydride afforded the acetyl derivative X. Therefore, the formation of IX, the structure of which has been unambiguously confirmed, could result from an abstraction reaction of a nitrene to give the amino derivative followed by ethylation of triethyl phosphite.

The second compound showed the same molecular ion peak and fragmentation pattern as rutaecarpine in their mass spectrometry, but their melting points and IR spectra were slightly different from each other. Therefore, this compound, which was named pseudorutaecarpine, could be formed *via* route B (Chart 1).

EXPERIMENTAL

Melting points are uncorrected. The IR were taken with a Hitachi EPI-S₂ spectrophotometer, and the NMR spectra were run on a Hitachi H-60 spectrometer using tetramethylsilane as an internal reference, and mass spectra were measured on a Hitachi RMU-7 mass spectrometer.

3-(2-Nitrobenzal)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (IV).

A mixture of 1.86 g. of 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (II) and 1.51 g. of *o*-nitrobenzaldehyde (III) was heated in an oil-bath at 140-145° for 1 hour. On cooling, the reaction mixture solidified and was collected by filtration and washed with a small amount of chloroform (5 ml.) on a filter. Recrystallization from chloroform-ethanol gave 1.8 g. (54.6%) of IV as pale yellow prisms, m.p. 264-266°; ν max (chloroform) cm^{-1} : 1665 (C=O), 1525, 1340 (NO₂); nmr (deuteriochloroform) δ : 3.25 (2H, triplet, $J = 6.3$ Hz, C₂-H₂), 4.49 (2H, triplet, $J = 6.3$ Hz, C₁-H₂), 7.42-8.60 ppm (9H, multiplet, aromatic and olefinic protons).

Anal. Calcd. for $C_{18}H_{13}N_3O_3$: C, 67.70; H, 4.11; N, 13.16. Found: C, 67.77; H, 4.30; N, 13.41.

Reaction of IV with Triethyl Phosphite.

A mixture of 1.9 g. (0.006 mole) of IV and 2 g. of triethyl phosphite was heated under reflux at 170° for 20 hours in a current of nitrogen, and the mixture was distilled at 100° (3 mm.) to remove a lower-boiling substance. The residue was chromatographed on silica gel using chloroform as the solvent. Removal of the first eluate gave 0.8 g. of 3-(2-ethylaminobenzal)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (IX). Recrystallization from ethanol afforded pale yellow leaflets, m.p. 182-183°; ν max (potassium bromide) cm^{-1} : 3300, 3150 (NH), 1665 (C=O); nmr (deuteriochloroform) δ : 1.30 (3H, triplet, $J = 6.8$ Hz, CH₂CH₃), 3.18 (5H, multiplet, C₂-H₂, CH₂CH₃, and NH, exchangeable with deuterium oxide), 4.18 (2H, triplet, $J = 6$ Hz, C₁-H₂), 6.50-8.36 ppm (9H, multiplet, aromatic and olefinic protons); mass (m/e) (%): 317 (M⁺) (100%).

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.68; H, 6.03; N, 13.24. Found: C, 75.27; H, 5.96; N, 13.53.

The second eluate afforded 0.1 g. of pseudorutaecarpine (VI).

Recrystallization from benzene-*n*-hexane gave pale brown needles, m.p. 261-263°; ν max (potassium bromide) cm^{-1} : 3160 (NH), 1650 (C=O); nmr (trifluoroacetic acid) δ : 3.38 (2H, triplet, $J = 6$ Hz, C₈-H₂), 4.63 (2H, triplet, $J = 6$ Hz, C₇-H₂), 7.28-8.40 ppm (8H, multiplet, aromatic protons); mass (m/e) (%): 287 (M⁺) (100%).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 75.23; H, 4.83; N, 14.36.

Acetylation of IX.

A mixture of 100 mg. of IX and 10 ml. of acetic anhydride was heated on a water-bath for 3 hours. On cooling, a mixture was poured onto 20 ml. of water, and then made basic with saturated aqueous sodium bicarbonate solution. Collection by filtration and recrystallization from benzene-*n*-hexane afforded 65 mg. of X as colorless needles, m.p. 195-197°; ν max (chloroform) cm^{-1} : 1665 (C=O); nmr (deuteriochloroform) δ : 1.14 (3H, triplet, $J = 6$ Hz, CH₂CH₃), 1.80 (3H, singlet, COCH₃), 3.00-3.51 (4H, multiplet, CH₂CH₃ and C₂-H₂), 4.27 (2H, triplet, $J = 6$ Hz, C₁-H₂), 7.21-8.37 ppm (9H, multiplet, aromatic and olefinic protons).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.97; H, 5.96; N, 11.59.

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