HETEROCYCLES FROM CARBOHYDRATE PRECURSORS. SYNTHESIS OF SOME FUSED NITROGEN TRI- AND PENTAHETEROCYCLES FROM KOJIC ACID

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ABSTRACT

The reaction of kojic acid with one and two equivalents of 1,2-diamino-4,5-dimethylbenzene afforded 2-hydroxy-5,6-dihydro-8,9-dimethyl-pyridono[1,2-a]quinoxaline and 2,3,10,11-tetramethyl-5,6-dihydro-13H-quinoxalino[2′,3′ : 4,5]pyrido[1,2-a]quinoxaline respectively.

INTRODUCTION

In continuation of our work on the synthesis of heterocyclic compounds from carbohydrate precursors[1], the reaction of kojic acid (1) with various types of hydrazines was investigated[2-4]. The reaction of (1) with *o*-phenylenediamine was reported to give fused nitrogen heterocycles[5,6], and the product (3) resulting from the reaction of equimolar equivalents of the reactants was found to be identical with the product of the reaction of D-*threo*-2,3-hexodiulose with *o*-phenylenediamine dihydrochloride. The formation of the pyridone ring fused to the quinoxaline ring was explained in terms of a β-hydroxycarbonyl elimination, 1,2-enolization and cyclization of the sugar moiety, as deduced from the formation of kojic acid from sugar derivatives. The formation of such fused heterocyclic systems is relatively uncommon and consequently we report here, the synthesis of some of these fused heterocyclic derivatives from kojic acid.

EXPERIMENTAL

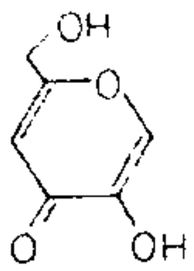
General methods: Melting points were determined with a kofler-block apparatus and are uncorrected. Infrared spectra were recorded with a Unicam SP 200 spectrometer. ^{1}H-NMR spectra were measured with EM-390 90 MHz NMR spectrometer for solutions in DMSO-d_6 or $CDCl_3$ using tetramethylsilane as external or internal standard respectively. Chemical shifts are given on the δ scale. Microanalyses were performed in the Chemistry Department, Cairo University, Cairo, Egypt.

2-Hydroxy-5,6-dihydro-8,9-dimethyl-pyridono [1,2-a] quinoxaline hydrochloride (4): A solution of kojic acid (1.42 g, 10 mmol) in water (40 ml) was treated with 1,2-diamino-4,5-dimethylbenzene hydrochloride (2.5 g, 12 mmol) (prepared by reaction of 2 with concentrated hydrochloric acid in ice), and the mixture was heated for 5 hr at 95° and evaporated to dryness and the residue was extracted with hot methanol. Crude product, obtained by evaporating the methanolic solution, was recrystallized from methanol (three times) in yellow needles (37% yield), m.p. 245–275°C (dec). IR (KBr) 3350 (OH); 1640 (C=O); 1615 cm^{-1} (C=C). NMR (DMSO-d_6); δ1.93 and 2.0 (2s, 6H, $2CH_3$); 4.63 (s, 2 H, CH_2); 6.23 (s, 1 H, H-4); 7.10 and 7.47 (2s, 2 H, aromatic protons) and 8.67 (s, 1 H, H-1). *Anal.* $C_{14}H_{15}ClN_2O_2$. Calc'd (%) C, 60.3; H, 5.4; N, 10.1. Found (%) C, 60.7; H, 5.7; N, 10.2.

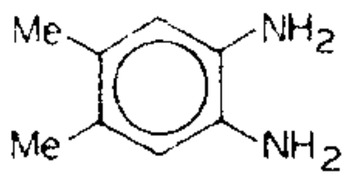
2-Hydroxy-5,6-dihydro-8,9-dimethyl-pyridono [1,2-a] quinoxaline (5): A solution of compounds 4 (0.70 g) in water was neutralized with potassium carbonate, and kept overnight in an ice-box. The product was collected by filtration, washed with water, and recrystallized from methanol to give needles of 5 (67% yield), m.p. 237-239°C. IR (KBr) 3410–3220 (OH); 1620 cm^{-1} (C=O and C=C). *Anal.* $C_{14}H_{14}N_2O_2$. Calc'd (%) C, 69.4; H, 5.8; N, 11.6. Found (%) C, 69.7; H, 5.9; N, 11.8.

6-Acetyl-2-acetoxy-5, 6-dihydro-8, 9-dimethyl-pyridono[1,2-a]-quinoxaline (6): A solution of 5 (0.3 g) in dry pyridine (5 ml) was treated with acetic anhydride (3 ml) and kept for overnight at room temperature. The mixture was poured onto crushed ice, and the product was collected by filtration, successively washed with water, and ethanol. It was recrystallized from ethanol-water in orange-red needles (75% yield), m.p. 194–195°C. IR (KBr) 1740 (OAc); 1660 (NAc); 1620 cm^{-1} (C=O and C=C). *Anal.* $C_{18}H_{18}N_2O_4$. Calc'd (%) C, 66.2; H, 5.6; N, 8.6. Found (%) C, 66, 3; H, 5.7; N, 8.8.

2, 3, 10, 11-Tetramethyl-5, 6-dihydro-13 H-quinoxalino-[2′3′ : 4,5]pyrido [1,2-a] quinoxaline (7): A



(1)



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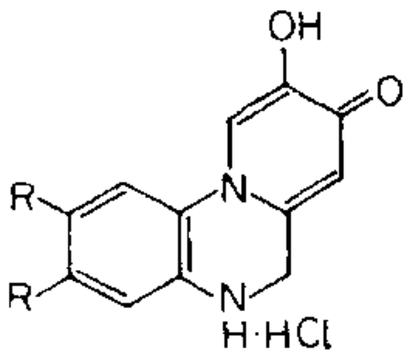
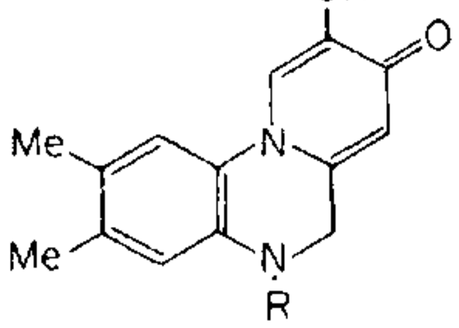
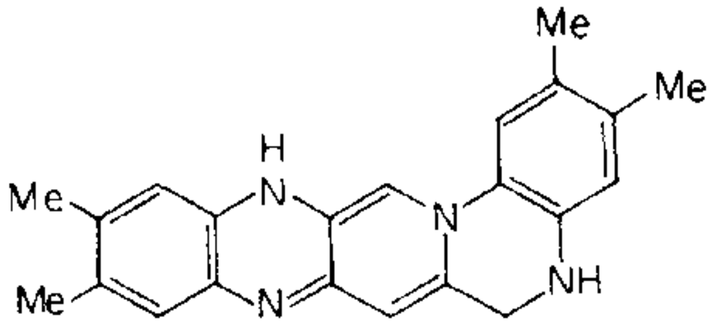


(3) R = H
(4) R = Me

OR



(5) R = H
(6) R = Ac



(7)

mixture of kojic acid (1.4 g, 10 mmol), 2 (2.7 g, 20 mmol) and 10% acetic acid (70 ml) was refluxed on a water-bath for 2 hr, and then kept for overnight at 0°C. The product was collected by filtration, washed repeatedly with water and then with ethanol. It was recrystallized from ethanol water in yellow needles (74% yield), m.p. 208–209°C. IR: (KBr) 3340 (NH); 1615 cm^{-1} (C = C and C = N). NMR (DMSO-d_6): δ 2.17, 2.33, 2.38 and 2.40 (4s, 12H, $4CH_3$); 2.98 (s, 2 H, CH_2); 6.13 (s, 1 H, H–C = C–N) and 7.53 (m, 5 H, aromatic protons). *Anal.* $C_{22}H_{22}N_4 . H_2O$ Calc'd (%) C, 73.3; H, 6.7. Found (%) C, 73.0; H, 6.8.

RESULTS AND DISCUSSION

Condensation of kojic acid with 1,2-diamino-4,5-dimethylbenzene dihydrochloride gave the hydrochloride (4) whose elemental analysis agreed with the condensation of 1:1 moles of the reactants. Its infrared spectrum showed the presence of the hydroxyl group at 3350 cm^{-1} and the C=O and C=C at 1640 and 1615 cm^{-1} respectively. The ^{1}H-NMR spectrum of (4) showed two singlets at δ 1.93 and 2.00 assigned for the two methyl groups of the diamine moiety. The singlets which appeared at δ 4.63, 6.23 and 8.67 were due to the methylene protons, H-4 and H-1 respectively, which corresponded to the kojic acid part of (4). The downfield shift of the latter proton (H-1) relative to the corresponding proton in kojic acid derivatives, may be due to its higher proximity to the deshielding region of the aromatic nucleus. The aromatic protons appeared as two singlets at δ 7.10 and 7.47, and the NH and OH appeared as a broad signal at $\sim \delta$ 3.2.

The free base (5) was obtained from the hydrochloride (4) by neutralization with potassium carbonate. Acetylation of (5) afforded the corresponding diacetyl derivative, 6-acetyl-2-acetoxy-5,6-dihydro-8,9-dimethyl-pyridono[1,2-a]quinoxaline (6). Its infrared spectrum showed three bands in the carbonyl frequency region at 1740, 1660 and 1620 cm^{-1} due to the OAc, NAc, CO and C=C of the pyridone ring respectively.

When the reaction of kojic acid was conducted with two molecules of the 1,2-diamino-4,5-dimethylbenzene, a product was isolated whose structure was formulated as the pentacyclic compound (7), based on the structure of the product resulting from similar reaction[6] using *o*-phenylenediamine. Its infrared spectrum showed the presence of bands at 3340 and 1615 cm^{-1} due to the NH, C=C and C=N groups respectively. Its ^{1}H-NMR spectrum showed the presence of the four methyl groups as four singlets at δ 2.17, 2.33, 2.38 and 2.40; and the methylene group at δ 2.98. One of the two H-C= appeared at δ 6.13, whereas the other one appeared under the multiplet of the aromatic protons at $\sim \delta$ 7.53. However, the structure (7) still need further confirmation.

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