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The Preparation and Rearrangement of Allyl Kojate

By W. M. McLamore, E. Gelblum and A. Bavley

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Allyl kojate has been prepared for the first time. It is shown that allyl kojate rearranges thermally to 6-allylkojic acid, which was previously reported in the literature as allyl kojate. The 6-allylkojic acid described in the literature is shown to be 6-propenylkojic acid.

As part of a general program on kojic acid derivatives, prompted by the recently announced commercial availability of the acid (I),[1] we wished to prepare the allyl ether (allyl kojate, II). The procedure of Hurd and Sims[2] was unsatisfactory in our hands, but after an unprofitable exploration of other methods, we obtained our best results by a modification of their method. The important feature of this modification was the avoidance of high temperatures at any point in the isolation of the ether. A further feature of our isolation procedure was the removal of unreacted kojic acid (which was always present in our experiments) by extraction of a chloroform solution of the reaction residue with sodium carbonate solution until the chloroform layer gave a negative ferric chloride test.[3] Surprisingly, the crystalline product, after purification, melted at 68° rather than 125°, as previously reported.[2]

In spite of the melting point discrepancy, the properties of the new compound II were in complete accord with the allyl ether structure. In addition to a correct analysis for $C_9H_{10}O_4$, II gave a negative ferric chloride test, did not precipitate with cupric acetate solution[3] and had 0.85 active hydrogens. The ultraviolet spectrum of the new substance was very similar to that of methyl kojate (Table I); the infrared spectra were also similar.

Thermal rearrangement of II occurred very rapidly at 180–200° (0.1 mm.), and III distilled in quantitative yield from the reaction vessel. The m.p. of III (124.2–125.2°) is again quite different from that reported for 6-allylkojic acid (160°)[2] but almost identical with that reported for allyl kojate (125–125.5°). Compound III had all the properties expected of 6-allylkojic acid: correct analyses for $C_9H_{10}O_4$, positive ferric chloride and copper chelate tests, 2.0 active hydrogens and a small bathochromic shift (9 mμ) in the ultraviolet absorption maximum with respect to kojic acid (Table I).

Unlike the "allyl kojate" of Hurd and Sims, II did not give the thermal rearrangement product III on treatment with alcoholic hydrogen chloride at 60°. Instead, a new compound VI was formed. That ethanol was not involved in the formation of VI was demonstrated by preparation of the same substance from II with hydrogen chloride in benzene. Although the m.p. of VI (123–124°) was almost identical with that of III, the compounds were very dissimilar; VI was unstable, gave an immediate precipitate with silver nitrate and gave negative ferric chloride and copper chelate tests. Finally, II was regenerated from VI on heating, attempted recrystallization or treatment with sodium bicarbonate. All these facts indicate that VI is a simple hydrochloride of II, by virtue of the weakly basic γ-pyrone system. Analyses of VI were variable, but an analytically pure sample was eventually obtained by treatment of pure II with alcoholic hydrogen chloride at low temperature.

Like II, III also gave an unstable hydrochloride IV on treatment with alcoholic hydrogen chloride. Although clearly distinct from the 6-allylkojic acid of Hurd and Sims (m.p. 160°), IV had a similar melting point (158–159.5°). Moreover, recrystallization of IV or drying in vacuum did not lead to recovery of III but to a different base, V, very similar in m.p. (163–164°) to the previously reported "6-allylkojic acid."[2] Compound V, contrary to the experience of the earlier investigators, could not be obtained consistently by thermal rearrangement of either III or II, although it was occasionally isolated in very small amounts.

Analyses of both IV and V indicated that V is isomeric with III, and the usual tests showed that the enolic function is free in V. Since we regard III as 6-allylkojic acid, the most likely structure for V appeared to be 6-propenylkojic acid. Strong confirmation of this hypothesis was afforded by the ultraviolet spectrum of V, which shows a large bathochromic shift (35 mμ) with respect to III (Table I). Further confirmation was obtained by hydrogenation of III and V to the same compound, 6-propylkojic acid (VII). The ultraviolet absorption spectrum of VII was almost identical with that of III, as expected (Table I). No structure for V other than 6-propenylkojic acid would appear to account for all of these facts.

On the evidence presented we now conclude that allyl kojate has been prepared for the first time and that the compound so designated in the literature[2] is probably 6-allylkojic acid. We are unable to explain the negative ferric chloride test reported for this substance, but all the other properties and reactions of the compound are in accord with the proposed structure. Furthermore, formation of 6-allylkojic acid under the conditions of the earlier experiment (160°) is perhaps not surprising in view of the ready rearrangement of allyl kojate at elevated temperatures. On the basis of our structure assignments, it is no longer necessary to rationalize the rather exceptional acid-catalyzed rearrangement of the allyl ether under mild conditions,[2] since the actual reaction observed is simply the rearrangement of an isolated double bond into con-

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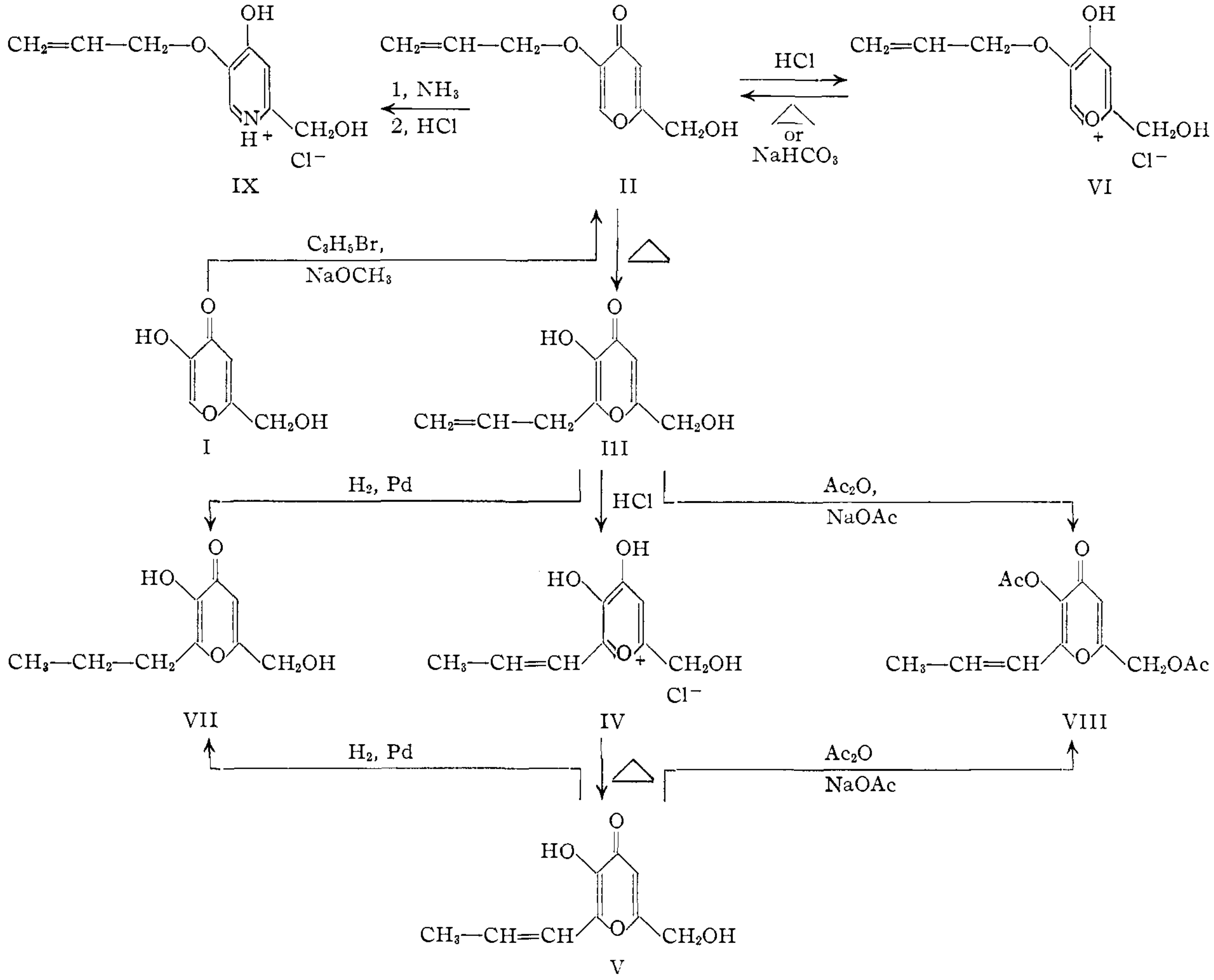
[1] *Chem. Eng. News*, **33**, 2556 (1955).

[2] Charles D. Hurd and Rex J. Sims, This Journal, **71**, 2440 (1949).

[3] Kojic acid and all its derivatives in which the acidic (5-) hydroxyl is free give typical enol tests with alcoholic ferric chloride, the colors being deep red or purplish. Presence of the free enolic function is further confirmed by formation of an insoluble copper chelate compound with cupric acetate.



jugation with the pyrone system, energetically a very favorable process.

Acetylation of either III or V gave the same diacetate VIII, as did the two compounds reported earlier.[2] The m.p. of VIII (114–115°) is in good agreement with that reported (112.5–113°), and it was demonstrated to be the diacetate of 6-propenylkojic acid (V) by hydrolysis to V under conditions (alkaline) shown not to rearrange III to V. Formation of the same diacetate from either III or V is also more readily explained on the present structural basis.

Finally, allyl kojate (II) was readily converted to the corresponding pyridone (isolated as hydrochloride IX) with ammonia, while we were unable to isolate a pyridone from the reaction of 6-allylkojic acid (III) with ammonia. This appears to be in accord with general experience in the kojic acid series, in which 5-ethers are much more smoothly convertible to pyridones than are compounds in which the acidic 5-hydroxyl is free.[4] The ultraviolet absorption maximum of IX is given in Table I, along with a summary of ultraviolet data for the other compounds described in this paper.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[5]

Compound	λ_{max}, mμ	log ε
I	268	3.92
I diacetate	251	4.01
Methyl kojate	265	3.96
II	264	3.92
III	277	3.95
V	312	4.19
VII	277	3.93
VIII	282	4.22
IX	273	4.08

It should be noted that the compound reported as allyl 6-allylkojate[2] is actually allyl 6-propenylkojate.

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Experimental

Allyl Kojate (I).—To a suspension of 200 g. of kojic acid in 1600 ml. of methanol was added a solution of 32.2 g. of

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(4) For example: T. Yabuta, *J. Chem. Soc.*, **125**, 575 (1924); J. W. Armit and T. J. Nolan, *ibid.*, 3023 (1931); K. N. Campbell, J. F. Ackerman and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950). Kojic acid itself is converted to the pyridone only with difficulty and in very low yield (private communication from Mr. P. N. Gordon).

(5) All spectra were determined in absolute ethanol on a Cary recording spectrophotometer, model 11.

sodium in 800 ml. of methanol. The resulting solution of sodium kojate was refluxed with 170 g. of allyl bromide for 2.5 hr. and left overnight. Although the mixture was neutral, it still contained kojic acid. Methanol was removed, and the residue was taken up in chloroform and extracted repeatedly with 10% sodium carbonate solution until the chloroform layer gave a negative ferric chloride test. The carbonate extracts were re-extracted with chloroform to avoid loss of allyl kojate, which is moderately soluble in water. The combined chloroform extracts were dried (anhydrous magnesium sulfate) and concentrated. The residue which solidified was recrystallized from acetone–petroleum ether with the aid of Darco to give 155.5 g. (47.0% yield) of somewhat impure allyl kojate, m.p. 61–64°. This material is quite satisfactory for conversion to 6-allylkojic acid, and even quite crude material can be used for the rearrangement. A purer product (m.p. 67–68°) can be obtained by a second recrystallization in the same way, but in substantially lower yield (118.5 g. or 35.8%). Ferric chloride and copper chelate tests[3] were both negative, and a pure sample had 0.85 active hydrogen.[6]

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.45; H, 5.70.

6-Allylkojic Acid (III).—Pure allyl kojate (3.0 g.) was placed in a large sublimation tube, the air displaced with nitrogen and the tube placed in a preheated (125–130°) block. As soon as the allyl kojate was melted, a plug of glass wool was introduced and the tube again flushed with nitrogen. The tube was then connected to an oil-pump (0.1 mm.) and heated rapidly to 180–200°. The 6-allylkojic acid distilled in quantitative yield[7] within 10–15 minutes and solidified to a very pale yellow, waxy solid, m.p. 124–125°. The analytical sample was obtained by recrystallization from isopropyl alcohol; m.p. 124.2–125.2°. Ferric chloride and copper chelate tests[3] were both positive, and the active hydrogen determination[6] gave a value of 2.0.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.40; H, 5.66.

6-Propenylkojic Acid Hydrochloride (IV).—Although IV was the initial product from III and alcoholic hydrogen chloride at 60°,[2] it could not be purified or even dried in vacuum without losing hydrogen chloride. Therefore, it was best prepared by treatment of a methanol solution of pure V (1.14 g.) with excess, saturated methanolic hydrogen chloride. The precipitated IV was immediately filtered and briefly air-dried to give 0.83 g. of white crystals, m.p. 158–159.5° dec. Ferric chloride and copper chelate tests were both positive.[3]

Anal. Calcd. for $C_9H_{11}O_4Cl$: C, 49.44; H, 5.07; Cl, 16.22. Found: C, 49.22; H, 5.22; Cl, 16.20.

6-Propenylkojic Acid (V).—Hydrogen chloride was passed into a solution of 4.0 g. of III in 200 ml. of anhydrous ethanol at 60° for 1 hr. Ethanol was removed under reduced pressure, and the solid residue was recrystallized from acetone with the aid of Darco. A total of 3.15 g.[8] of V was obtained in three crops, m.p. from 157° to 164°. A second recrystallization from acetone gave a pure sample, m.p. 163.5–164°. The compound gave positive ferric chloride and copper chelate tests[3] and showed 1.6 active hydrogen.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.53; H, 5.60.

Allyl Kojate Hydrochloride (VI).—Although VI was formed on treatment of an ethanol (or benzene) solution of allyl kojate (II) with hydrogen chloride at 60°, it was not pure and, like IV, it could not be purified without loss of hydrogen chloride. A pure sample eventually was prepared by treatment of a cold, concentrated solution of II (1.0 g.) in methanol with excess, saturated methanolic hydrogen chloride. The crystalline product, which separated only after addition of ether and acetone, was filtered at once and briefly dried, yield 0.94 g., m.p. 123–124° dec. Ferric chloride and copper chelate tests[3] were negative, but the compound gave a strong Beilstein halogen test and an immediate precipitate with silver nitrate. A small sample of VI was dissolved in water (very soluble) and the acidic solution neutralized with sodium bicarbonate. Ether extraction of this solution led to allyl kojate (II), identified by m.p. and mixed m.p.

Anal. Calcd. for $C_9H_{11}O_4Cl$: C, 49.44; H, 5.07; Cl, 16.22. Found: C, 49.11; H, 5.30; Cl, 15.96.

6-Propylkojic Acid (VII).—Hydrogenation of 911 mg. (5 millimoles) of 6-allylkojic acid in 50 ml. of absolute ethanol, with 250 mg. of pre-reduced 5% palladium-on-charcoal catalyst, resulted in the rapid uptake of 115 ml. (5.14 millimoles) of hydrogen. The hydrogenation, which had become very slow, was interrupted, the catalyst filtered and the filtrate concentrated to 15 ml. A total of 710 mg. of VII was obtained by crystallization (two crops), m.p. 98.5–100°. Recrystallization from ether with the aid of Darco afforded pure VII, m.p. 101–101.5°. Compound VII was obtained in similar fashion from 6-propenylkojic acid; identity was established by mixed m.p. and by ultraviolet and infrared spectra. The spectra also ruled out the possibility of partial hydrogenation of the γ-pyrone system. The compound gave positive ferric chloride and copper chelate tests[3] and showed 1.7 active hydrogens.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.34; H, 6.79.

6-Propenylkojic Acid Diacetate (VIII).—Acetylation of 6-propenylkojic acid (500 mg.) was effected by heating it 3 hr. at 95° with acetic anhydride (3 ml.) and sodium acetate (10 mg.). The reaction mixture was evaporated under reduced pressure, and the residue was crystallized directly from isopropyl alcohol. Two recrystallizations (the second from ethanol–acetone) afforded pure VIII, m.p. 114–114.5°. The same diacetate was obtained in a similar way from 6-allylkojic acid (III), and the identity of the two samples was established by mixed m.p., ultraviolet and infrared spectra.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.38; H, 5.38.

The diacetate VIII (440 mg.) was hydrolyzed by 5% methanolic sodium hydroxide (8 ml.) during 3 hr. at room temperature. After acidification with acetic acid and evaporation, the product was crystallized from acetone; it was identified as 6-propenylkojic acid by m.p. (161–162°) and mixed m.p. (162.5–163.2°). 6-Allylkojic acid (II) was recovered unchanged when it was subjected to these same conditions.

2-Hydroxymethyl-5-allyloxy-4-pyridone Hydrochloride (IX).—A solution of 4.0 g. of allyl kojate (II) in 20 ml. of concentrated aqueous ammonia was heated on a water-bath for 2 hr. with a Dry Ice reflux condenser. A nitrogen atmosphere was maintained during the reaction. The dark solution was evaporated under reduced pressure, and the residue was taken up in methanol, treated with Darco and filtered. Treatment of the filtrate with saturated methanolic hydrogen chloride precipitated the pyridone hydrochloride (IX), yield 2.05 g., m.p. 174–175°. The analytical sample was recrystallized from isopropyl alcohol, m.p. 178.5–179°.

Anal. Calcd. for $C_9H_{12}O_3NCl$: C, 49.66; H, 5.56; N, 6.44; Cl, 16.29. Found: C, 49.91; H, 5.72; N, 6.54; Cl, 16.24.

Treatment of II with aqueous ammonia under pressure was less clean and gave an impure hydrochloride. The pyridone also formed a picrate, m.p. 173–175°, that was not investigated further. Several attempts to isolate the pyridone base from the hydrochloride were unsuccessful, apparently owing to the extraordinary solubility of the pyridone.

Brooklyn 6, New York

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(6) F. A. Hochstein, This Journal, **71**, 305 (1949).

(7) The yield was of course lower when less pure allyl kojate was used, and yields were also lower on larger-scale experiments, owing to partial decomposition.

(8) It is probable that the yield of IV and therefore of V could be increased by working under milder conditions, since small-scale attempts to prepare the hydrochloride of 6-allylkojic acid under mild conditions always proceeded cleanly, but only to the rearranged hydrochloride IV.