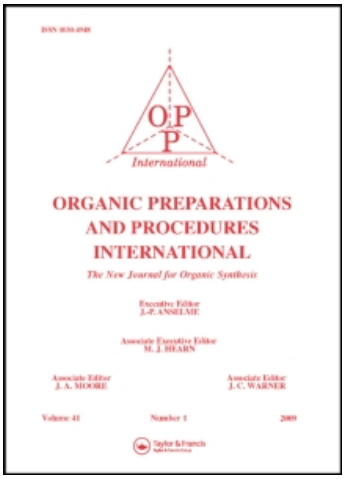

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AN IMPROVED SYNTHESIS OF 1, 2-DEHYDRO-N-ACETYLDOPAMINE

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AN IMPROVED SYNTHESIS OF 1,2-DEHYDRO-N-ACETYLDOPAMINE

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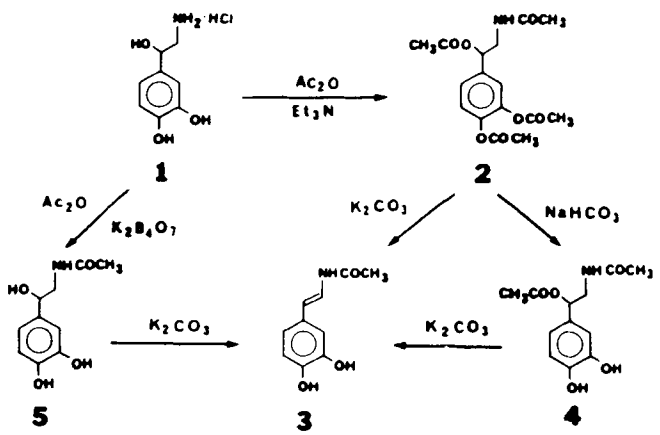
The well-established[1,2] participation of catecholamines and their derivatives in the hardening and tanning of insect cuticle (sclerotization) is essential for the survival of most insects. Cuticular phenoloxidase is known to play a crucial role in this process by oxidizing the catecholamine derivatives which may then crosslink with structural protomers in cuticle to generate protein-protein as well as protein-chitin crosslinks.[1-4] Three major reactive species have been characterized so far as reaction products of phenoloxidases on catecholamine derivatives.

These include well characterized quinones,[1-3] quinone methides[2,4] and 1,2-dehydro-N-acetyldopamine.[5] Quinones and quinone methides undergo spontaneous nucleophilic 1,4- and 1,6-Michael additions with available nucleophiles, which account for crosslinking in cuticle. The stability of 1,2-dehydro-N-acetyldopamine, recently isolated from sclerotized cuticle by hot alkali treatment,[5] cannot account for direct crosslinking. In order to clarify its role in sclerotization, 1,2-dehydro-N-acetyldopamine was synthesized in low yield from 3,4-dimethoxycinnamic acid via a long and tedious route.[6]

Since verification of the claim that 1,2-dehydro-N-acetyldopamine is a key intermediate in sclerotization, could lead to a clear understanding of the methanisms of sclerotization and thus to the development of new types of insecticides, we have therefore examined simpler and more efficient routes for the synthesis of 1,2-dehydro-N-acetyldopamine starting from commercially available norepinephrine as shown below.



SCHEME. 1.

Tetraacetylnorepinephrine (2) was synthesized in nearly quantitative yield by acetylation of norepinephrine hydrochloride with acetic anhydride in the presence of triethylamine. Synthesis of 1,2-dehydro-N-acetyldopamine (3) could be achieved either by direct deacetylation of 2, or by

deacetylation of diacetate 4 by treatment with potassium carbonate. N-acetylnorepinephrine (5) synthesized from 1 by N-acetylation in potassium tetraborate, can also be converted to 3 with potassium carbonate in moderate yield.

EXPERIMENTAL SECTION

Solvents were evaporated in vacuo on a rotary evaporator at a bath temperature not exceeding 30°. Mps are uncorrected and were determined on a Fisher-John apparatus. ^{1}H-NMR spectra were recorded on a 60 MHz Perkin-Elmer Model R-24 spectrometer in $CDCl_3$ or DMSO-d_6 as solvent using TMS as internal standard. IR spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. TLC was performed on silica gel plates (Kodak) using the solvent system: A = ethyl acetate; B = 10% methanol in ethyl acetate.

(±) Tetraacetylnorepinephrine (2).- A mixture of (±) norepinephrine hydrochloride (1, 25 g, 0.12 mol), acetic anhydride (150 mL) and triethylamine (25 mL) was stirred under nitrogen at 100° for 1 hr. The cooled mixture was poured onto ice and extracted with 700 mL of ethyl acetate. The organic extract was washed with water, followed by brine and dried over anhydrous $MgSO_4$. Removal of solvent gave 2 which was recrystallized from hexane to give 40 g (97%) of white solid, mp. 104-105°; Rf (A): 0.46. ^{1}H-NMR ($CDCl_3$): δ 1.85 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.30-3.70 (m, 2H, CH_2), 5.60-6.00 (m, 1H, CH), 6.80-7.40 ppm (m, 4H, ArH and NH). IR (nujol): 3250 (NH), 1805 (CO), 1780 (CO), 1730 (CO), 1630 (NH), 1370 (CH_3) cm^{-1}. MS: m/e 337 (M^+).

1,2-Dehydro-N-acetyldopamine (3).- A mixture of tetraacetylnorepinephrine (2, 2.0 g, 6 mmol) and anhydrous potassium carbonate (2 g) in dimethyl sulfoxide (15 mL) was heated under nitrogen at 110° for 2 hrs. The reaction mixture was then poured into water and extracted with 350 mL of ethyl acetate. The organic solution was washed with brine solution and dried over anhydrous $MgSO_4$. Solvent removal on a rotary evaporator gave 1.4 g of an oily product. Crystallization from 0.2 N acetic acid produced

0.64 g (55%) of pure 3, mp. 197-198°, as white crystals. The NMR, IR, UV, and MS were identical as reported earlier.[6]

(±) α-(Acetamidomethyl)-3,4-dihydroxybenzyl Acetate (4).- Compound 2 (0.9 g, 2.7 mmol) was stirred under nitrogen in 1 N sodium bicarbonate solution (10 mL) at 60° for 2 hrs, cooled and extracted with 200 mL of ethyl acetate. The organic extract was washed with brine and dried over anhydrous $MgSO_4$. Solvent removal by flash evaporation gave 0.456 g (82%) of 4 as an oil, single spot on tlc with Rf (A): 0.18.

^{1}H-NMR (DMSO-d_6): δ 1.80 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.80-3.50 (m, 2H, CH_2), 4.10-4.60 (m, 1H, CH), 6.40-7.00 (m, 3H, ArH), 7.80 (br s, 1H, NH), 8.70 ppm (br s, 2H, OH).

The reaction of compound 4 (0.4 g, 1.5 mmol) with anhydrous potassium carbonate (0.5 g) in dimethyl sulfoxide (5 mL) gave 3 as a white solid, 0.075 g (25%), mp. 195-196°, identical to the product previously reported.[6]

(±) N-Acetylnorepinephrine (5).- A mixture of (±) norepinephrine hydrochloride (1.0 g), 10% aqueous potassium tetraborate solution (50 mL) and acetic anhydride (0.5 mL) was stirred at room temperature for 1 hr. The solution was acidified with 1 N NCl and extracted with 250 mL of ethyl acetate. The organic extract was dried over anhydrous $MgSO_4$ and evaporated using rotary evaporator to give 0.87 g (84%) of 5 as white solid, mp. 52-53°.

^{1}H-NMR (DMSO-d_6): δ 1.80 (s, 3H, CH_3), 2.80-3.30 (m, 3H, CH_2 + OH), 4.10-4.60 (m, 1H, CH), 6.00-6.80 (m, 5H, ArH + OH), 7.60-8.10 ppm (br s, 1H, NH). IR (nujol): 3400-3100 (br, OH, NH), 1650 (CO), 1530 (NH), 1370 (CH_3) cm^{-1}. MS: m/e 211 (M^+).

(±) N-Acetylnorepinephrine (5, 60 mg) and anhydrous potassium carbonate (50 mg) in dimethyl sulfoxide (2 mL) also gave 3.

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