

one drop of 48% hydrobromic acid) was heated under reflux for 4 h. The resulting solid was recrystallized from 50% aqueous acetic acid to yield 1.28 g (64%) of yellow powder; mp 189–190 °C [lit.⁵ mp 190 °C]; IR (KBr) 2200 (CN) and 1675 cm⁻¹ (α -pyridone CO).

Registry No.—4, 1613-37-2; 5a, 13017-53-3; 5b, 5447-87-0; 7a, 63702-22-7; 7b, 63702-23-8; 13, 3759-28-2; 14, 63702-24-9; 15, 63702-25-0.

References and Notes

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- (3) The designation α indicates that the carbonyl group is adjacent to the nitrogen atom. This is to avoid the confusion which arises from the numbering of the various benzoquinolizones; e.g., both 4*H*-quinolizin-4-one and 1*H*-benzoquinolizin-1-one and α -quinolizones.
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Reaction of Kojic Acid and Its Derivatives with Acrylonitrile. A New Look at an Old Problem

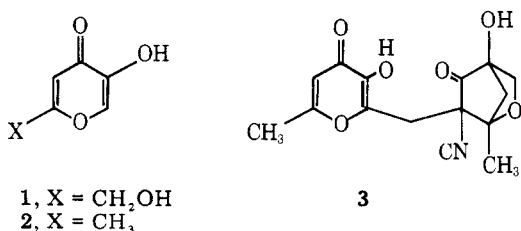
R. A. Volkmann, P. D. Weeks, D. E. Kuhla,
E. B. Whipple, and G. N. Chmurny

Central Research Laboratories, Pfizer Inc.,
Groton, Connecticut 06340

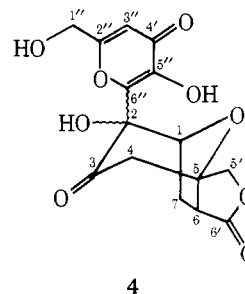
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The reaction of kojic acid (1) with acrylonitrile was initially studied by Woods¹ and later extensively investigated by Hurd and co-workers,² who examined the reaction of various 3-hydroxy-4-pyrones with acrylonitrile and acrylate esters. Unidentified, yet well-characterized products involving two molecules of pyrone and one molecule of acrylonitrile or acrylate ester were formed in these reactions rather than the expected simple Michael addition products. Hurd and Trofimenko³ later focused their attention on the reaction of α -deoxykojic acid (2) with acrylonitrile in an effort to solve this intriguing structural problem. Structure 3 was suggested as the product of this reaction on the basis of experimental findings and a complex mechanistic rationale. We now wish to report structural assignments for the reaction products of kojic acid (1) and its derivatives with acrylonitrile and acrylate esters, proposing a general reaction mechanism for their formation and revising the structure of the α -deoxykojic acid-acrylonitrile reaction product.

The base-catalyzed addition of acrylonitrile to kojic acid (1) provided the necessary data for solving this structural



problem. In accordance with Hurd's observations, product 4, mp 264–265 °C, is formed on acid workup and analyzes for C₁₅H₁₄O₉. Compound 4 gives a positive ferric chloride test and is easily acetylated. Its infrared spectrum shows a strong hydroxyl band at 2.94 μ m, carbonyl bands at 5.63 and 5.78 μ m, and pyrone bands at 6.02, 6.18, and 6.36 μ m. Under appropriate conditions, a labile nitrogen-containing intermediate (7) can be isolated.² Its infrared spectrum shows carbonyl



bands at 5.76 and 5.93 μ m, and 7 is smoothly converted to 4 under acidic conditions.² On the basis of key ¹H and ¹³C NMR studies (Tables I and II) and the data obtained by Hurd, we have assigned 4 the following tricyclic structure.

Compound 4 is a rigid 2,2-disubstituted 8-oxabicyclo[3.2.1]octan-3-one containing a cis fused γ -lactone ring at carbon atoms 5 and 6 whose structure is uniquely described by ¹H NMR and ¹³C NMR data. The presence of a pyrone moiety in the molecule is substantiated by the appearance of an olefin signal in the ¹H NMR spectrum at δ 6.90 and an allylic methylene signal at δ 4.77. Two distinct AB patterns are present and can be assigned to the H-4 ($J_{AB} = 14$ Hz) and H-5' (J_{AB}, Hz) protons of the molecule. The broad doublet at δ 5.60 can be assigned H-1 on the basis of its chemical shift and the coupling ($J = 7$ Hz) of this bridgehead proton to the exo H-7 proton. As anticipated,⁵ the coupling of H-1 to the endo H-7 proton is small ($J < 2$ Hz). The H-7 signals appear as a complex ABXY pattern as a result of coupling with H-1 and H-6. H-7(exo), as expected,⁵ is coupled with H-7(endo) ($J_{AB} = 14$ Hz) and is weakly coupled ($J = 4$ Hz) to the trans-oriented H-6 proton. A larger coupling constant ($J = 10$ Hz) results from the cis relationship of H-7(endo) and H-6.

¹³C NMR further strengthens the structural assignment for 4. The chemical shifts of the pyrone carbon atoms (C-1'–C-6'') correspond to those reported for kojic acid.⁶ The presence of two additional carbonyl groups (C-3 and C-6') and four saturated carbon atoms bound to oxygen (C-1, C-2, C-5, C-5') is confirmed by the ¹³C chemical shifts. ¹³C–¹H coupling further demonstrates that two of these carbon atoms bound to oxygen are tertiary (C-5, C-2), one is secondary (C-1), and one is primary (C-5'). The chemical shifts and ¹³C–¹H coupling of the remaining carbon atoms (C-4, C-7, and C-6) are also consistent with the structure of 4.

A mechanistic pathway leading to 4 is shown in Scheme I. The reaction is initiated with an ionic (4 + 2) cyclization⁷ involving kojic acid (1) and acrylonitrile to afford bicyclic intermediate⁸ 5 which enolizes to relieve the electrostatic interactions⁹ present in cyclic α -diketones. As a result, only the ketone moiety α to the bridge (which cannot enolize) is susceptible to nucleophilic attack. Base-catalyzed addition of another molecule of kojic acid occurs at this site to generate 6.¹⁰ Addition¹¹ of the hydroxymethyl group of 6 to the exo nitrile functionality then generates imidolactone 7 which was originally isolated by Hurd.² Acid workup of 7 yields tricyclic structure 4.

The other reaction products of γ -pyrones with acrylonitrile and acrylate esters² can be explained by the same general mechanism. The reaction of α -deoxykojic acid (2) with acrylonitrile yields, as reported by Hurd,² two products 8 and 9 in

Table I. ^1H NMR Assignments for Compounds 4, 8, and 9

Proton attached to C atom	δ^a and multiplicity ^b		
	4	8	9
1	5.60 (d)	5.55 (dd)	5.52 (dd)
4A	3.67 (d)	3.40 (d)	3.40 (d)
4B	3.13 (d)	3.00 (d)	3.40 (d)
6	3.51 (dd)	3.59 (dd)	3.28 (dd)
7(exo)	2.62 (m)	2.61 (m)	2.73 (m)
7(endo)	2.90 (m)	2.88 (m)	2.64 (m)
5'A	4.70 (d)	1.72 (s)	1.50 (s)
5'B	4.40 (d)		
1''	4.77 (s)	2.10 (s)	2.06 (s)
3''	6.90 (s)	6.28 (s)	6.28 (s)

	Coupling constants ^c		
	4	8	9
1,7(exo)	7	8	8
1,7(endo)	<2	2	2
6,7(exo)	4	4	12
6,7(endo)	10	10	8
5'A, 5'B	10		
7(exo), 7(endo)	14	14	14
4A, 4B	14	14	

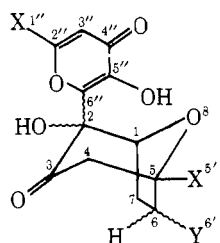
^a Chemical shift in ppm deshielded from TMS. ^b Multiplicities apparent from spectra: s = singlet; d = doublet; dd = doublet of doublets; m = multiplet. ^c Line splitting $|J|$ (Hz) obtained from proton homonuclear decoupling experiments, direct observations, or by spectral analysis.

Table II. ^{13}C NMR Assignments (δ^a) for 4, 8, and 9

Carbon atom	4	8	9
1	80.1 (d)	78.4 (d)	78.6 (d)
2	80.1 (s)	79.2 (s)	79.4 (s)
3	201.8 (s)	202.1 (s)	201.6 (s)
4	46.5 (t)	52.5 (t)	50.2 (t)
5	88.7 (s)	84.3 (s)	84.3 (s)
6	47.3 (d)	36.9 (d)	36.7 (d)
7	28.2 (t)	31.1 (t)	29.5 (t)
1''	60.0 (t)	19.5 (q)	19.4 (q)
2''	168.3 (s)	165.3 (s)	165.1 (s)
3''	109.0 (d)	111.1 (d)	111.0 (d)
4''	174.4 (s)	174.1 (s)	174.0 (s)
5''	142.4 (s)	141.8 (s)	141.7 (s)
6''	146.5 (s)	146.4 (s)	146.1 (s)
5'	71.6 (t)	23.1 (q)	23.8 (q)
6'	177.9 (s)	120.8 (s)	119.1 (s)

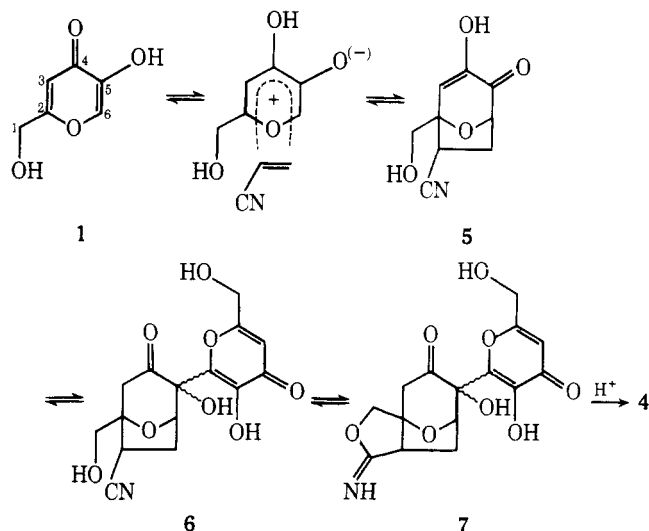
^a δ is chemical shift in ppm relative to CDCl_3 assigned as 76.9 downfield from Me_4Si .

a ratio of 10:1, which analyze for $\text{C}_{15}\text{H}_{15}\text{NO}_6$. We have assigned the following structures for 8 and 9 which are entirely consistent with the experimental results reported by Hurd.² Compounds 8 and 9 are isomeric about C-6 and the identity of each can be resolved by ^1H NMR. The coupling constant



- 8, X = CH_3 ; Y = CN (exo)
 9, X = CH_3 ; Y = CN (endo)
 10, X = CH_2Cl ; Y = CN
 11, X = CH_3 ; Y = CO_2CH_3
 12, X = H; Y = CN

Scheme I



of H-1 and H-7(exo) of 8 is, as expected, large ($J = 8$ Hz). The small coupling ($J = 4$ Hz) between H-7(exo) and H-6 indicates the trans relationship of these protons and thus the exo cyano moiety. In a similar manner 9 can be assigned as the endo C-6 nitrile on the basis of large coupling ($J = 12$ Hz) between H-7(exo) and H-6.

Finally, the reaction products 10, 11, and 12 which were originally isolated by Hurd have been identified and are formed in an analogous fashion. The ready availability of substituted 4-pyrone suggests the utility of this reaction in generating bicyclic structures that could well serve as useful intermediates in organic synthesis (e.g., for the preparation of substituted tropolones).

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 21 and Model 727B spectrometer. NMR spectra were obtained with a Varian XL-100 spectrometer with Me_4Si as an internal standard. Mass spectra were taken with an AEI-MS-30 mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department.

Preparation of the Pyrone Adducts. General Method. The procedure outlined by Hurd was used to prepare the following adducts: kojic acid and acrylonitrile, adduct 4, mp 264–265 °C (lit.^{2b} mp 261–262 °C); α -deoxykojic acid and acrylonitrile, major adduct 8, mp 268–270 °C (lit.^{2b} mp 262–264 °C); α -deoxykojic acid and acrylonitrile, minor adduct 9, mp 220–221.5 °C (lit.^{2b} mp 221–222 °C); α -chloro- α -deoxykojic acid and acrylonitrile, adduct 10, mp 246–247 °C (lit.^{2b} mp 243–244 °C); α -deoxykojic acid and methyl acrylate, compound 11, mp 224–226 °C (lit.^{2b} mp 219–220 °C); and pyromeconic acid and acrylonitrile, adduct 12, mp 212–214 °C (lit.^{2b} mp 208 °C). Analytical samples of all the above adducts ($\pm 0.4\%$ for C, H, N, and Cl) were obtained by acetonitrile recrystallizations. Small parent peaks were observed in the mass spectra for all of the above adducts. Large peaks indicative of 2–6'' bond cleavage were also observed.

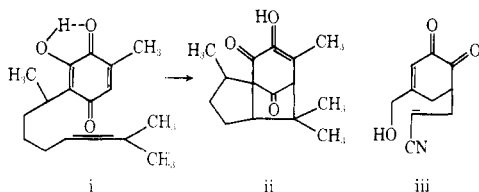
Acknowledgment. The authors are grateful to Dr. D. S. Kemp and Dr. I. M. Goldman for helpful discussions.

Registry No.—1, 501-30-4; 2, 644-46-2; 4, 63702-76-1; 8 and 9, 63702-77-2; 10, 63702-78-3; 11, 63702-79-4; 12, 63702-80-7; acrylonitrile, 107-13-1; α -chloro- α -deoxykojic acid, 7559-81-1; methyl acrylate, 96-33-3; pyromeconic acid, 496-63-9.

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- The original products were assigned letters by Hurd (see ref 2b). In accordance with this nomenclature, 4 corresponds to A, 7 to A', 8 to D, 9 to D', 10 to C, 11 to E, and 12 to F.
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nitrile to afford iii, followed by a second intramolecular Michael addition to position 2 of the kojic moiety. For if iii were an intermediate, its conversion to 5 must be extremely rapid, or cyanoethylated kojic acid resulting from a favorable prototropic shift of iii would be expected as a major product.

- (9) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Reinhart and Winston, New York, N.Y., 1959, p 379.
 (10) Neither the stereochemistry at position 2 nor the conformation of the fused six-membered ring in 4 has been rigorously defined. Exo addition by the pyrone moiety is presumably favored since this side of the molecule is more accessible to nucleophilic attack.
 (11) The precise order of events in the formation of 7 is not known (i.e., whether lactonization occurs before or after ketone attack by a second pyrone molecule).

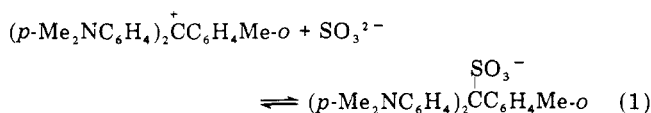
Equilibria and Rates in the Reaction of *o*-Methyl Malachite Green with Sulfite Ions¹

Jack Hine* and V. Thiagarajan

Department of Chemistry, The Ohio State University,
Columbus, Ohio 43210

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A study of the reaction of the *o*-methyl malachite green cation (M^+) with sulfite ions was initiated as part of an extension of earlier work on rate-equilibrium correlations in Lewis acid-base reactions.² We were not able to obtain the



additional data to permit us to draw broader generalizations, but the rate and equilibrium constants obtained are described here.

Results

Equilibrium Constants. Equilibrium in eq 1 was studied by absorbance measurements on mixtures of known concentrations of M^+ and SO_3^{2-} at 25 °C and ionic strength 0.5. Inasmuch as the pK values of HM^{2+} and M^+ at 20 °C and ionic strength 0.5 have been reported to be 1.31 and 9.07, respectively,³ we took the concentrations of HM^{2+} and MOH to be negligible over the pH range 4.8–7.2 over which we made measurements. The sulfite adduct was assumed to be present in forms with and without an amino group protonated (HMSO_3 and MSO_3^- , respectively). If A is the absorbance of a solution of M^+ , A_s is the absorbance of an equilibrium mixture of C mL of this solution and B mL of sulfite solution, and M_t is the concentration of M^+ in the original solution,

then the total concentration of adduct is given by eq 2.

$$[\text{MSO}_3^-] + [\text{HMSO}_3] = \left(\frac{C}{B+C} - \frac{A_s}{A} \right) M_t \quad (2)$$

$$[M^+] = M_t A_s / A \quad (3)$$

$$K(1 + [H^+]/K_a) = \frac{AC}{A_s(B+C)[\text{SO}_3^{2-}] - [\text{SO}_3^{2-}]} \quad (4)$$

The equilibrium concentration of M^+ is given by eq 3. Division of eq 2 by eq 3 and then by $[\text{SO}_3^{2-}]$ and rearrangement gives eq 4, in which K_a is the acidity constant of HMSO_3 and K is the equilibrium constant for addition of sulfite ions to M^+ . Over the pH range 4.8–7.2 58 points were taken, with A_s/A ranging from 0.21 to 0.95. The concentrations of hydrogen and sulfite ions were calculated from the pH ($-\log a_{H^+}$), an acidity constant of 1.96×10^{-7} M for bisulfite ions interpolated from data at surrounding ionic strengths,⁴ and ionic activity coefficients calculated from the Davies equation.⁵ The equilibrium concentrations of sulfite ions ranged from 1.6×10^{-5} to 0.013 M. Equation 4 was solved for A_s and then K and K_a were calculated by an unweighted nonlinear least-squares method.⁶ The values (\pm standard deviations) of $173 \pm 2 \text{ M}^{-1}$ and $(1.3 \pm 0.1) \times 10^{-6}$ M for K and K_a , respectively, fit the observed A_s values with a standard deviation of 0.010.

Rate Constants. Stopped flow kinetic runs were made using about 2×10^{-5} M M^+ and 0.005–0.05 M total sulfite over the pH range 6.16–7.58. In each run the approach to equilibrium was first order in $[M^+]$. Each first-order rate constant (k_{obsd}) is equal to the sum of a forward first-order rate constant (k_f) and a reverse first-order rate constant (k_r). Equation 5 allows for an uncatalyzed and an acid-catalyzed addition of sulfite ions to M^+ .

$$k_f = k_0[\text{SO}_3^{2-}] + k_h[H^+][\text{SO}_3^{2-}] \quad (5)$$

Equation 6 then follows from the principle of microscopic reversibility.

$$k_r = \frac{k_f}{K[\text{SO}_3^{2-}](1 + [H^+]/K_a)} \quad (6)$$

Combination of eq 5 and 6 gives eq 7.

$$k_{\text{obsd}} = (k_0 + k_h[H^+]) \times \left([\text{SO}_3^{2-}] + \frac{1}{K(1 + [H^+]/K_a)} \right) \quad (7)$$

Least-squares treatment of 52 k_{obsd} values, using the reciprocal of the standard deviation as the weighting factor, gave k_0 and k_h values (\pm standard deviations) of $24.5 \pm 0.2 \text{ M}^{-1} \text{ s}^{-1}$ and $(1.3 \pm 0.1) \times 10^7 \text{ M}^{-2} \text{ s}^{-1}$, respectively.

Discussion

The K_a value obtained corresponds to a pK_a value of 5.88 ± 0.04 or 5.58 on a per amino group basis. This is not far from the value 5.627 reported at 25 °C for the conjugate acid of *N,N*-dimethyl-*p*-toluidine,⁷ a reasonable model compound for the sulfite ion adduct of M^+ . The equilibrium constant K is smaller by more than 5000-fold than the value $>10^6 \text{ M}^{-1}$ reported⁸ for malachite green itself at 23 °C and ionic strength 0.001. Under the same conditions the rate constant for reaction of malachite green cations with sulfite ions was reported⁸ to be $4000 \text{ M}^{-1} \text{ s}^{-1}$, which is 160 times as large as our value at 25 °C and ionic strength 0.5. A considerably smaller rate constant ($280 \text{ M}^{-1} \text{ s}^{-1}$) for the reaction of malachite green with sulfite has been reported⁹ at 30 °C and ionic strength 1.0, but little experimental detail was given. Ritchie and Virtanen noted that the difference in rate constants reported is about that expected from the Debye-Hückel limiting law, which