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On the Nuclear Bromination in the Kojic Acid Series

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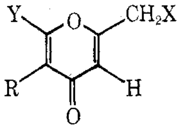
We recently corrected previous reports on the Friedel-Crafts acylation and aroylation reactions of kojic acid (1),[1] and as we contemplate no further work in the area we now wish to describe some observations concerning the ring bromination in this series.



1, R = OH; X = OH; Y = H
2, R = OH; X = Cl; Y = H
3, R = OH; X = Cl; Y = Br
4, R = X = OH; Y = Br
5, R = X = $OCOCH_3$; Y = H
6, R = X = $OCOC_6H_5$; Y = H
7, R = X = $OCOCH_3$; Y = Br
8, R = X = $OCOC_6H_5$; Y = Br
9, R = OH; X = $OCOCH_3$; Y = H
10, R = OH; X = $OCOC_6H_5$; Y = H
11, R = OH; X = $OCOCH_3$; Y = Br
12, R = OH; X = $OCOC_6H_5$; Y = Br

Woods described the reaction of chlorokojic acid (2) with *N*-bromosuccinimide (NBS) in benzene and tentatively assigned the 2-chloromethyl-5-hydroxy-6-bromo-4*H*-pyrone structure (3) to the product, mp 163°.[2] However, his compound was characterized only by its elemental analysis and a $FeCl_3$ test, and there was no additional chemical or spectroscopic data in support of the proposed structure.

When the reaction was repeated following the published procedure, a product, mp 162–163°, was obtained in 22% yield after two recrystallizations from ethanol. That it was not the starting material, mp 165–166°, was shown by mixture melting point depression, mass spectroscopy (mol wt 238), and the nmr (Table I), which clearly indicated that the ring proton absorbing at 8.13 ppm in 2 had been substituted. We previously showed that this signal corresponded to H-6,[1] and Woods' tentative structural assignment is therefore confirmed. The same product was also obtained by brominating 2 in a phosphate buffer.

We could not improve on Woods' results with kojic acid itself,[2] which consistently yielded a black tar when treated with NBS. Likewise, we did not observe the ring bromination with NBS of either its diacetate (5) or dibenzoate (6), which would have yielded 7 and 8, respectively. Molecular bromine in water or in a phosphate buffer was not effective either. Treatment of either the monoacetate 9 or the monobenzoate 10 with NBS, on the other hand, yielded the products of ring bromination, 11 and 12, respectively.

The bromination of kojic acid with bromine water was described by Yabuta,[3] who obtained a product, mp 159–160°, alleged to be a monobromokojic acid, and yielding a diacetyl derivative, mp 94–95°, and a dibenzoyl derivative, mp 133–134°. These values are to be compared to 165–166, 101–102, and 133–134° for 1, its diacetate, and its dibenzoate, respectively.[1] When Yabuta's procedure was repeated, a black tar was always formed, but the desired bromokojic acid (4) was also obtained in *ca.* 1% yield. It melted at 171–172° and was characterized by its mass spectrum (mol wt 221) and nmr, which indicated that bromination had taken place in the ring and supported the assignment of the bromine to the 6 position in preference to the 3 position.[1] The same product 4 was also obtained in good yield by brominating 1 in a phosphate buffer.[4] It gave a diacetate 7, mp 67–68°, and a dibenzoate 8, mp 123–125°. The discrepancy between these values and those reported by Yabuta is noteworthy, but in the absence of direct comparison no definitive conclusion may be drawn concerning the nature of his compound melting at 159–160°. Yabuta also claimed to have converted in poor yield his bromokojic acid into an otherwise unidentified hydroxykojic acid, but we could not duplicate this reaction when 2 was treated with either barium hydroxide or potassium hydroxide, where extensive decomposition took place.[5]

Finally, Woods and Dix reported the dibromination of 1 in trifluoroacetic acid,[6] but this result could not be duplicated and the only product which we succeeded in isolating was the monobromokojic acid (4), obtained in low yield.

Table I
Nmr Spectra of Kojic Acids

Compd	Solvent	$-CH_2R$	H-3	H-6	Phenyl	CH_3CO	OH
1	DMSO-d_6	4.50	6.60	8.10			5.68, 9.09
2	DMSO-d_6	4.67	6.70[a]	8.13			9.26
3	DMSO-d_6	4.74	6.66				10.18
4	DMSO-d_6	4.32	6.40				10.46
7	$CDCl_3$	4.97	6.52			2.20 2.37	
8	DMSO-d_6	5.13	6.53		7.40–8.20		
11	$CDCl_3$	4.93	6.50			2.17	10.15
	DMSO-d_6	4.93	6.51			2.08	10.17
12	DMSO-d_6	5.20	6.57		7.43–8.03		10.20

[a] This value was erroneously printed as 7.70 in ref 1.

In conclusion, the ring bromination of kojic acid derivatives takes place at the 6 position, but the reaction occurs only when the 5-hydroxyl is free.

Experimental Section

Bromination of Chlorokojic Acid (2) with NBS. A mixture of 1.54 g of **2**, 1.8 g of NBS, and 10 ml of C_6H_6 was refluxed for 1 hr and was concentrated under vacuum. The residue was washed with water and recrystallized twice from absolute C_2H_5OH to yield 0.49 g of **3**: mp 162–163°; positive $FeCl_3$; ir (Nujol) 3150, 1580 cm^{-1}.

Bromination of Kojic Acid Monoacetate (9) with NBS. The same procedure was used with 0.197 g of **9**, and yielded 0.217 g of **11** after recrystallization from CCl_4, mp 131–133°, ir (Nujol) 3350, 1740, 1640 cm^{-1}.

Anal. Calcd for $C_8H_7O_5Br$: C, 36.52; H, 2.66; Br, 30.39. Found: C, 36.29; H, 2.72; Br, 30.68.

Treatment of Kojic Acid Diacetate (5) with NBS. The same procedure was used with 2.13 g of **5**. There was no reaction, as shown by comparing the product (melting point, mixture melting point, tlc, and nmr) with the starting material and with the expected product **7**.

Bromination of Kojic Acid Monobenzoate (10) with NBS. The same procedure was used with 1 g of **10**. After recrystallization from CH_3OH there was obtained 0.450 g of **12**, mp 206–207°, ir (Nujol) 3350, 1720, and 1640 cm^{-1}.

Anal. Calcd for $C_{13}H_9O_5Br$: C, 48.01; H, 2.79; Br, 24.59. Found: C, 48.22; H, 2.78; Br, 24.48.

Treatment of Kojic Acid Dibenzoate (6) with NBS. The same procedure was used with 0.5 g of **6**. There was no reaction, as shown by direct comparison (melting point, mixture melting point, tlc, and nmr) with **6** and with the expected product **8**.

Treatment of Kojic Acid Diacetate (5) with Bromine. To a suspension of 0.872 g of **5** in 10 ml of water, 0.15 ml of Br_2 in 10 ml of H_2O was added dropwise with stirring at 0°. After an additional 12 hr of stirring at room temperature, the solid material was filtered, recrystallized from H_2O, and shown to be the starting material by direct comparison. Tlc analysis of the filtrate against an authentic sample showed the absence of **7**. Similarly, no reaction took place when the bromination was performed in the H_3PO_4–KH_2PO_4 buffer.

Treatment of Kojic Acid Dibenzoate (6) with Bromine. The above procedures were used with **6** and yielded the recovered starting material identified by tlc, melting point, mixture melting point, and nmr.

Bromination of Kojic Acid (1) in Water. To 2 g of **1** in 20 ml of H_2O, 0.8 ml of Br_2 in 10 ml of H_2O was added dropwise at 0° with stirring. After stirring for 12 hr at 10° the mixture was extracted with ether which was dried over $MgSO_4$ and evaporated. After recrystallization from EtOAc, there was obtained 0.036 g of **4**, mp 170–171°.

Bromination of 1 in Trifluoroacetic Acid. After a 2-hr reflux, a mixture of 5 g of **1**, 4 ml of Br_2, and 5 ml of CF_3COOH was chilled overnight. A black solid was separated and taken up in hot EtOAc. This solution was chilled and 6-bromokojic acid precipitated. After two recrystallizations from EtOAc there was obtained 0.12 g of **4**, mp 169–170°.

Bromination of 1 in H_3PO_4–NaH_2PO_4. A solution of 4 g of Br_2 and 13.2 g of NaH_2PO_4 in 150 ml of H_2O was added dropwise with stirring to 3 g of **1** in 30 ml of 50% aqueous H_3PO_4 at 0°. After stirring overnight at 10°, a pale orange solid was filtered and recrystallized from acetone. There was obtained 1.7 g of **4**, mp 171–172°.

Acetylation of 6-Bromokojic Acid (4). A mixture of 0.446 g of **4** and 5 ml of CH_3COCl was refluxed overnight, concentrated under vacuum, and treated with 10 ml of H_2O. It was neutralized with 10% aqueous $NaHCO_3$ and filtered. The precipitate was recrystallized several times from H_2O to yield 0.014 g of **7**, mp 69–70°, ir ($CHCl_3$) 1780, 1750, and 1660 cm^{-1}. The product completely decomposed upon standing at room temperature for 1 week.

Benzoylation of 4. A mixture of 0.614 g of **4**, 2 ml of C_6H_5COCl, and 20 ml of $CHCl_3$ was refluxed overnight, concentrated under vacuum, taken up in ether, and extracted with aqueous $NaHCO_3$ and with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated, and yielded an oil which was chromatographed over silica gel. Elution with $CHCl_3$ yielded **8**. After three recrystallizations from 50% aqueous ethanol there was obtained 0.304 g, mp 123–125°, ir ($CHCl_3$) 1734, 1754, and 1674 cm^{-1}.

Anal. Calcd for $C_{20}H_{13}O_6Br$: C, 55.90; H, 3.03; Br, 18.59. Found: C, 56.10; H, 3.20; Br, 18.46.

Bromination of 1 in H_3PO_4–NaH_2PO_4. A solution of 4 g of Br_2 **KH_2PO_4.** A solution of 3 g of KH_2PO_4 and 0.4 ml of Br_2 in 20 ml of H_2O was added dropwise with stirring at 0° to 0.5 g of **9** in 10 ml of 50% aqueous H_3PO_4. After further stirring overnight at room temperature, the solution was extracted twice with 10 ml of $CHCl_3$, which was washed with water, dried, and concentrated. The solid residue was recrystallized from CCl_4 and yielded 0.1 g of **11**, mp 131–133°, identical with the sample prepared with NBS.

Bromination of Chlorokojic Acid (2) in H_3PO_4–KH_2PO_4. The same procedure was used on 0.422 g of **2** and yielded 0.180 g of **3**, mp 162–163° after two recrystallizations from EtOH, which was identical with the product obtained with NBS.

Registry No.—**1**, 501-30-4; **2**, 7559-81-1; **3**, 40838-36-6; **4**, 40838-32-2; **7**, 51568-23-1; **8**, 51568-24-2; **9**, 25552-08-3; **10**, 33777-42-3; **11**, 51568-25-3; **12**, 51568-26-4.

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(2) L. L. Woods, *J. Amer. Chem. Soc.*, **74**, 1107 (1952).
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(5) The ring opening of 4-pyrones and their conversion into triketones susceptible of undergoing decomposition, condensation, or cyclization reactions is well known. For example, it was used in 1893 by Collie in his pioneering work on the synthesis of phenolic compounds by the polyacetate route, and leading references in this area may be found in T. Money, *Chem. Rev.*, **70**, 553 (1970), and W. E. Hillis and Y. Yazaki, *Phytochemistry*, **10**, 1051 (1971).
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Optically Active Amines. XVII.[1] Partial Kinetic Resolution of α-Phenylbutyric Acid Using Chiral Primary Amines and Their Salts[2]

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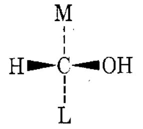
The kinetic resolution procedure of Horeau has been applied successfully to correlate the configurations of chiral secondary alcohols and in certain cases can be used to determine their absolute configurations.[5] The chiral alcohol is allowed to react with excess racemic α-phenylbutyric anhydride, and if the configuration of the alcohol is as shown in **1**, where L is a group with a larger steric requirement than M, partially resolved (*R*)-(−)-α-phenylbutyric acid [(*R*)-**2a**] will be recovered. The empirical nature of the method becomes evident when two of the carbinol substituents are not greatly different in steric requirement and other effects may be important. An example is the alkylphenylcarbinols, for which the phenyl group has an apparent steric requirement larger than any alkyl group, including the *tert*-butyl group.[6]



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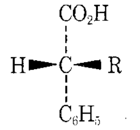

(*R*)-**2a**, R = C_2H_5
(*R*)-**2b**, R = CH_3

The method should be applicable to correlation of the absolute configurations of chiral primary and secondary amines, but few examples are available. Weidmann and Horeau[6] noted that excess racemic α-phenylethylamine [(±)-**3a**], α-benzylethylamine [(±)-**4**], and isobornylamine