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Synthesis of 1, 2, 3, 9-Tetrahydro-7-bromo-6-hydroxy-5-methoxypyrrolo-[2, 1-b]-quinazoline: A New Analog of Deoxyvasicine

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SYNTHESIS OF 1, 2, 3, 9-TETRAHYDRO-7-BROMO-6-HYDROXY-5-METHOXYPYRROLO-[2, 1-b]-QUINAZOLINE: A NEW ANALOG OF DEOXYVASICINE

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Abstract: A new deoxyvasicine analog (**9**) was synthesized by condensation of 2-amino-5-bromovanillin (**6**) with 4-aminobutyraldehyde (**7**) in phosphate buffer (pH 5.8) followed by hydrogenation of the resulting quinazolinium complex (**8**) at 65°C in presence of 5 % palladium-on-barium sulfate.

There has been a considerable interest in the synthesis[1-6] of vasicine and related analogs due to their extensive use in the traditional medicine[7] as as a remedy for cold, cough, bronchitis, asthma and related cardiovascular disorders. Although the synthesis of vasicine and deoxyvasicine from ortho-aminobenzaldehyde and gamma-amino-alpha-hydroxybutyraldehyde diethyl acetal using the Schopf-Oechler scheme of vasicine synthesis has been well documented,[4] there has been no literature report of the synthesis of 6-bromo-5-hydroxy-4-methoxydeoxyvasicine from vanillin. The bromo analog was synthesized to aid in establishing further structure-activity relationships within the quinazoline class of compounds. We now wish to report here the convenient synthesis of a new analog of deoxyvasicine from vanillin.

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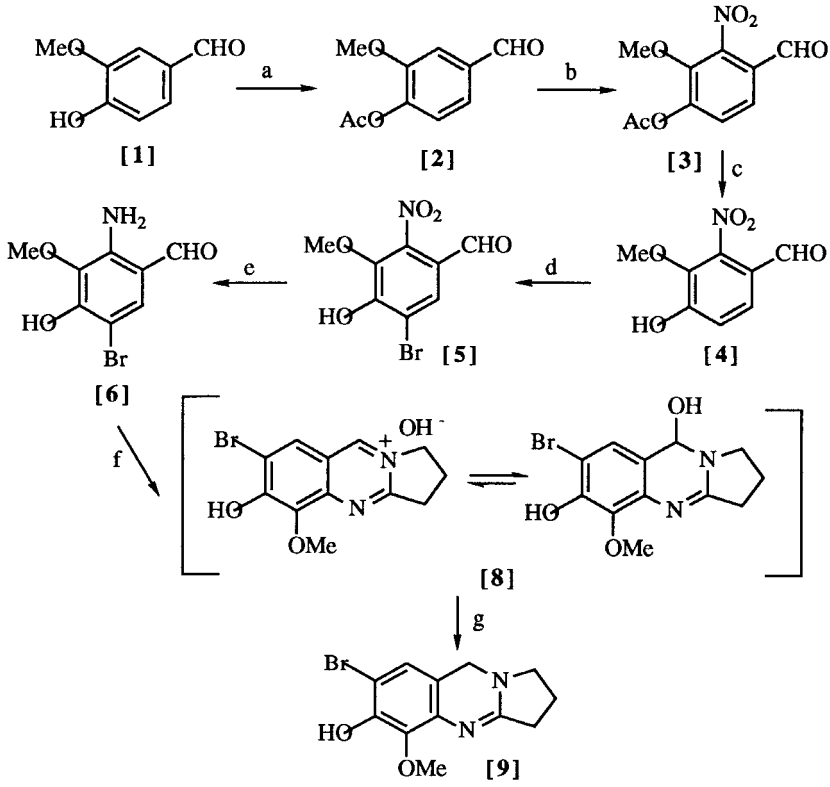
Vanillin (**1**) was converted through (**5**) to 2-amino-5-bromovanillin (**6**)[8,9]. Liberation of **7** from the diethyl acetal in dilute aqueous solution at pH 2 at 80°C during 30 minutes followed by reaction[4] with **6** at pH 5.8 (aqueous phosphate buffer) for 72 h at room temperature gave an orange solution of the 1, 2-dihydroquinazolinium cation (**8**).



SCHEME 1

REACTION CONDITIONS: a = Acetic anhydride, reflux, 3.5 h., b = HNO_3, 2-6°C., c = KOH, MeOH., d = Br_2, AcOH, Iodine (catalyst)., e = $FeSO_4$, NH_4OH., f = 4-aminobutyraldehyde **[7]**, pH 5.8 (aq. phosphate buffer), room temperature, 72 h., g = H_2, 5 % Pd-on-barium sulfate, 65°C, 1.5 h.

Compound **8** was stirred vigorously with 5 % palladium-on-barium sulfate catalyst under a stream of hydrogen at 65°C for 1.5 h. The filtrate was basified with ammonia solution, then extracted (6 x 100 mL) with chloroform, the extracts were combined and dried (Na_2SO_4). Evaporation of solvents *in vacuo* and recrystallization from benzene and petroleum ether gave a gummy substance of 6-bromo-5-hydroxy-4-methoxydeoxyvasicine (**9**) (65 % overall yield) as the free base, then converted to the hydrochloride salt.

Experimental Section

1, 2, 3, 9-tetrahydro-7-bromo-6-hydroxy-5-methoxypyrrolo-[2, 1-b]-quinazoline

2-Amino-5-bromovanillin (0.5 g, 2.03 mmol) was dissolved with stirring and gentle heat in 90 % methanol (50 mL), then cooled to room temperature. 4-Aminobutyraldehyde diethyl acetal (0.4 g, 2.48 mmol) was dissolved in water (10 mL) and kept at 80°C at pH 2 for 30 minutes to liberate the free aldehyde. The pH of the solution of the aldehyde was adjusted to pH 5.5 with phosphate buffer and the solution was added to the solution of of 2-amino-5-bromovanillin and the pH of the mixture adjusted to pH 5.8 with aqueous phosphate buffer. The mixture was kept at room temperature for 72 h to give an orange solution of the quinazolinium complex. The orange solution was then stirred vigorously at 65°C in an atmosphere of hydrogen in the presence of 5 % palladium-on-barium sulfate (1.5 g) for 1.5 h. The catalyst was removed by filtration, the filtrate basified with ammonia and extracted with chloroform (100 mL x 6). The chloroform extracts were washed with water and dried (Na_2SO_4). Evaporation of solvents *in vacuo* and attempted crystallization (benzene and petroleum ether) gave a brown gummy substance. The hydrochloride salt was obtained by addition of 1.0 M HCl in ether to a benzene solution of the gummy substance to give a voluminous white precipitate, which was then filtered and recrystalized (benzene and petroleum ether) to give white crystals (0.3 g, 65 %) mp 215-217°C. ^{1}H-nmr ($CDCl_3$): δ 7.50 (1H, s, C_7-H), 6.15 (1H, s, phenolic-H), 3.89 (3H, s, OCH_3), 2.9-3.6 (2H, m, C_1-H), 3.25 (2H, t, C_3-H), 2.26 (2H, m, C_2-H), 1.8-2.7 (2H, m, C_8-H).

IR (KBr): 3450-3300 (phenolic OH), 1650 (entire conjugative system), 1625-1460 (dihydroquinazoline ring system), 1632 (-C = N), 860 cm-1 (substituted benzene). UV (Absorption max., EtOH): 220, 276, 336 nm. Calc. for $C_{12}H_{13}N_2O_2Br.HCl$: C 43.20, H 4.23, N 8.40, Br 23.95., Found: C 43.14, H 4.15, N 8.38, Br 23.89.

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