83. The Oxidation of the Side Chain in Kojic Acid Benzyl Ether.

By Alan F. Thomas.

Conversion of the hydroxymethyl group in kojic acid benzyl ether into a formyl group has been effected with manganese dioxide. The effect of other oxidizing agents is described.

The direct oxidation of kojic acid derivatives (I; $R' = CH_2{\cdot}OH$) has been relatively little examined, possibly because of early difficulties in passing from the series having a 2-hydroxymethyl group to the comenic acid series having a 2-carboxyl group.[1,2] Previous attempts to prepare the corresponding aldehyde (I; $R = H$, $R' = CHO$) were also unsuccessful.[2,3] Since this work was completed, the successful preparation of this aldehyde has been reported.[4] Woods and Dix have described the preparation of substances purporting to be 3-formyl derivatives of the kojic acid series,[5] but little credence can be attached to their existence since their m. p.s are very close to those of the starting materials (no mixed m. p. is reported), the published infrared spectra show no formyl-carbonyl absorption, the only derivatives prepared had properties almost identical with those of the starting materials, and the nuclear magnetic resonance spectra, though anomalous for the structures postulated by Woods and Dix, would fit the non-formylated kojic acid quite well. Oxidations by chloranil described by the same authors [6] have given results to which similar remarks apply.

The benzyl ether [7] (I; $R = CH_2Ph$, $R' = CH_2{\cdot}OH$) of kojic acid was chosen as the most suitable derivative for an examination of the effect of oxidizing agents on the hydroxymethyl group, since it is sparingly water-soluble and the benzyl group is readily hydrogenolysed.

The chromic oxide–pyridine complex oxidized the compound directly to the benzyl ether of comenic acid (I; $R = CH_2Ph$, $R' = CO_2H$) in low yield, comenic acid (I; $R = H$, $R' = CO_2H$) being obtained after debenzylation; this appears to be the first reported conversion of kojic into comenic acid.

Treatment of the benzyl ether (I; $R = CH_2Ph$, $R' = CH_2{\cdot}OH$) with manganese dioxide in chloroform yielded a mixture, having infrared absorption at 1727 $cm.^{-1}$ from which derivatives of the aldehyde (5-benzyloxy-2-formyl-4-pyrone) could be prepared, but purity was not improved on crystallization. A pure product was obtained by using the earlier percolation technique for manganese dioxide oxidations,[8] the unoxidized alcohol being

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[1] Yabuta, *J.*, 1924, 575; Armit and Nolan, *J.*, 1931, 3023.

[2] Heyns and Vogelsang, *Chem. Ber.*, 1954, **87**, 1377; Heyns and Paulsen, *Angew. Chem.*, 1957, **69**, 600.

[3] Obata and Yamanishi, *J. Agric. Chem. Soc. Japan*, 1951, **24**, 334 (*Chem. Abs.*, 1952, **46**, 11,474).

[4] Becker, *Acta Chem. Scand.*, 1961, **15**, 683.

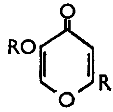
[5] Woods and Dix, *J. Org. Chem.*, 1961, **26**, 1028.

[6] Woods and Dix, *J. Org. Chem.*, 1961, **26**, 2588.

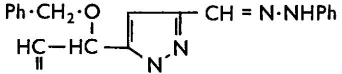
[7] Thomas and Marxer, *Helv. Chim. Acta*, 1960, **43**, 469.

[8] Wald, *J. Gen. Physiol.*, 1948, **31**, 489.

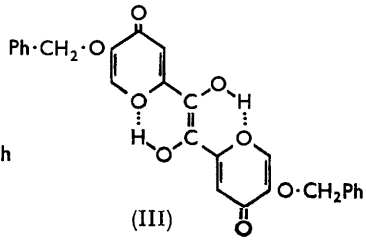
retained on the column. The ultraviolet absorption of the aldehyde in carbon tetrachloride was very similar to that of benzaldehyde though less intense,[9] but in ethanol was almost identical with that of the starting material; although the aldehyde did not crystallize from ethanol it was recovered unchanged on evaporation, showing that hemiacetal formation and decomposition must take place very readily. With phenylhydrazine, a normal phenylhydrazone (I; $R = CH_2Ph$, $R' = CH{:}N{\cdot}NHPh$) was first obtained, which on vigorous treatment with an excess of the reagent yielded a product involving three equivalents of phenylhydrazine, presumably the pyrazole (II).[10] From 2,4-dinitrophenylhydrazine, only the normal derivative was obtained. With a trace of sodium cyanide, the aldehyde yielded the deep yellow enediol form of an acyloin (III);[11] this structure was allotted on the grounds of the colour, the infrared spectrum (no carbonyl absorption other than the customary pyrone bands), and the fact that it was insufficiently soluble for the ultraviolet spectrum to be measured in any solvent tried, though it gave a deep purple solution in sodium hydroxide solution which slowly faded. It dissolved in hot dimethylformamide and hot glacial acetic acid, but could only be recovered provided it was immediately precipitated with water.



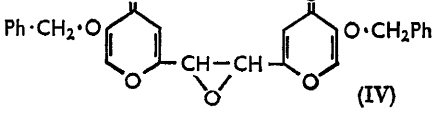
(I)



(II)



(III)



(IV)

Hydrogenolysis of the benzyl group in the ether (I; $R = CH_2Ph$, $R' = CHO$) gave a mixture from which " comenic aldehyde " (2-formyl-5-hydroxy-4-pyrone) was isolated. This compound was characterized as its 2,4-dinitrophenylhydrazone and semicarbazone, but the phenylhydrazone, though apparently formed initially, decomposed to a dark oil on attempted recrystallization.

An attempt to prepare aldehydes of this series by treatment of 5-benzyloxy-2-chloromethyl-4-pyrone with hexamine gave polymeric material.

Finally, some experiments were undertaken to test the applicability of the dimethyl sulphoxide method for oxidation of the toluene-*p*-sulphonic and benzenesulphonic esters (I; $R = CH_2Ph$, $R' = CH_2{\cdot}OAcyl$).[12] Two compounds, A and B, were obtained from each of these reactions, one with m. p. 145°, the other with m. p. 212°. The yields were very poor, and some difficulty was experienced in purifying the substances. Both had twice the molecular weight required for a simple pyrone, and neither had infrared hydroxyl or carbonyl absorption (apart from the pyrone bands). The compounds did not react with 2N-sulphuric acid; sodium hydroxide caused extensive decomposition; but compound A (m. p. 145°) yielded with 2N-hydrochloric acid a product which gave analytical results concordant with its being a chlorohydrin. Since their infrared spectra were very similar, these compounds were tentatively allotted the structures of *cis*- and *trans*-2,3-di-(5-benzyloxy-4-oxopyran-2-yl)oxiran (IV). This supposition was supported by the proton magnetic resonance spectra (see Table), kindly measured by Dr. R. F. Zürcher of CIBA, Basle.

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[9] Cf. Braude in Braude and Nachod, " Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, 1955.

[10] Marxer and Thomas, *Chimia*, 1960, **14**, 126.

[11] For a similar structure for α-pyridoin, see Eistert and Schade, *Chem. Ber.*, 1958, **91**, 1404.

[12] Kornblum, Jones, and Anderson, *J. Amer. Chem. Soc.*, 1959, **81**, 4113.

TABLE 1.

Proton magnetic resonance spectra; measurements were made at 60 Mc./sec. for $CDCl_3$ solutions. Chemical shifts are relative to tetramethylsilane as internal reference.

Frequency		Chem. shift (p.p.m.)		Relative intensity	Allocation
A	B	A	B		
451	449	7·52	7·48	1	Pyrone 2-H
442	441	7·37	7·35	5	Phenyl H
392	387	6·53	6·45	1	Pyrone 5-H
305	302	5·08	5·03	2	Benzyl CH_2
234	245	3·90	4·08	1	Epoxide H

EXPERIMENTAL

M. p.s are corrected. Infrared data are for $CHCl_3$ solutions unless otherwise stated.

5-Benzyloxy-4-pyrone-2-carboxylic Acid (*Benzylcomenic Acid*).—(A) *From kojic acid.* 5-Benzyloxy-2-hydroxymethyl-4-pyrone[7] (1·4 g.) was dissolved in pyridine (15 ml.), and pyridine–chromic oxide complex (from chromic oxide, 2·4 g., and pyridine, 10 ml.) was added with cooling. After 24 hr. the mixture was treated with ice and concentrated hydrochloric acid, then with powdered sodium sulphite until the red colour disappeared. The product was extracted with ether, which was then shaken with sodium hydrogen carbonate solution, and the *acid* (0·4 g.) was precipitated with dilute sulphuric acid. Crystallized from ether–light petroleum, it had m. p. 196°, $\lambda_{max.}$ (in EtOH) 221 (ε 8300) and 250 mμ (ε 2500) (Found: C, 63·6; H, 3·9. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%).

(B) *From comenic acid.* 5-Hydroxy-4-pyrone-2-carboxylic acid[13] (7·2 g.), sodium hydroxide (4·1 g.), and benzyl chloride (15·6 g.) were heated under reflux in 4 : 1 water–ethanol for 1 hr. and the product that separated on cooling was crystallized from methanol to m. p. 196°, undepressed on admixture with that prepared by method (A).

Comenic Acid (I; R = H, R′ = CO_2H).—Benzylcomenic acid was shaken in alcohol with 5% palladium–charcoal in hydrogen (uptake 1 mol. in 15 min.). Filtration and evaporation yielded crystals identical with comenic acid (infrared spectrum in Nujol) prepared from meconic acid.[13]

5-Benzyloxy-2-formyl-4-pyrone.—5-Benzyloxy-2-hydroxymethyl-4-pyrone (3 g.) and manganese dioxide (14 g.; from Hopkin and Williams, Ltd.) were shaken together in chloroform (300 ml.). After 2 hr. the intensity of the band at 1727 cm.$^{-1}$ did not increase further, and the solution was filtered and evaporated to yield a syrup (3·1 g.) which was used for the preparation of derivatives of the aldehyde. Pure " *benzylcomenic aldehyde* " was prepared by suspending 5-benzyloxy-2-hydroxymethyl-4-pyrone (5 g.) in chloroform (50 ml.) and percolating the mixture through a column of manganese dioxide (50 g.) with chloroform (1·5 l.). Evaporation yielded crystals (2·5 g., 48%), m. p. 126—135°, which, recrystallized from carbon tetrachloride, had m. p. 141° (mixed with starting material, m. p. 101—109°) (Found: C, 67·1; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·1; H, 4·4%), $\lambda_{max.}$ (in EtOH) 217 (ε 9200) and 264 mμ (ε 6600), $\lambda_{max.}$ (in CCl_4) 256 (ε 8100) and 264 mμ (ε 6600), $\nu_{max.}$ 2725, 1721, 1645, and 1623 cm.$^{-1}$.

The *semicarbazone*, made in ethanol and recrystallized from glacial acetic acid, had m. p. 275—277° (decomp.) (Found: N, 14·5. $C_{14}H_{13}N_3O_4$ requires N, 14·6%). The *2,4-dinitrophenylhydrazone*, made in and recrystallized from ethanol, had m. p. 275—277° (decomp.) (Found: C, 55·5; H, 3·5; N, 13·7. $C_{19}H_{14}N_4O_7$ requires C, 55·6; H, 3·4; N, 13·7%).

The *phenylhydrazone* was made by warming the starting materials in alcohol for 2 min. at 50° and recrystallizing the product from alcohol; it had m. p. 188° (Found: C, 71·3; H, 5·0; N, 8·8. $C_{19}H_{16}N_2O_3$ requires C, 71·2; H, 5·0; N, 8·8%), $\nu_{max.}$ (in Nujol) 3175, 1634, 1610, 1543, 1497, 1466 (infl.), 1451vs cm.$^{-1}$. 5-Benzyloxy-2-formyl-4-pyrone (0·5 g.) was heated at 120° under nitrogen for 15 hr. with phenylhydrazine (10 ml.) and the mixture diluted with alcohol (25 ml.); yellow *α-benzyloxy-α-(3-formyl-1-phenyl-5-pyrazolyl)acetaldehyde bisphenylhydrazone* (II) that separated recrystallized from ethanol, then having m. p. 170—171° (Found: C, 74·5; H, 5·6; N, 16·7. $C_{31}H_{28}N_6O$ requires C, 74·4; H, 5·6; N, 16·8%), $\nu_{max.}$ (in Nujol) 3175, 1605, 1560 (infl.), 1520, 1504, 1499, 1464 cm.$^{-1}$.

1,2-Di-(5-benzyloxy-4-oxopyran-2-yl)ethylene-1,2-diol (III).—5-Benzyloxy-2-formyl-4-pyrone (0·5 g.) was dissolved in ethanol (15 ml.), and sodium cyanide (*ca* 1 mg.) added. Brief warming

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[13] Robiquet, *Annalen*, 1833, **82**, 82.

caused bright yellow prisms of the *product* (III) (0·35 g.) to appear. Washed with hot chloroform and ethanol, it had m. p. 231° (decomp.) (Found: C, 67·7; H, 4·4. $C_{26}H_{20}O_8$ requires C, 67·8; H, 4·4%), $\nu_{max.}$ (in Nujol) 1647, 1629, 1582, 1562 cm.$^{-1}$, broad band at 3340—3325 cm.$^{-1}$ partially obscured by the Nujol absorption. The substance gave a permanganate colour in sodium hydroxide solution; immediate neutralization of an alkaline solution caused reprecipitation of the yellow crystals, but this solution slowly decomposed.

2-Formyl-5-hydroxy-4-pyrone ("*Comenic Aldehyde*").—The 5-benzyloxy-aldehyde (I; R = CH_2Ph, R′ = CHO) (1 g.) was shaken with 5% palladium–charcoal in hydrogen. After 100 ml. had been absorbed (calc., 97 ml. at N.T.P.) hydrogenation was stopped, the catalyst removed, and the solution evaporated. Several crystallizations from ethyl acetate gave a small amount of kojic acid from the less soluble fractions, then 2-formyl-5-hydroxy-4-pyrone from the more soluble fractions. The latter had m. p. 157—159° (mixed with kojic acid, m. p. 128—135°) (Found: C, 51·6; H, 3·1. Calc. for $C_6H_4O_4$: C, 51·4; H, 2·9%), $\nu_{max.}$ at 1721, 1645, and 1592 cm.$^{-1}$. The crystals decomposed slowly in air; they gave a wine colour in alcohol with ferric chloride. Becker [4] gives m. p. 162—163°; he does not mention any by-products from his reaction, so that it seems possible that the product described in the present work may still have contained a trace of kojic acid which further crystallization and sublimation did not remove.

The *semicarbazone*, made in and recrystallized from aqueous alcohol, decomposed at 265—270° (Found: C, 39·3; H, 4·3; N, 19·6. $C_7H_7N_3O_4,H_2O$ requires C, 39·1; H, 4·3; N, 19·5%). The *2,4-dinitrophenylhydrazone*, made in and recrystallized from ethanol, decomposed at *ca.* 270° (Found: C, 45·0; H, 2·6; N, 17·4. $C_{12}H_8N_4O_7$ requires C, 45·0; H, 2·5; N, 17·5%).

5-Benzyloxy-2-chloromethyl-4-pyrone.—When 5-benzyloxy-2-hydroxymethyl-4-pyrone (5 g.) and thionyl chloride (5 g.) had reacted in chloroform (30 ml.), this *compound* was precipitated by light petroleum (b. p. 40—60°); recrystallized from ethanol–ether, it had m. p. 118—120° (Found: C, 62·4; H, 4·3; Cl, 14·4. $C_{13}H_{11}ClO_3$ requires C, 62·3; H, 4·4; Cl, 14·2%). Heating it with hexamine in chloroform for 4 hr. yielded a hexamine salt, but this give a resin on treatment with 50% acetic acid or 60% ethanol.

*5-Benzyloxy-2-toluene-*p*-sulphonyloxymethyl-4-pyrone.*—5-Benzyloxy-2-hydroxymethyl-4-pyrone (7·0 g.) and toluene-*p*-sulphonyl chloride (5·75 g.) were shaken in acetone (100 ml.). Sodium hydroxide (1·23 g.) in water (5 ml.) was added and the mixture shaken for 10 min. Dilution with water precipitated the *toluene-*p*-sulphonate* (11·1 g.) which, crystallized from methanol–water and ethyl acetate–light petroleum (b. p. 40—60°), had m. p. 112° (Found: C, 62·4; H, 4·7; S, 8·4. $C_{20}H_{18}O_6S$ requires C, 62·2; H, 4·7; S, 8·3%).

In the same way, the *benzenesulphonate*, m. p. 98° (from ethyl acetate–light petroleum) (Found: C, 61·1; H, 4·2; S, 8·7. $C_{19}H_{16}O_6S$ requires C, 61·3; H, 4·3; S, 8·6%), was prepared.

1,2-Di-(5-benzyloxy-4-oxopyran-2-yl)oxiran (IV).—5-Benzyloxy-2-toluene-*p*-sulphonyloxymethyl-4-pyrone (3 g.) was heated at 80° in a current of nitrogen for 10 min. with dimethyl sulphoxide (50 ml.) and sodium hydrogen carbonate (10 g.). A dark brown resin (1 g.) was precipitated with water, which, on crystallization from carbon tetrachloride, then from toluene–light petroleum (b. p. 40—60°), yielded *oxide A* as plates, m. p. 145° [Found: C, 70·5; H, 4·6%; *M* (Rast, in camphor), 459. $C_{26}H_{20}O_7$ requires C, 70·3; H, 4·5%; *M*, 444·4], $\nu_{max.}$ 2985, 1660, 1605 cm.$^{-1}$. The residue from the resin extracted with carbon tetrachloride was treated with ethyl acetate; a few crystals of *oxide B* were obtained. Crystallization from ethyl acetate raised the m. p. to 212° [Found: C, 70·4; H, 4·6%; *M* (Rast in camphor), 438, 443], $\nu_{max.}$ 1656 and 1597 cm.$^{-1}$.

1,2-Di-(5-benzyloxy-4-oxopyran-2-yl)-2-chloroethanol.—The oxide A (0·05 g.) was boiled with N-hydrochloric acid (15 ml.) for 10 min. and the mixture was filtered. The resulting precipitate of *chlorohydrin*, crystallized from ethyl acetate, had m. p. 194—196° (Found: C, 64·4; H, 4·4; Cl, 7·5. $C_{26}H_{21}ClO_7$ requires C, 64·9; H, 4·4; Cl, 7·4%).

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