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Re-examination of Nucleophilic Substitution in Chlorokojic Acid

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Summary. Chlorokojic acid was reacted with $S_2O_3^{2-}$, NO_3^-, N_3^-, I^-, and SCN^-. Only the three latter nucleophiles substituted the chlorine atom in the 2-CH_2Cl group of kojic acid. In none of the products nucleophilic substitution at position 6 of the 4-pyrone could be found. Regular substituion of chlorokojic acid with I^- (iodokojic acid), N_3^- (azidokojic acid), and SCN^- (thiocyanato and isothiocyanato kojic acids) was accompanied by formation of allomaltol. Reaction pathways for the formation of allomaltol and 6-substituted allomaltol derivatives are proposed. The latter has been formerly discovered in the reaction of chlorokojic acid with secondary amines.

Keywords. Allomaltol; Azidokojic acid; Iodokojic acid; Isothiocyanatokojic acid; Thiocyanatokojic acid.

Introduction

As could be anticipated, the chlorine atom in chlorokojic acid (2-chloromethyl-5-hydroxy-pyran-4-one), (**1**) [1,2] has been shown to readily undergo nucleophilic substitution [3–5]. Among the nucleophiles employed, secondary amines have revealed a rather unusual behaviour. Apart from regular nucleophilic substitution in the 2-chloromethyl group, attack at position 6 of the ring accompanied by elimination of the chlorine atom in the 2-chloromethyl group has been observed providing 5-hydroxy-2-methyl-6-substituted pyran-4-ones, *i.e.* 6-substituted allomaltols. Attempts to elucidate the mechanism of this reaction [6] prompted us to re-investigate the nucleophilic substitution in chlorokojic acid with several nucleophiles. One might assume that other nucleophiles could also produce 6-substituted allomaltols. In order to contribute to the knowledge of the mechanism of 6-substitution by secondary amines, so far characterized as an electrophilic substitution of the onium electrophile [6, 7], the reaction of chlorokojic acid with N_3^-, I^-, NO_2^-, $S_2O_3^{2-}$, and SCN^- was studied. Some of these substitutions were attempted also on 5-methoxy and 5-benzyloxy derivatives of chlorokojic acid. A revised view of the reaction mechanism is presented.

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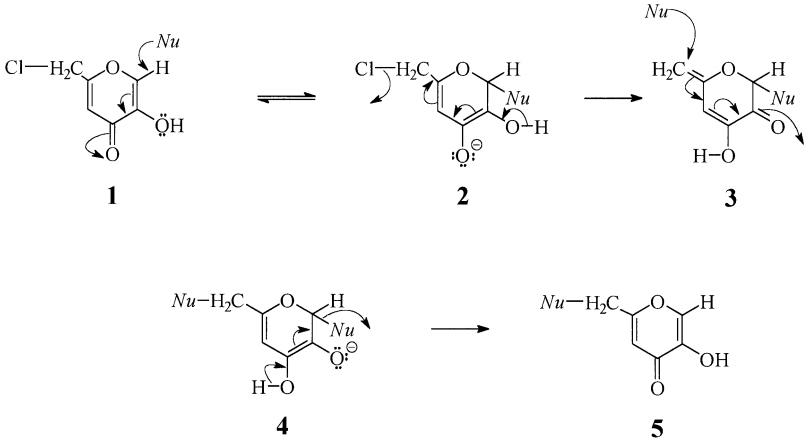
Results and Discussion

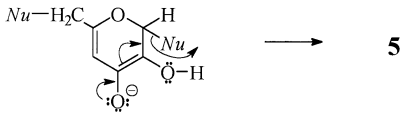
Among the nucleophiles employed, a total lack of reaction was observed in the cases of $S_2O_3^{2-}$ and NO_2^-. Neither products of nucleophilic substitution of the chlorine atom in the side chain at position 2 nor the product of 6-substitution were formed. In addition, 5-alkoxy derivatives of **1** appeared to be passive in the reaction. In contrast, N_3^-, I^-, and SCN^- did react. The corresponding 2-iodo- [2, 8] and 2-azido kojic acids [3, 9] were isolated and identified by comparison with authentic samples. Their structures were additionally proved by mass spectroscopic fragmentation and IR speectra. In none of the cases any relevant products of 6-substitution could be isolated. However, the regular products of substitution of the chlorine atom were found to be accompanied by allomaltol. It was also observed that the 5-methoxy derivative of chlorokojic acid reacted to 5-O-methyl allomaltol, whereas the 5-benzyloxy derivative did not. It should be stressed that contrary to **1** its 5-alkoxy derivatives did not produce 6-substituted allomaltols when reacted with secondary amines [3, 10].

The following interpretation rationalized our results; the reasons for the failure of the reaction with NO_2^- and $S_2O_3^{2-}$ remain unclear. Nucleophilic substitution in the 2-chloromethyl group possibly proceeds according to a standard mechanism close to the S_N2 type. This reaction could be faciliated by interaction of nucleophile with the ring carbon atom 6 as shown in Scheme 1.

However, this mechanism would involve the proton of the 5-hydroxyl group. Since the 5-methoxy derivative also reacted with nucleophiles, the mechanism according to Scheme 1 seemed to be unlikely. The 5-benzyloxy derivative was passive in this reaction, probably for steric reasons. This pointed out that C_6-nucleophile interactions could be essential. Thus, the polarization in **2** could be sufficiently strong to facilitate further substitution. The final product might be available after the electron shifts presented in Scheme 2.

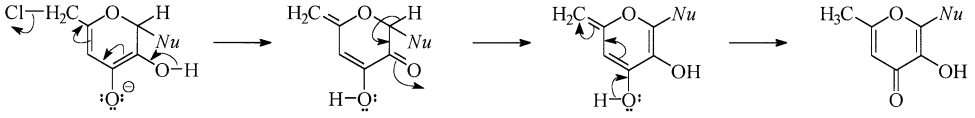


Scheme 1



6 **5**

Scheme 2



2 **7** **8** **9**

Scheme 3

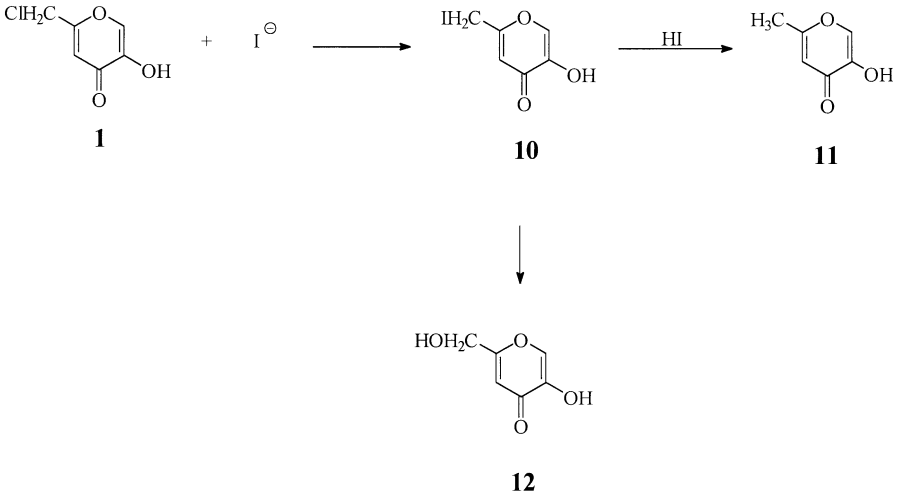
Obviously, the reaction of **1** with nucleophiles to 6-substituted allomaltols involves the 5-hydroxyl group. As a consequence, 5-alkoxy derivatives of **1** should be passive towards nucleophiles. This agrees with recent results [3, 10]. Thus, in contrast to former suggestions that position 6 of the 4-pyrone ring is attacked by the protonated secondary amine (electrophile), the reaction can be explained as the result of the attack of the free amine (nucleophile) as illustrated in Scheme 3.

The formation of allomatol is more difficult to explain. Iodokojic acid (**10**), which was primarily formed, was unstable upon heating as well as upon exposure to sunlight. In solution it generated molecular iodine, allomaltol (**11**, $m/z = 126$), and kojic acid (**12**, $m/z = 142$). Also, iodoacetone ($m/z = 184$, lachrymatory property) could be detected from the reaction of the solvent acetone with liberated iodine [11–13]. As a consequence of the latter reaction, HI was produced as indispensable reagent. The reaction did not proceed in chloroform because HI could not be generated in this case from the solvent and I_2. Hydrogen iodide could reduce iodokojic acid allomaltol as is known for other organic iodine compounds [14]. Based on the IR, ^{1}H NMR, and mass spectroscopic results, a pathway of the reaction is proposed in Scheme 4.

When 5-benzyloxy chlorokojic acid was reacted, the HI necessary for the generation of **11** induced a side reaction. As the consequence of an obvious etheral cleavage apart from kojic acid, both benzyl iodide and benzyl alcohol were formed.

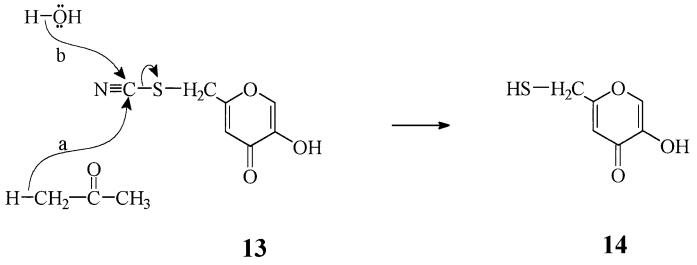
Three products resulted from the reaction of chlorokojic acid with SCN^-: thiocyanatokojic acid (**13**), isothiocyanatokojic acid, and **11**. In the mass spectrum of the reaction mixture, thiolokojic acid (**14**) could be tentatively identified based on an intensive peak at $m/z = 158$, (100%) and a weak peak at $m/z = 125$ (30%), $-$SH). The reaction could be induced either by the carbanion generated from acetone (a) or by water present in the solvent (b) (Scheme 5).

The formation of **11** may be explained as the result of liberation of Cl^+ from **1** and the uptake of a proton from acetone. Abstraction of the Cl^+ ion could be facilitated by the SCN^- nucleophile, which modifies the molecular electron density distribution by interaction with the 4-one group of the pyrone skeleton and chlorine as shown in Scheme 6.



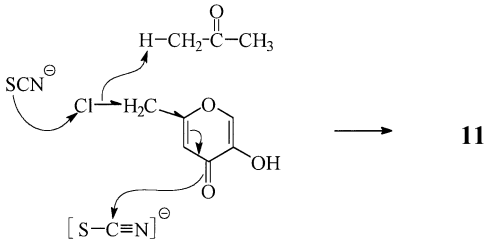
1 **10** **11** **12**

Scheme 4



13 **14**

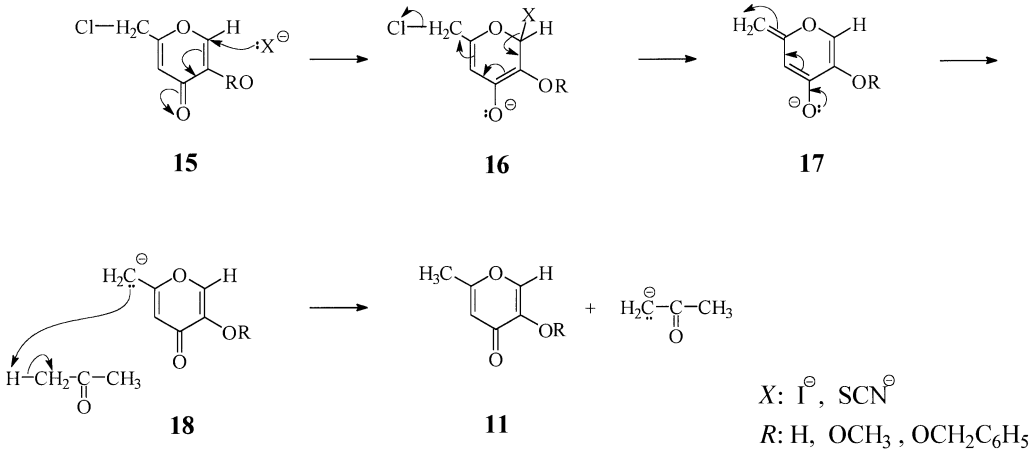
Scheme 5



11

Scheme 6

In the reaction of **1** with N_3^-, the yield of **11** was rather low. Scheme 6 neglects the role of the proton of the 5-hydroxy group in the formation of **11**. Indeed, also 5-methoxy-chlorokojic acid reacted to **11**. Both esters of **1** produced 5-alkoxy-2-formyl-pyran-4-ones as the result of an oxidation of the corresponding anion **18** (R = OMe or OBz). A similar aldehyde resulting from an oxidation of the anion **18** (R=H) could not be found. Thus, it might be speculated that the hydrogen bridge



Scheme 7

5–O···H···O=C-4, promoting withdrawal of electrons from the 2-CH_2^- moiety *via* resonance inhibits the oxidation (Scheme 7).

An alternative route for the formation of **11** in the reaction of **1** with I^- and SCN^- (Scheme 7) is based on the softness of both species [20]. They could attack the pyrone ring of **1** in position 6 donating electrons to the molecule followed by their departure as cations. Such an attack would facilitate removal of the Cl^- anion from the 2-CH_2-Cl moiety and formation of the 2-methyl group by abstraction of a proton from acetone; indeed, iodoacetone was formed. Additionally, in this route the proton of the 5-hydroxyl group is not involved in the reaction which is in agreement with the experimental results.

Experimental

*Reaction of chlorokojic acid (**1**) and its esters with nucleophiles; general procedure*

Chlorokojic acid [15], methyl chlorokojate [8], or benzyl chlorokojate [5] (3 m *M*) and 3 *M* Na*X* ($X = N_3^-$, I^-, SCN^-; all salts purchesed from POCh, Gliwice, Poland) were suspended in 30 cm^3 of acetone (analytical grade; POCh, Gliwice, Poland) and maintained at 45°C for 24 h. Reaction was controlled for the presence of non-reacted substrate TLC (plastic sheets, silica gel 60 F_{254} 0.2 mm, Merck, Darmstadt, Germany). The plates were developped with $CHCl_3$:CH_3OH:petrol ether = 17:3:7 as eluent except for the filtrate after reaction of methyl chlorokojate with NaI ($CHCl_3$:CH_3OH = 4:1). Precipitated NaCl was filtered off, and the filtrate was GC-MS analyzed as well as separated on preparative TLC silica gel 60 F_{254} 2 mm plates (Merck, Darmstadt, Germany; same eluent as above. Collected products were crystallized from ethyl acetate (analytical grade, POCh, Gliwice, Poland).

The GC-MS analyses were performed with a Hewlett-Packard (Germany) gas chromatograph coupled with a quadruple mass detector MSD 5971A. A capillary column HP-5 MSD (30 m × 0.25 mm × 0.25 μm) with helium as carrier gas was heated in the range of 60–260° (20% min). The ^1H NMR spectra (room temperature, *DMSO*-d_6) were obtained with a Bruker AMX 500 MHz instrument with a QNP head and 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. The infrared spectra were recorded as KBr discs using a Mattson 3000 FT-IR spectrometer (Madison, WI, USA).

Reaction with NaN_3 (only with **1**)

GC-MS estimation: allomaltol (**11**; $C_6H_6O_3$; traces; retention time: 6.5 min) was manifested by peaks at $m/z = 126$ (100%), 98 (15%, –CO), 85 (5%, –CH), 69 (45%, –CHO) in the GC-MS.

Azidokojic acid ($C_6N_5N_3O_3$): yield: 40% white-beige crystals; m.p.: 18–120°C (Ref [6, 7]: m.p.: 120°C); IR (KBr): $\nu = 3239$ (ν_{OH}), 2118 (ν_{N3}), 1665 (ν_{CO}) cm^{-1}; MS: $m/z = 167$ (80%), 139 (70%,–N_2), 125 (20%, –N), 110 (–CH_2), 97, 69, 54 (identical with that of an authentic sample).

Reaction with NaSCN (only with chlorokojic acid)

GC-MS estimation: **11** (retention time: 6.5 min, $m/z = 126$, fragmentation identical as above) chlorokojic acid (**1**; $C_6H_5ClO_3$; retention time: 8.32 min, $m/z = 160$ (100%), 125 (80%, –Cl), 97 (40%), 69 (50%), 39 (70%), 29 (45%)), thiolokojic acid (**14**; $C_6H_6SO_3$; retention time: 9.17 min, $m/z = 158$ (100%), 125 (30%, –SH), 97, 69, 41), thiocyanatokojic acid (**13**; $C_7H_5NO_3S$; retention time: 10.82 min, $m/z = 183$ (100%), 158 (10%, –CN), 125 (30%, –S), 97, 67, 39), isothiocyanatokojic acid (retention time: 11.08, $m/z = 183$ (30%), 125 (100%, –NCS), 97, 67, 39).

Allomaltol (**11**) was isolated by preparative TLC. Colourless prisms; m.p.: 145–149°C (Ref. [8]: m.p.: 149–150°C, Ref. [18]: 152–153°C); GC-MS: identical to those given above; IR (KBr): $\nu = 3215$ (ν_{OH}), 2926 (ν_{CH_3}), 1652 (ν_{CO}), 1615 ($\nu_{CO\cdots HO}$), 1231 (δ_{COC}) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ): 9.00 (s, 1H, H_{OH}), 7.99 (s, 1H, H_6), 6.25 (s, 1H, H_3), 2.24 (t, 3H, H_{CH_3}) ppm.

The residual crude mixture of thiocyanato-, isothiocyanato-, and thiolo-kojic acids could not be separated.

Reaction of **1** with NaI

GC-MS analysis: iodoacetone (C_3H_5IO; (retention time: 4.80 min, $m/z = 184$ (80%), 169 (10%, –CH_3), 141 (30%, –CO), 127 (30%, –I), 43 (100%, C_2H_3O)), **11** (retention time : 7.8 min, $m/z = 126$, fragmentation identical to that given above), iodokojic acid (**10**; $C_6H_5IO_3$; retention time: 11.0 min, $m/z = 252$ (15%), 125 (100%, –I), 97, 67, 39). The filtrate gradually decomposed with liberation of elemental iodine (blue staining of starch paper strips) when stored on air and exposed to sunlight.

Isolated on preparative TLC plates: iodokojic acid (**10**); yellow leaflets (78%), m.p.: 175–178°C (Ref. [8]: m.p.: 176–177°C, Ref. [2]: m.p. 180–181°C); sublime at about 130°C; MS: m/z and fragmentation identical to those given above; IR (KBr): $\nu = 3241$ (ν_{OH}), 1653 (ν_{CO}), 1615 ($\nu_{CO\cdots OH}$), 501 (ν_{CI}) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ): 9.24 (s, 1H, OH), 8.05 (s, 1H, H6), 6.57 (s, 1H, H_3) 4.39 (d, 2H, CH_2) ppm; in addition **11** (up to 30%) with MS, IR, and ^{1}H NMR spectra identical to those reported above.

Reaction of methyl chlorokojate with NaI

GC-MS analysis: 5-O-Methyl allomaltol (**11**, $R = OMe$;$C_7H_7IO_3$; retention time: 5.7 min, $m/z = 140$ (80%), 111 (30%, –CH_3), 95 (100%, –CH_2O), 69 (30%); the fragmentation is in agreement with that reported in Ref. [19]), 2-formyl-5-methoxypyran-4-one (retention time: 6.7 min, $m/z = 154$ (60%), 126 (40%, –CHO), 95 (100%)), methyl chlorokojate (**15**, $R = OMe$; $C_7H_7ClO_3$; unreacted, retention time: 7.25 min, $m/z = 174$ (25%), 139 (50%, –Cl), 111 (25%, –CO), 95 (100%, $C_5H_3O_2$)), iodoacetone (retention time: 7.54, $m/z = 184$, fragmentation as above), methyl kojate (**12**, $R = OMe$; $C_7H_8O_4$; retention time: 8.26 min, $m/z = 156$ (50%), 138 (15%, –O), 125 (30%, –CH), 95 (100%)), methyl iodokojate (**10**, $R = OMe$; $C_7H_7IO_3$; retention time: 8.7 min, $m/z = 266$ (25%), 139 (100%, –I), 111 (80%, –CO), 95 (50%)).

Isolated on preparative TLC plate: methyl iodokojate; yellow crystals, m.p.: 118–122°C; MS: $m/z = 266$ with fragmentation identical to that given above; IR (KBr): $\nu = 1646$ (ν_{CO}), 1421 (ν_{OCH_3}), 524 (ν_{Cl}) cm^{-1}.

Reaction of benzyl chlorokojate with Nal

GC-MS analysis: benzyl alcohol (C_7H_8O; retention time: 3.6 min, $m/z = 108$ (100%), 91 (15%, –OH), 79 (90%)), benzyl iodide (C_7H_7I; retention time: 8.0 min, $m/z = 218$ (5%), 127 (5%, –I), 91 (100%)), 5-O-benzyl-2-formylpyran-4-one (retention time: 10.2 min, $m/z = 230$ (5%), 91 (100)), benzyl kojate (**12**, $R = OBz$; $C_{13}H_{12}O_4$; retention time: 11.7 min, $m/z = 232$ (10%), 126 (8%, C_6H_5CHO), 91 (100%)).

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