

SYNTHESSES AND STRUCTURE DETERMINATIONS OF SOME SELENOCYANATO- AND THIOCYANATO-KOJIC ACID DERIVATIVES.

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Abstract: Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyranone) and analogues have been reported as biologically active compounds. Four kojic acid thiocyanato- and selenocyanatoanalogues have been prepared in order to investigate them for antineoplastic effects.

Background: Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyranone) and analogues have been reported as biologically active compounds. Most of these compounds have been tested for effects on selected biological processes in a variety of *in vitro* test systems^{1,2}. Some of the kojic acid derivatives have been shown to exert antineoplastic effects *in vivo*^{3,4}. Among the kojic acid derivatives there are some sulphur-containing compounds, e.g. 5-benzyloxy-2-thiocyanatomethyl-4-pyranone (1) that have been shown to significantly inhibit neoplastic cell growth as well as DNA and RNA synthesis⁵. There has since many years been a debate about anticarcinogenic effects of selenium and selenite compounds in nutritionally acceptable low doses. This debate has stimulated the search for anticancer selenium agents and drugs with low toxicity. The majority of organic selenium compounds investigated for antineoplastic activity have been selenium analogues of sulphur compounds. Benzyl thiocyanate and benzyl selenocyanate have been investigated for antitumour activity. The benzyl selenocyanate, administered in the diet, has been shown to inhibit intestinal carcinogenesis in rats and mice while the benzylthiocyanate was inactive at the same doses⁶. Due to these results we found it interesting to synthesize some kojic acid derivatives of thio- and selenocyanates for testing of antineoplastic activity.

Results: We have prepared four analogues (Fig 1) in order to investigate them for antineoplastic effects. The preparation method for the substances has been in three steps according to Uher et al.⁷ with some modifications; benzylation or methylation of kojic acid, chlorination with thionyl chloride, nucleophilic substitution with thio- or selenocyanate.



Fig. 1: Structures of kojic acid derivatives

Experimental:

5-Benzyl-2-selenocyanatomethyl-4-pyranone. A solution of 1.7 g (0.012 mol) potassium selenocyanate in 10 ml acetone was added to a suspension of 2.5 g (0.010 mol) 5-benzyl-2-chloromethyl-4-pyranone⁴ in 50 ml acetone. During reflux for 1 h a precipitation of potassium chloride was observed. After addition of approximately 100 ml of distilled water the resulting mixture was filtered and the precipitate was washed with water. Recrystallization from ethanol gives a pure sample in 88 % yield, mp 128-130 °C. ¹H NMR (DMSO-d₆): 8.26 (s, 1H, H6), 7.40 (s, 5H, H_{arom}), 6.40 (s, 1H, H3), 4.95 (s, 2H, Ph-CH₂), 4.17 (s, 2H, CH₂-Se). Mass spectrum, m/z (I, %): 321 (2) (M⁺); 215 (80); 91 (100); 65 (18)⁸

5-Methoxy-2-selenocyanatomethyl-4-pyranone. A solution of 0.21 g (1.2 mmol) potassium selenocyanate in 2 ml acetone was added to a suspension of 0.20 g (1.4 mmol) 5-methoxy-2-chloromethyl-4-pyranone [8] in 10 ml acetone. The solution was filtered and evaporated. The residue was crystallized and recrystallized from ethanol to give a pure sample in 75 % yield, mp 128-131 °C. ¹H NMR (DMSO-d₆): 8.16 (s, 1H, H6), 6.36 (s, 1H, H3), 4.16 (s, 2H, CH₂-Se), 3.67 (s, 3H, CH₃). Mass spectrum, m/z (I, %): 245 (78) (M⁺); 139 (100); 215 (36)⁸.

5-Benzyl-2-thiocyanatomethyl-4-pyranone was prepared according to Uher et al. 1995, mp 128-130 °C^{5,9}. Mass spectrum, m/z (I, %): 273 (20) (M⁺); 215 (40); 91 (100); 65 (86).

5-Methoxy-2-thiocyanatomethyl-4-pyranone. A solution of 0.87 g (5.0 mmol) potassium thiocyanate in 5 ml acetone was added to a suspension of 0.6 g (6.0 mmol) 5-methoxy-2-chloromethyl-4-pyranone⁸ in 20 ml acetone. After reflux for 1 h the mixture was filtered and the filtrate evaporated. The residue was crystallized and recrystallized from toluene to give a pure sample in 50 % yield, mp 119-126 °C. ¹H NMR (DMSO-d₆): 8.20 (s, 1H, H6), 6.44 (s, 1H, H3), 4.32 (s, 2H, CH₂-S), 3.67 (s, 3H, CH₃). Mass spectrum, m/z (I, %): 197 (24) (M⁺); 167 (12); 139 (100).

The elemental analyses (C, H, N) gave acceptable results for all syntheses.

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