Reaction of 5-Hydroxy-2-hydroxymethyl-4*H*-pyran-4-one with Aromatic Aldehydes and Amines (Betti Reaction)

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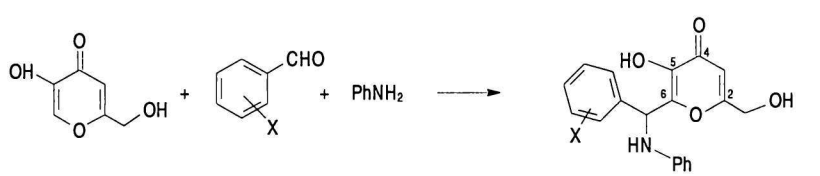
Received 18 May 1993

Preparation and spectral characteristics of 6-(α-anilino-X-benzyl) derivatives of 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one are described. The substituent in position 5 hinders entering of another substituent to position 6. Some products of Betti reaction are thermolabile and decompose.

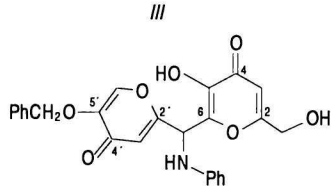
Due to its easy biodegradability 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid, *I*) has plenty of uses in food and cosmetic industry [1]. The well known fungicidal effects of some of its derivatives [2, 3] make it an advantageous starting material in organic synthesis. The high reactivity of 5-hydroxy group and of the primary alcohol in position 2 enables preparation of a number of 5- and 2-substituted derivatives of kojic acid. Besides the hydroxyl substitution kojic acid can be derivatized in position 6, which is highly reactive in S_E reactions due to the activation by 5-hydroxy group. Kojic acid is more reactive in comparison to some phenols in these reactions [4].

We have prepared 6-(α-anilino-X-benzyl) derivatives of kojic acid *IIIa*—*IIIe* by the reaction of *I* with substituted aromatic aldehydes *II* (X = H, 4-CH_3, 3,4-$(OCH_3)_2$, 3-NO_2, 4-NO_2) and aniline (Scheme 1, Table 1). The structure of products and the fact that primarily created Schiff base reacts with kojic acid in position 6 were confirmed by ^{1}H and ^{13}C NMR spectra. For example, proton spectra of *IIIb* exhibit characteristic methylene signals at δ = 4.24, 2-hydroxyl signal at δ = 5.65, 5-hydroxyl signal at δ = 9.34, and H-3 signal at δ = 6.27. Entering of substituent to position 6 is confirmed by the disappearance of H-6 signal, usually occurring around δ = 8.00. This fact is in accordance with ^{13}C NMR data, showing C-6 signal as singlet at δ = 149.21. CH and NH signals are visible in ^{1}H NMR spectra as doublets with various chemical shifts (for *IIIb* the signals were at δ = 5.83 and 6.36, respectively, with J_{CH-NH} = 6.347 Hz), carbon atom signal of CH has δ = 59.49.

UV spectra of the prepared compounds show absorption maxima around λ = 245 nm and 275 nm, which corresponds to the UV data of analogous Betti products [4, 5].



I *II* *III*



IV

	X
a	H
b	4-CH_3
c	3,4-$(OCH_3)_2$
d	3-NO_2
e	4-NO_2

Scheme 1

Table 1. Characterization of the Prepared Compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
			C	H	N	%	°C
IIIa	$C_{19}H_{17}O_4N$	323.33	70.57 70.35	5.30 5.33	4.33 4.44	50	169—173[a]
IIIb	$C_{20}H_{21}O_4N$	337.35	71.20 71.15	5.67 5.61	4.15 4.08	44	149—152
IIIc	$C_{21}H_{21}O_6N$	383.38	65.78 65.80	5.52 5.40	3.65 3.65	56	142—145
IIId	$C_{19}H_{16}O_6N_2$	368.34	61.95 61.79	4.37 4.29	7.64 7.52	12	193—196
IIIe	$C_{19}H_{16}O_6N_2$	368.34	61.95 61.84	4.37 4.32	7.64 7.61	15	106—109
IV	$C_{25}H_{21}O_7N$	447.42	66.97 66.97	4.80 4.80	3.13 3.24	20	159—162

a) Ref. [11] gives for *IIIa* m.p. = 176—177 °C, for *IIIb* m.p. = 175 °C (decomp.).

The high reactivity of 5-hydroxy-4-oxo-4*H*-pyran-2-carbaldehyde and experience with its condensation reactions [6, 7] led us to use it in the Betti reaction. Thus kojic acid reacted with aniline and 5-benzyloxy-4-oxo-4*H*-pyran-2-carbaldehydes to give product *IV*, containing two kojic acid skeletons in one molecule. ^{1}H and ^{13}C NMR spectra testify to the presence of two 4*H*-pyran-4-one skeletons.

The reaction of kojic acid with aniline and 3-nitro- or 4-nitrobenzaldehyde gave low yields of compounds *IIId* and *IIIe*. The creation of *IIIe* confirms the assumption of high reactivity of kojic acid in the position 6, since other phenols failed to react with benzaldehyde in the Betti reaction [5]. In the case of 5-methoxy- or 5-benzyloxy-2-hydroxymethyl-4*H*-pyran-4-one, the Betti reaction produced Schiff base and unreacted 5-substituted kojic acid. ^{1}H NMR spectra of raw reaction mixtures indicated small amounts of Betti type products. This result could be explained by the hindrance that the substituent in position 5 exerts for entering of another bulky substituent to the neighbouring position. However, the decisive factor influencing the result of reaction is the much lower activation of position 6 for an S_E reaction by the 5-methyloxy- or 5-benzyloxy group. The above-mentioned result is in agreement with literature data [8, 9].

Experimental results showed thermolability of some Betti products. Products *IIId* and *IIIe* decomposed to Schiff base and kojic acid when their crystallization was attempted. This phenomenon was observed also in the reaction of kojic acid with benzaldehyde and benzylamine or phenylethylamine. The comparison of ^{1}H NMR data of raw reaction mixtures and crystallized compounds showed decomposition of products under crystallization.

Betti products of kojic acid with pre-synthesized Schiff bases behaved similarly under crystallization. These results are accounted for by the known negative influence of temperature on the yield of reaction [5]. No products were obtained from the reaction with primary amines [6].

Testing of biological activity of products showed only anti-yeast activity of 6-(α-anilinobenzyl)-5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (*IIIa*) against *Candida utilis*, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. There was no activity observed against prokaryotic cells of G^- and G^+ bacteria or against eukaryotic filamentous fungi.

EXPERIMENTAL

Kojic acid, aldehydes and amines were commercial products. Melting points are not corrected. ^{1}H NMR spectra were recorded on Tesla BS 487 C (80 MHz) and Varian VXR 300 instruments in deuterated DMSO with tetramethylsilane as internal standard. UV spectra were recorded on M 40 spectrometer (Zeiss, Jena) in temperated cuvettes in methanol. The progress of reaction and purity of products were checked by TLC on Silufol plates (Lachema, Brno) with detection under UV or iodine vapours.

Antimicrobial activity was assayed by the disc diffusion technique [10]. 18 h vegetative inoculum of bacteria and yeasts was used for inoculation of media. 21 d sporulated cultures of filamentous fungi were used, spore suspension was prepared by using 0.1 % Tween solution.

6-(α-Anilino-X-benzyl)-5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one *IIIa—IIIe* and 6-[α-Anilino-(5-benzyloxy-4*H*-pyran-4-on-2-yl)]-methyl-5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (*IV*)

Kojic acid (0.01 mol) was added to a solution of aniline (0.01 mol) in ethanol (100 cm^3). The reaction mixture was allowed to stay at room tempera-

ture for 5 d or 8 d until the reaction was completed. The solvent from the resulting mixture was evaporated *in vacuo* and the product obtained was crystallized from ethanol.

IIIa (X = H): ^{1}H NMR spectrum, δ: 4.26 (s, 2H, CH_2), 5.46 (br, 1H, OH), 6.44 (d, 1H, NH, J_{CH-NH} = 8.1 Hz), 5.90 (d, 1H, CH), 6.29 (s, 1H, H-3), 6.60—7.50 (m, 10H, H_{arom}), 9.40 (s, 1H, OH-5). ^{13}C NMR spectrum, δ: 59.43 (t, CH_2), 52.93 (d, CH), 108.89 (d, C-3), 147.25 (s, C-5), 148.92 (s, C-6), 167.54 (s, C-2), 173.63 (s, C-4), 112.94, 116.94, 127.06, 127.67, 128.63, 128.95, 139.24, 141.57 (C_{arom}). UV spectrum, λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 243 (2.11), 278.7 (2.08).

IIIb (X = 4-methyl): ^{1}H NMR spectrum, δ: 2.27 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 5.65 (br, 1H, CH, J_{CH-NH} = 6.3 Hz), 6.27 (d, 1H, H-3), 6.36 (d, 1H, NH), 6.56—7.37 (s, 1H, OH-5). ^{13}C NMR spectrum, δ: 20.72 (q, CH_3), 52.70 (t, CH_2), 59.49 (d, CH), 108.89 (d, C-3), 147.29 (s, C-5), 149.21 (s, C-6), 167.54 (s, C-2), 173.71 (s, C-4), 112.98, 116.95, 126.97, 128.99, 129.23, 136.28, 136.93, 141.44 (C_{arom}). UV spectrum, λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 244.9 (2.38), 280 (2.26).

IIIc (X = 3,4-dimethoxy): ^{1}H NMR spectrum, δ: 3.73 (s, 6H, 2 × OCH_3), 4.28 (s, 2H, CH_2), 5.67 (br, 1H, OH), 5.80 (d, 1H, CH, J_{CH-NH} = 8.1 Hz), 6.27 (s, 1H, H-3), 6.35 (d, 1H, NH), 6.37—7.13 (m, 8H, H_{arom}), 9.32 (s, 1H, OH-5). ^{13}C NMR spectrum, δ: 52.76 (t, CH_2), 55.55 (q, 2 × OCH_3), 59.59 (d, CH), 108.98 (d, C-3), 167.37 (s, C-2), 173.70 (s, C-4), 147.33, 148.40, 148.68, 149.31 (4 × s, C-5, C-6, C_{arom}), 110.86, 111.73, 112.98, 116.94, 119.38, 128.98, 131.50, 141.34, 141.97 (C_{arom}). UV spectrum, λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 282 (2.12).

IIId (X = 3-nitro): ^{1}H NMR spectrum, δ: 4.28 (s, 2H, CH_2), 5.62 (br, 1H, OH), 6.18 (d, 1H, CH, J_{CH-NH} = 6.0 Hz), 6.36 (d, 1H, NH), 6.33 (s, 1H, H-3), 6.37—8.62 (m, 9H, H_{arom}).

IIIe (X = 4-nitro): ^{1}H NMR spectrum, δ: 4.33 (s, 2H, CH_2), 5.62 (br, 1H, OH), 6.10 (d, 1H, CH, J_{CH-NH} = 8 Hz), 6.35 (s, 1H, H-3), 6.56—7.12 (m, 6H, NH and 5H, H_{arom}).

IV: ^{1}H NMR spectrum, δ: 4.28 (s, 2H, CH_2), 4.91 (s, 2H, CH_2O), 5.69 (br, 1H, OH), 5.81 (d, 1H, CH, J_{CH-NH} = 8.1 Hz), 6.57 (d, 1H, NH), 6.35 (s, 1H, H-3), 6.53 (s, 1H, H-3), 6.55—7.40 (m, 5H, H_{arom}), 8.24 (s, 1H, H-6), 9.70 (s, 1H, OH-5). ^{13}C NMR spectrum, δ: 51.49 (d, CH), 59.40 (t, CH_2), 70.55 (t, CH_2O), 109.12 (d, C-3), 113.93 (d, C-3), 141.37 (d, C-6), 144.90 (s, C-5), 146.25, 146.82 (2 × s, C-5 and C-6), 164.09 (s, C-2), 167.91 (s, C-2), 172.94 (s, C-4), 173.68 (s, C-4), 112.86, 128.37, 135.99, 142.82 (C_{arom}). UV spectrum, λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 240 (2.58), 272 (2.34).

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Translated by V. Mastihuba